TITLE: Conventional compared to network meta-analysis to evaluate antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients

RUNNING HEAD: Network meta-analysis

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**ABSTRACT**

Our purpose was to compare conventional meta-analysis and network meta-analysis to evaluate efficacy of different prophylactic systemic antibiotic classes in patients undergoing chemotherapy or HSCT. We included randomized trials if patients had cancer or were HSCT recipients and the intervention was systemic antibacterial prophylaxis. Three types of control groups were used: 1) placebo, no antibiotic and non-absorbable antibiotic separately; 2) placebo and no antibiotic combined; 3) all three combined. These gave different network geometries. Strategies synthesized were fluoroquinolone, trimethoprim-sulfamethoxazole, cephalosporin and parenteral glycopeptide vs. control groups. In total 113 trials met the eligibility criteria. Where treatment effects could be estimated with both conventional and network meta-analysis, values were generally similar. However, where events were sparse, network meta-analysis could be more precise. For example, trimethoprim-sulfamethoxazole vs. placebo for infection-related mortality showed relative risk (RR) 0.55, 95% confidence interval (0.21-1.44) with conventional and RR 0.43, 95% credible region (0.20-0.82) with network meta-analysis. Cephalosporin vs. fluoroquinolone was comparable only indirectly using the network approach and yielded RR 0.59, 95% credible region (0.28-1.20) to reduce bacteremia. Incoherence (difference between direct and indirect estimates raising concerns about network meta-analysis validity) was observed with network geometry where control groups were separated, but not where control groups were combined. In this situation, conventional and network meta-analysis yielded similar results in general. Network meta-analysis results could be more precise when events were rare. Some analysis could only be performed with the network approach. These results identify scenarios in which network meta-analysis may be advantageous.

**INTRODUCTION**

Invasive bacterial infections are important causes of morbidity and mortality in patients undergoing intensive chemotherapy and hematopoietic stem cell transplant (HSCT).[1](#_ENREF_1)[2](#_ENREF_2) There are many approaches to reduce bacterial infection in these populations[3](#_ENREF_3)[4](#_ENREF_4) with antibacterial prophylaxis being one evaluated strategy. In attempting to reduce this outcome, there have been more than 100 randomized trials of antibacterial prophylaxis performed but yet, there continues to be uncertainty about the optimal approach. To facilitate understanding of the benefits and risks of prophylaxis, we recently performed a systematic review of randomized trials.[5](#_ENREF_5) The primary method of analysis was conventional meta-analysis whereby each study contributed one intervention and one control group. There were two main limitations with this approach. First, in studies that randomized patients to more than two groups, valuable information was lost.[6](#_ENREF_6) Second, some studies compared an intervention to a common control group but never compared interventions of clinical interest directly. In a conventional meta-analysis, the relative effect of these two interventions of interest cannot be estimated.[7](#_ENREF_7) Both limitations can be overcome through network meta-analysis.

 Network meta-analysis allows comparisons of more than two interventions in a single analysis using all the relevant data. The main advantages of this approach are: (1) estimation of relative effects using both direct and indirect evidence; and (2) incorporation of information from multi-arm trials. Appendix 1 illustrates an example where we want to compare three treatments (A, B and C) using the mean difference (MD). In this example, there was one trial that compared A vs. B and found a MD of 4.0 (95% confidence interval (CI) 3.0 to 5.0) and one trial that compared A vs. C with a MD of 2.3 (95% CI 1.4 to 3.2). From this hypothetical comparison, we can see that B and C are likely better than A if a reduction is desirable. If the trial samples are clinically homogenous, then we can estimate that B is better than C by 1.7 (95% CI 0.4 to 3.0) through an indirect comparison. If a new trial was then conducted that compared B and C directly, network meta-analysis could combine the indirect estimate of B to C (1.7) and the resulting direct estimate from the new trial.

 While network meta-analysis is well established, its conduct requires more specialized analytic skills than conventional meta-analysis, the latter of which can easily be conducted using widely available software such as RevMan.[7](#_ENREF_7) Further, in network meta-analysis, it is important to evaluate incoherence (substantially different results between direct and indirect estimates) as incoherence may suggest bias and reduces the trustworthiness of the results.[6](#_ENREF_6) It might be helpful to delineate circumstances in which network meta-analysis may be particularly advantageous relative to conventional meta-analysis and thus, would make any additional analytic complexities worthwhile. Consequently, our objective was to compare conventional meta-analysis and network meta-analysis to evaluate the efficacy of different prophylactic systemic antibiotic classes in patients undergoing chemotherapy or HSCT.

**METHODS**

 This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting.[8](#_ENREF_8)

**Data Sources and Searches**

 As previously described,[5](#_ENREF_5) the search included Ovid MEDLINE, MEDLINE in-process and Embase; and Wiley Cochrane Central Register of Controlled Trials and included articles indexed up to November 26, 2018. The search strategy included the Medical Subject Heading terms and text words that identified patients with cancer or HSCT recipients receiving antibacterial prophylaxis, and the set was limited to randomized trials published in 1980 or more recently. Publications in all languages were included. The search strategy can be found in Egan et al.[5](#_ENREF_5)

**Study Selection and Data Abstraction**

 This meta-analysis included fully published primary randomized or quasi-randomized trials with a parallel group design comparing the administration of a systemic antibacterial agent to any control group as prophylaxis. Studies were eligible if at least 90% of participants were patients undergoing chemotherapy for cancer or HSCT for any indication. We excluded studies if the antibacterial agent was given as peri-procedural prophylaxis only.

 Screening of titles and abstracts, evaluation of full text articles for eligibility and data abstraction were conducted independently in duplicate by two reviewers (PDR and GE) and disagreements were resolved by consensus. Adjudication by a third reviewer (LS) occurred if required.

 In the conventional meta-analysis, outcome measures included those related to antibacterial prophylaxis efficacy and adverse effects. In this comparison of conventional and network meta-analysis, we focused on two clinically important efficacy measures, namely bacteremia and infection-related mortality. In addition to being clinically important, these two were also chosen because one was relatively common (bacteremia) while the other was relatively rare (infection-related mortality).

**Intervention and Control Groups Evaluated**

 As in the conventional meta-analysis, comparisons of interest focused on fluoroquinolone, trimethoprim-sulfamethoxazole, cephalosporin and parenteral glycopeptide. Each of these were evaluated against three types of control groups. With the first control group type, placebo, no antibiotic and non-absorbable antibiotic were all evaluated separately (separate control groups) and each was a separate node. This comprised the first network geometry (Appendix 2). With the second control group type, placebo and no antibiotic were given the same label (placebo and no antibiotic control groups combined), comprising the second network geometry (Appendix 3). With the third control group type, placebo, no antibiotic and non-absorbable antibiotic were given the same label (all control groups combined) (Appendix 4). As any of these three geometries could have been chosen for the primary analytic approach, we wanted to determine whether results could change based upon geometry.

 In addition, the following antibiotic combinations were evaluated: fluoroquinolone vs. trimethoprim-sulfamethoxazole, rifamycin and fluoroquinolone vs. fluoroquinolone, macrolide and fluoroquinolone vs. fluoroquinolone, and cephalosporin vs. fluoroquinolone. These were chosen based upon frequency of studies and clinical relevance.

 In the conventional meta-analysis, we used the following rule for trials with more than two randomized study groups to determine the intervention and control groups. Control group was chosen in the following order: (1) placebo; (2) no antibiotic; and (3) non-absorbable antibiotic. If different fluoroquinolones were examined in the same study, the fluoroquinolone with the broadest spectrum of activity was considered the intervention.

**Assessment of Study Quality**

 Risk of bias was evaluated using the Cochrane Collaboration’s tool.[9](#_ENREF_9) We described random number generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting.

**Approach to Compare Conventional and Network Meta-analysis**

 In order to compare conventional and network meta-analysis approaches, we evaluated four features. First, we determined whether the estimates from the two approaches were similar. Where they were dissimilar, we evaluated whether we could determine the reason for the disparity. Second, we searched for incoherence in the network meta-analysis as it would affect interpretation of the results. Incoherence describes the situation where the direct and indirect estimates are substantially different. In the previous example where B was better than C using indirect comparisons, if trials comparing B and C directly showed that B was worse than C, this situation would be described as incoherence. Third, we chose a comparison (namely cephalosporin vs. fluoroquinolone) in which only indirect comparisons were available to emphasize an analysis only possible with network and not conventional meta-analysis. Finally, as there were three different clinically relevant possible control groups (placebo, no antibiotic and non-absorbable antibiotic control groups separate, placebo and no antibiotic control groups combined and all control groups combined) with three distinct network geometries, we determined whether results differed based upon this decision.

**Statistical Methods**

For the conventional meta-analysis, data were synthesized using the risk ratio (RR) as the effect measure with its 95% CI. A RR < 1 indicates that the intervention is better than the control group. Treatment effects were estimated by the Mantel-Haenszel approach and weighted by the inverse variance. A random effects model was used. In the conventional meta-analysis, we incorporated two additional standard approaches. First, we only reported synthesis where there were at least two studies with outcome data available. Second, studies with no events in either group were not included in synthesis.[9](#_ENREF_9) We conducted conventional meta-analysis using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre).

The network meta-analysis model used a Bayesian approach to estimate RRs and their 95% credible regions (CR). We fitted a Bayesian random-effect hierarchical model with non-informative priors and adjusted for correlation between effects in multi-arm trials. We assumed common heterogeneity within the network. We generated posterior samples using Markov Chain Monte-Carlo simulation technique running the analysis in three parallel chains. We used 10,000 burn-in simulations to allow convergence and then a further 100,000 simulations to produce the outputs.[10](#_ENREF_10) To check for the assumption of coherence, the node-splitting approach was used.[11](#_ENREF_11) This approach assesses whether direct and indirect evidence on a specific comparison are in agreement by re-fitting the network model without nodes making the direct comparison.[12](#_ENREF_12) Wherever there were direct and indirect estimates, the node-splitting procedure calculated the two-sided P value that the indirect and direct estimates significantly differed.

This evaluation was conducted for the three different network geometries with respect to control group (three separate control groups, placebo and no antibiotic combined and all control groups combined). In addition, we showed all pairwise comparisons for the two outcomes of interest, namely bacteremia and infection-related mortality. The Bayesian network meta-analysis was conducted using R 3.5.2[13](#_ENREF_13) through the library gemtc.[14](#_ENREF_14)

**RESULTS**

As previously reported, 20,984 citations were identified by the search strategy. After review of titles and abstracts and evaluation of 194 full articles for eligibility, 113 studies were included in the systematic review. Characteristics of the studies are summarized in Appendix 5. There were 104 studies that included two randomized groups, seven studies that included three randomized groups and two studies that included four randomized groups.

 Tables 1, 2 and 3 show results of conventional and network meta-analysis. Table 1 shows the effect of antibiotic prophylaxis in which placebo, no antibiotic and non-absorbable antibiotic were kept as separate control groups. There were 15 comparisons in which conventional meta-analysis yielded no results related to the number of head-to-head studies where network meta-analysis yielded a result. Only network meta-analysis was possible for the comparison between cephalosporin vs. fluoroquinolone as there were no studies that directly compared these antibiotics.

**Table 1: Prophylaxis Comparisons with Separate Control Groups (Placebo, No Antibiotic and Non-Absorbable Antibiotic) Network Geometry**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Comparison and Outcomes** | **Number****Studies** | **Conventional****RR (95% CI)** | **Network****Total RR (95% CR)** | **Direct RR\*\* (95% CR)** | **Network****Indirect RR (95% CR)** | **P Value for Inc** |
| **Fluoroquinolone vs. Placebo, No Antibiotic or Non-absorbable Antibiotic** |  |
| **Fluoroquinolone vs. Placebo** |  |
| Bacteremia | 9 | 0.59(0.38 to 0.91) | 0.59(0.40 to 0.77) | 0.63 (0.42 to 0.91) | 0.45(0.23 to 0.83) | 0.352 |
| Infection-related mortality | 12\* | 0.68(0.42 to 1.12) | 0.71(0.40 to 1.22) | 0.91(0.50 to 1.75) | 0.26(0.06 to 0.91) | 0.072 |
| **Fluoroquinolone vs. No Antibiotic** |  |
| Bacteremia | 5 | 0.53(0.40 to 0.71) | 0.47(0.30 to 0.71) | 0.46(0.26 to 0.78) | 0.50(0.24 to 1.00) | 0.869 |
| Infection-related mortality | 4\* | 1.63(0.21 to 12.52) | 0.62(0.28 to 1.30) | 0.35(0.04 to 1.90) | 0.71(0.29 to 1.70) | 0.478 |
| **Fluoroquinolone vs. Non-Absorbable antibiotic**  |  |
| Bacteremia | 0 | NSP | 0.75 (0.24 to 2.40) |  |  |  |
| Infection-related mortality | 3 | 0.43(0.18 to 1.05) | 0.56(0.22 to 1.40) | 0.30(0.08 to 0.95) | 1.30(0.33 to 6.20) | 0.098 |
|  |  |
| **Trimethoprim-sulfamethoxazole vs. Placebo, No Antibiotic or Non-absorbable Antibiotic** |  |
| **Trimethoprim-sulfamethoxazole vs. Placebo**  |  |
| Bacteremia | 3 | 0.65(0.44 to 0.98) | 0.56(0.37 to 0.82) | 0.60(0.30 to 1.10) | 0.53(0.32 to 0.86) | 0.787 |
| Infection-related mortality | 4 | 0.55(0.21 to 1.44) | 0.43(0.20 to 0.82) | 0.28(0.07 to 0.91) | 0.51(0.21 to 1.20) | 0.418 |
| **Trimethoprim-sulfamethoxazole vs. No Antibiotic**  |  |
| Bacteremia | 4 | 0.37(0.15 to 0.88) | 0.46(0.28 to 0.73) | 0.29(0.09 to 0.80) | 0.52(0.29 to 0.88) | 0.340 |
| Infection-related mortality | 9 | 0.56(0.29 to 1.08) | 0.37(0.18 to 0.67) | 0.32(0.14 to 0.64) | 0.53(0.12 to 2.00) | 0.511 |
| **Trimethoprim-sulfamethoxazole vs. Non-absorbable Antibiotic**  |  |
| Bacteremia | 0 | NSP | 0.73(0.23 to 2.30) | 0.24(0.03 to 1.50) | 1.60(0.34 to 8.30) | 0.114 |
| Infection-related mortality | 2 | 1.01(0.15 to 6.65) | 0.33(0.12 to 0.84) | 0.69(0.19 to 2.60) | 0.15(0.03 to 0.56) | 0.101 |
|  |  |
| **Cephalosporin vs. Placebo, No Antibiotic or Non-absorbable Antibiotic** |  |
| **Cephalosporin vs. Placebo** |  |
| Bacteremia | 1 | NSP | 0.34(0.15 to 0.71) | 0.12(0.00 to 0.99) | 0.38(0.16 to 0.88) | 0.355 |
| Infection-related mortality | 1 | NSP | 0.48(0.08 to 2.20) | <0.01(<0.01 to 0.05) | 0.74(0.12 to 4.30) | 0.013 |
| **Cephalosporin vs. No Antibiotic** |  |
| Bacteremia | 3 | 0.31(0.14 to 0.66) | 0.28(0.15 to 0.50) | 0.30(0.15 to 0.55) | 0.10(0.00 to 0.79) | 0.349 |
| Infection-related mortality | 3\* | 1.33(0.30 to 5.83) | 0.41(0.08 to 1.60) | 0.57(0.11 to 2.60) | <0.01(<0.01 to 0.07)  | 0.013 |
| **Cephalosporin vs. Non-absorbable Antibiotic** |  |
| Bacteremia | 0 | NSP | 0.44 (0.11 to 1.70) |  |  |  |
| Infection-related mortality | 0 | NSP | 0.36(0.05 to 2.00) |  |  |  |
|  |  |
| **Parenteral Glycopeptide vs. Placebo, No Antibiotic or Non-absorbable Antibiotic** |  |
| **Parenteral Glycopeptide vs. Placebo** |  |
| Bacteremia | 0 | NSP | 0.81 (0.33 to 1.90) |  |  |  |
| Infection-related mortality | 0 | NSP |  2.00(0.41 to 10.00) |  |  |  |
| **Parenteral Glycopeptide vs. No Antibiotic** |  |
| Bacteremia | 3 | 0.45(0.08 to 2.66) | 0.67 (0.32 to 1.30) |  |  |  |
| Infection-related mortality | 3 | 1.13(0.30 to 4.23) | 1.70 (0.45 to 7.00) |  |  |  |
| **Parenteral Glycopeptide vs. Non-absorbable Antibiotic**  |  |
| Bacteremia | 0 | NSP | 1.10(0.25 to 4.30) |  |  |  |
| Infection-related mortality | 0 | NSP | 1.50 (0.28 to 9.30) |  |  |  |
|  |  |
| **Comparison of Different Antibiotics** |  |
| **Fluoroquinolone vs. Trimethoprim-sulfamethoxazole**  |  |
| Bacteremia | 7 | 0.86(0.48 to 1.54) | 1.03(0.77 to 1.41) | 0.91(0.63 to 1.33) | 1.33(0.77 to 2.38) | 0.237 |
| Infection-related mortality | 6 | 1.10(0.50 to 2.39) | 1.67(0.91 to 3.13) | 2.50(1.12 to 6.25) | 1.18(0.50 to 2.78) | 0.197 |
| **Rifamycin and Fluoroquinolone vs. Fluoroquinolone**  |  |
| Bacteremia | 3 | 0.36(0.17 to 0.77) | 0.28 (0.11 to 0.65) |  |  |  |
| Infection-related mortality | 3\* | NSP | 0.22 (0.01 to 2.00) |  |  |  |
| **Macrolide and Fluoroquinolone vs. Fluoroquinolone**  |  |
| Bacteremia | 1 | NSP | 0.83 (0.34 to 1.90) | 0.87(0.31 to 2.40) | 0.61(0.07 to 3.40) | 0.728 |
| Infection-related mortality | 1 | NSP | 0.46 (0.10 to 1.90) | 1.10(0.08 to 13.0) | 0.28(0.03 to 1.60) | 0.378 |
| **Cephalosporin vs. Fluoroquinolone** |  |
| Bacteremia | 0 | NSP | 0.59 (0.28 to 1.20) |  | 0.59 (0.28 to 1.20) |  |
| Infection-related mortality | 0 | NSP | 0.65 (0.11 to 3.0) |  | 0.65 (0.11 to 3.0) |  |

Abbreviations: RR - risk ratio; CI – confidence interval; CR – credible region; NSP – no synthesis possible as less than 2 studies with synthesizable data including studies with 0 events in both arms; Inc - incoherence

\* At least one study had zero events in both groups

\*\* Direct estimates are Bayesian estimates from a random effects model for the same data that are in the conventional RR column

**Table 2: Prophylaxis Comparisons with Placebo and No Antibiotic Control Groups Combined Network Geometry\*\***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Comparison and Outcomes** | **Number****Studies** | **Conventional****RR (95% CI)** | **Network****Total RR (95% CR)** | **Direct RR\*\*\*** **(95% CR)** | **Network****Indirect RR (95% CR)** | **P Value for Inc** |
| **Fluoroquinolone vs. Placebo or No Antibiotic** |  |
| Bacteremia | 14 | 0.56(0.41 to 0.76) | 0.56(0.43 to 0.71) | 0.63(0.43 to 0.83) | 0.45(0.26 to 0.77) | 0.332 |
| Infection-related mortality | 16\* | 0.72(0.45 to 1.16) | 0.91(0.56 to 1.45) | 1.10(0.63 to 2.13) | 0.50(0.20 to 1.23)  | 0.139 |
| **Trimethoprim-sulfamethoxazole vs. Placebo or No Antibiotic** |  |
| Bacteremia | 7 | 0.59(0.41 to 0.85) | 0.55(0.38 to 0.75) | 0.50(0.29 to 0.82) | 0.58(0.36 to 0.89) | 0.659 |
| Infection-related mortality | 13 | 0.61(0.39 to 0.94) | 0.44(0.26 to 0.70) | 0.32(0.15 to 0.58) | 0.78(0.33 to 1.90) | 0.091 |
| **Cephalosporin vs. Placebo or No Antibiotic** |  |
| Bacteremia | 4 | 0.30(0.16 to 0.58) | 0.29 (0.15 to 0.51) |  |  |  |
| Infection-related mortality | 4\* | 1.03(0.27 to 3.95) | 0.42 (0.09 to 1.70) |  |  |  |
| **Parenteral Glycopeptide vs. Placebo or No Antibiotic** |  |
| Bacteremia | 3 | 0.45(0.08 to 2.66) | 0.67 (0.33 to 1.30) |  |  |  |
| Infection-related mortality | 3 | 1.13(0.30 to 4.23) | 1.70(0.44 to 7.10) |  |  |  |
| **Comparison of Different Antibiotics** |  |
| **Fluoroquinolone vs. Trimethoprim-sulfamethoxazole**  |  |
| Bacteremia | 7 | 0.86(0.48 to 1.54) | 1.04(0.77 to 1.43) | 0.91(0.63 to 1.32) | 1.39(0.83 to 2.44) | 0.191 |
| Infection-related mortality | 6 | 1.10(0.50 to 2.39) | 2.00(1.19 to 3.70) | 2.50(1.12 to 6.25) | 1.69(0.83 to 3.70) | 0.489 |
| **Rifamycin and Fluoroquinolone vs. Fluoroquinolone**  |  |
| Bacteremia | 3 | 0.36(0.17 to 0.77) | 0.28 (0.11 to 0.64) |  |  |  |
| Infection-related mortality | 3\* | NSP | 0.23 (0.01 to 2.00) |  |  |  |
| **Macrolide and Fluoroquinolone vs. Fluoroquinolone**  |  |
| Bacteremia | 1 | NSP | 0.79(0.33 to 1.80) | 0.87(0.32 to 2.30) | 0.53(0.06 to 2.70) | 0.620 |
| Infection-related mortality | 1 | NSP | 0.39 (0.08 to 1.50) | 1.20(0.09 to 15.0) | 0.20(0.02 to 1.29) | 0.262 |
| **Cephalosporin vs. Fluoroquinolone** |  |
| Bacteremia | 0 | NSP | 0.51 (0.26 to 0.96) |  | 0.51 (0.26 to 0.96) |  |
| Infection-related mortality | 0 | NSP | 0.48 (0.09 to 2.10) |  | 0.48 (0.09 to 2.10) |  |

Abbreviations: RR - risk ratio; CI – confidence interval; CR – credible region; NSP – no synthesis possible as less than 2 studies with synthesizable data including studies with 0 events in both arms; Inc - incoherence

\* At least one study had zero events in both group

\*\* Non-absorbable antibiotic control group not shown as conventional meta-analysis identical to the separate control group analysis

\*\*\* Direct estimates are Bayesian estimates from a random effects model for the same data that are in the conventional RR column

**Table 3: Prophylaxis Comparisons with Placebo, No Antibiotic and Non-absorbable Antibiotic (All Control Groups Combined) Network Geometry**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Comparison and Outcomes** | **Number****Studies** | **Conventional****RR (95% CI)** | **Network****Total RR (95% CR)** | **Direct RR\*\* (95% CR)** | **Network****Indirect RR (95% CR)** | **P Value for Inc** |
| **Fluoroquinolone vs. Placebo, No Antibiotic or Non-absorbable Antibiotic**  |  |
| Bacteremia | 14 | 0.56(0.41 to 0.76) | 0.59(0.43 to 0.71) | 0.63(0.43 to 0.83) | 0.50(0.29 to 0.77) | 0.467 |
| Infection-related mortality | 19\* | 0.64(0.42 to 0.98) | 0.91(0.59 to 1.39) | 1.00(0.59 to 1.64) | 0.71(0.29 to 1.69) | 0.538 |
| **Trimethoprim-sulfamethoxazole vs. Placebo, No Antibiotic or Non-absorbable Antibiotic**  |  |
| Bacteremia | 7 | 0.59(0.41 to 0.85) | 0.55(0.39 to 0.76) | 0.48(0.27 to 0.77) | 0.62(0.39 to 0.95) | 0.424 |
| Infection-related mortality | 15 | 0.62(0.41 to 0.93) | 0.43(0.27 to 0.66) | 0.38(0.21 to 0.63) | 0.57(0.24 to 1.30) | 0.402 |
| **Cephalosporin vs. Placebo, No Antibiotic or Non-absorbable Antibiotic**  |  |
| Bacteremia | 4 | 0.30(0.16 to 0.58) | 0.29(0.15 to 0.51) |  |  |  |
| Infection-related mortality | 4\* | 1.03(0.27 to 3.95) | 0.43 (0.09, 1.60) |  |  |  |
| **Parenteral Glycopeptide vs. Placebo, No Antibiotic or Non-absorbable Antibiotic**  |  |
| Bacteremia | 3 | 0.45(0.08 to 2.66) | 0.68(0.33 to 1.30) |  |  |  |
| Infection-related mortality | 3 | 1.13(0.30 to 4.23) | 1.70(0.48 to 6.80) |  |  |  |
| **Fluoroquinolone vs. Trimethoprim-sulfamethoxazole**  |  |
| Bacteremia | 7 | 0.86(0.48 to 1.54) | 1.04(0.77 to 1.41) | 0.91(0.63 to 1.32) | 1.35(0.83 to 2.33) | 0.199 |
| Infection-related mortality | 6 | 1.10(0.50 to 2.39) | 2.08(1.25 to 3.70) | 2.44(1.12 to 5.88) | 1.82(1.00 to 4.00) | 0.594 |
| **Rifamycin and Fluoroquinolone vs. Fluoroquinolone**  |  |
| Bacteremia | 3 | 0.36(0.17 to 0.77) | 0.28 (0.11 to 0.64) |  |  |  |
| Infection-related mortality | 3\* | NSP | 0.24 (0.01 to 2.10) |  |  |  |
| **Macrolide and Fluoroquinolone vs. Fluoroquinolone** |  |
| Bacteremia | 1 | NSP | 0.78(0.33 to 1.80) | 0.87(0.33 to 2.30) | 0.50(0.06 to 2.60) | 0.579 |
| Infection-related mortality | 1 | NSP | 0.37(0.08 to 1.40) | 1.00(0.08 to 12.00) | 0.20(0.02 to 1.10) | 0.277 |
| **Cephalosporin vs. Fluoroquinolone** |  |
| Bacteremia | 0 | NSP | 0.50 (0.26 to 0.94) |  | 0.50 (0.26 to 0.94) |  |
| Infection-related mortality | 0 | NSP | 0.49 (0.09 to 1.90) |  | 0.49 (0.09 to 1.90) |  |

Abbreviations: RR - risk ratio; CI – confidence interval; CR – credible region; NSP – no synthesis possible as less than 2 studies with synthesizable data including studies with 0 events in both arms; Inc- incoherence

\* At least one study had zero events in both groups

\*\* Direct estimates are Bayesian estimates from a random effects model for the same data that are in the conventional RR column

Where both conventional and network meta-analysis was possible, estimates were generally similar. There were two comparisons in which conventional and network meta-analysis differed, both related to infection-related mortality. In the comparison between fluoroquinolone vs. no antibiotic, conventional estimate was 1.63 (95% CI 0.21 to 12.52) while network estimate was 0.62 (95% CR 0.28 to 1.30). Similarly, comparison between trimethoprim-sulfamethoxazole vs. non-absorbable antibiotic was 1.01 (95% CI 0.15 to 6.65) by conventional meta-analysis and 0.33 (95% CR 0.12 to 0.84) by network meta-analysis. In addition, precision could be different with a similar estimate. For example, trimethoprim-sulfamethoxazole vs. placebo for infection-related mortality showed relative risk (RR) 0.55, 95% confidence interval (0.21-1.44) with conventional and RR 0.43, 95% credible region (0.20-0.82) with network meta-analysis.

The network meta-analysis showed incoherence for the comparison of cephalosporin vs. placebo for the outcomes of infection-related mortality where the direct estimate was <0.01 (95% CR <0.01 to 0.05) whereas indirect estimate was 0.74 (95% CR 0.12 to 4.30). Incoherence was also observed for the comparison of cephalosporin vs. no antibiotic for the outcome of infection-related mortality where the direct estimate was 0.57 (95% CR 0.11 to 2.60) while the indirect estimate was <0.01 (95% CR <0.01 to 0.07).

 Tables 2 and 3 show the effect of antibiotic prophylaxis in which placebo and no antibiotic control groups were combined (Table 2) and where all control groups were combined (Table 3). In both of these analyses, differences between conventional and network meta-analyses were not observed. In addition, incoherence was not observed in any of these analyses.

 Appendices 6 and 7 show pairwise estimates for bacteremia and infection-related mortality where all control groups were combined. Estimates were extremely imprecise (CR crossed < 0.01 or >99) for many comparisons, particularly for infection-related mortality.

**DISCUSSION**

In this comparison of two approaches to conduct meta-analysis,we showed that in this example, conventional and network meta-analysis yielded similar results in general. However, where events were sparse, network meta-analysis could yield different results and even where estimates were similar, network meta-analysis could yield results that were more precise. Network meta-analysis also allowed estimates where only indirect comparisons were available. Differences between conventional and network meta-analysis and patterns of incoherence in network meta-analysis could differ based upon chosen network geometry.

While this research was primarily methodology-focused in terms of comparing two approaches to meta-analysis, there are potential clinical consequences of our findings. For example, in the comparison between fluoroquinolone vs. no antibiotic to reduce infection-related mortality, conventional estimate was 1.63 (95% CI 0.21 to 12.52) suggesting harm of fluoroquinolone while network estimate was 0.62 (95% CR 0.28 to 1.30) suggesting benefit of fluoroquinolone. This difference may be related to the number of studies with no events in both groups. These studies were excluded in conventional meta-analysis, thus emphasizing studies with any events. Interestingly, when evaluating the geometry in which placebo and no antibiotic control groups were combined, the conventional estimate for infection-related mortality was 0.72 (95% CI 0.45 to 1.16) compared to the network estimate of 0.91 (95% CR 0.56 to 1.45). This suggests that when incorporating indirect estimates and more appropriate handling of zero events, fluoroquinolone does not reduce infection-related mortality. This also emphasizes the potential for bias if network geometry is not specified *a priori.*

We evaluated three different geometries that could have been chosen as the primary analytic approach. Distinguishing two or more control groups allows that they could have different efficacy compared to each other, while not distinguishing them assumes that in a head-to-head comparison, the RR would be 1.This has important consequences in the case that, for example, we have a study of treatment A vs. placebo and a study of treatment B vs no antibiotic. Maintaining separate control groups, these two studies have no information about A vs B, but when control groups are not distinguished, we have an indirect estimate of A vs. B (Appendix 1).

 Put together, these results yielded insights into how network meta-analysis could be used in future meta-analysis. Major advantages include the ability to provide results, both when no or few head-to-head comparisons exists and when events are sparse. However, network meta-analysis requires more complex modelling and the need to evaluate incoherence. Interestingly, dissimilarities between conventional and network approaches as well as incoherence differed based upon network geometry, thus stressing the importance of network geometry choice. This is important as incoherence threatens the validity of network meta-analysis. This finding also suggests that geometry choice should be made based upon clinical rationale prior to seeing results to avoid selectively choosing models with more favorable properties.

 A strength of this study is direct applicability of this comparison of two approaches of meta-analysis that could influence how others interpret network meta-analysis and the decision of whether to undertake one in future research. However, our analysis must be interpreted in light of its limitations. We restricted the analysis to two outcomes for illustrative purposes, and purposely included an outcome with small numbers of events, which placed limits on the precision of estimates from meta-analysis no matter how it was carried out. Different patterns could have emerged if we had compared other outcomes included in the conventional meta-analysis. Second, comparisons cover both a technical and a statistical framework in that the conventional meta-analysis used a frequentist statistics approach, while the network meta-analysis used Bayesian methods. In fact, the biggest advantage of network meta-analysis in our example was the inclusion of multiple studies with zero events in both arms. A Bayesian approach in a conventional meta-analysis also could have addressed this issue. Third, the effect of antibacterial prophylaxis may be different in cancer and HSCT populations although we previously failed to demonstrate that population type significantly explained heterogeneity in prophylaxis effects.[5](#_ENREF_5)

 In conclusion, in this example, conventional and network meta-analysis yielded similar results in general. Where events were sparse, network meta-analysis results could be more precise. Some analysis could only be performed with the network approach. Findings of incoherence differed based upon geometry and thus, choice of geometry can influence validity of a network meta-analysis. These results identify scenarios in which network meta-analysis may be advantageous.

**DECLARATIONS**

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**Competing interests**

JPDM, PDR, BP, CK, GE, LLD, RAA, SA, SC, GT and LS declare no potential conflicts of interest

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**Authors’ contributions**

JPM, PDR, GT and LS conceptualized the study, designed the study, analyzed the network meta-analysis and wrote the manuscript; GE and PDR collected the data and conducted the conventional meta-analysis. All authors critically revised the manuscript for important content. All authors approve the final version of the manuscript.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

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