Comparing antibiotic treatment for leptospirosis using network meta-analysis: a tutorial

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Abstract

Background: Network meta-analysis consists of simultaneous analysis of both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials based on a common comparator. In this paper, we aimed to characterise the conceptual understanding and the rationale for the use of network meta-analysis in assessing drug efficacy.

Methods: We selected randomized controlled trials, assessing efficacy of antibiotics for the treatment of leptospirosis as a case study. A pairwise meta-analysis was conducted using a random effect model, assuming that different studies assessed different but related treatment effects. The analysis was then extended to a network meta-analysis, which consists of direct and indirect evidence in a network of antibiotics trials, using a suite of multivariate meta-analysis routines of STATA (mvmeta command). We also assessed an assumption of ‘consistency’ that estimates of treatment effects from direct and indirect evidence are in agreement.

Results: Seven randomised controlled trials were identified for this analysis. These RCTs assessed the efficacy of antibiotics such as penicillin, doxycycline and cephalosporin for the treatment of human leptospirosis. These studies made comparisons between antibiotics (i.e. an antibiotic versus alternative antibiotic) in the primary study and a placebo, except for cephalosporin. These studies were sufficient to allow the creation of a network for the network meta-analysis; a closed loop in which three comparator antibiotics were connected to each other through a polygon. The comparison of penicillin versus the placebo has the largest contribution to the entire network (31.8%). The assessment of rank probabilities indicated that penicillin presented the greatest likelihood of improving efficacy among the evaluated antibiotics for treating leptospirosis.

Conclusions: Findings suggest that network meta-analysis, a meta-analysis comparing multiple treatments, is feasible and should be considered as better precision of effect estimates for decisions when several antibiotic options are available for the treatment of leptospirosis.

Background

Systematic reviews use explicit, pre-specified methods to identify, appraise and synthesize all available evidence related to a (clinical) question of research interest. If appropriate, systematic reviews may include a quantitative data synthesis (i.e. meta-analysis), which is the statistical combination of results from ≥ 2 individual studies [1]. However, systematic reviews conventionally compare only 2 interventions, despite having the existence of more than two interventions for a disease of interest. For instance, a randomised controlled trial (RCT) on antibiotics for treating leptospirosis included three arms [2]. As such, a conventional pairwise meta-analysis may be conducted, but the comparative effectiveness of all available interventions for a given condition will not be addressed [3]. Individual pair-wise comparisons, which in isolation fall short of informing clinical decisions when there are a greater number of treatment options available [4]. A network meta-analysis (NMA), also known as mixed treatment comparison or multiple treatment comparison, is a method for simultaneous comparison of multiple treatments in a
single meta-analysis [3]. It expands the scope of a traditional (conventional) pairwise meta-analysis by analysing simultaneously both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator [5–7]. The multivariate approach, therefore, allows one to ‘borrow strength’ across correlated outcomes, to potentially reduce the impact of outcome reporting bias [8].

Leptospirosis is a zoonosis caused by infection with pathogenic Leptospira species that has a global distribution with a significant health impact, particularly in resource-poor tropical countries [9]. The clinical course in humans ranges from mild to lethal with a broad spectrum of symptoms and clinical signs [10]. A recent systematic review estimated that there are 1.03 (95% CI 0.43–1.75) million cases of leptospirosis worldwide each year and 58,900 deaths (95% CI 23,800–95,900) [11, 12], which corresponds to an estimated 2.9 million disability-adjusted life years per annum, including 2.8 million years of life lost due to premature death [9]. Thus far, the optimal treatment of leptospirosis remains a subject of debate, mainly due to the wide and biphasic clinical spectrum of the disease and the distinct pathogenesis in these two phases [13, 14].

Taken together, the objective of this study was to characterise the conceptual understanding and the rationale for the use of NMA in assessing drug efficacy. As such, we used results from RCTs of antibiotics for the treatment of leptospirosis as a case study.

Methods
Searching studies
First, we searched for RCTs evaluating the efficacy of antibiotics for the treatment of patients with leptospirosis in electronic databases (Medline, EMBASE) up to June 2016. We used a search strategy with terms relevant to leptospirosis, RCTs and antibiotics individually and in combination (Additional file 1: Table S1). We also searched the relevant studies in the Cochrane Central Register of Controlled Trials (CENTRAL) and EBSCO CINAHL. Two investigators within the reviewing team independently screened the title and abstract retrieved from the searches. Individual studies were selected based on the following predetermined criteria in PICOSS, described elsewhere [1, 15]: Population (P): those patients diagnosed with leptospirosis; Interventions (I): antibiotics; Comparisons (C): an antibiotic versus alternative antibiotic or placebo; Outcomes (O): mortality; and Study design (S): RCTs. We defined mortality as death of a patient at any follow-up time point given in the primary study, after administration of a selected treatment option. This primary outcome was chosen because it is the most important estimate of treatment efficacy.

For each identified study that met the selection criteria we extracted data on study design, study population characteristics and interventions (type of antibiotics, dosage, route of administration, day of treatment initiation and follow-up duration). We rated the methodological quality of each included RCT, using a risk of bias (RoB) tool recommended by the Cochrane Collaboration for assessment criteria. The RoB tool is a domain-based assessment to detect random sequence generation, allocation concealment, blinding in the studies (patients, assessors and physicians), incomplete outcome data, selective outcome reporting, and evidence of major baseline imbalance [15].

Assessing the feasibility of a network meta-analysis
We assessed whether an NMA would provide a method to indirectly compare an antibiotic in terms of the specified outcomes for patients diagnosed with leptospirosis. The placebo-controlled clinical trial has a long history of being the standard for clinical investigations of new drugs [16]. Published RCTs that assessed the efficacy of antibiotics for the treatment of human leptospirosis included penicillin, doxycycline and cephalosporin. These studies made comparisons between antibiotics (i.e. an antibiotic vs alternative antibiotic) in the primary study and a placebo, except for cephalosporin. This exception might be due to the ethical issues associated with withholding treatment for a fatal illness or possibly due to the lack of sponsorship by industry. In the absence of trials involving a direct comparison of interventions, an indirect comparison can provide valuable evidence for the relative treatment effects between competing interventions [17, 18]. If we want to make best use of the evidence, it is necessary to analyse all the evidence jointly [19]. In order to do a network plot, we used the STATA command (network map) [20, 21].

Statistical analysis
The number of deaths and corresponding total number of participants in each treatment arm were extracted from the included studies and used to calculate the outcome measure of treatment efficacy as an odds ratio (OR) and corresponding 95% confidence interval (CI). A pairwise meta-analysis was conducted by synthesising studies that compared the same interventions with a random effect model, assuming that different studies assessed different but related treatment effects. Between-study heterogeneity was assessed with $I^2$ statistics ($I^2 > 50\%$ was considered to show substantial heterogeneity) [15]. The analysis was then extended to an NMA, which consists of direct and indirect evidence in a network of antibiotics trials, using a suite of multivariate meta-analysis routines of STATA (mvmeta command) to evaluate the assumptions in the studies and provide graphical presentation of results [20, 21]. In the suite, the assumption of ‘consistency’ and ‘inconsistency’ in NMA was assessed using a data augmentation approach.
The assumption of ‘consistency’ implies that estimates of treatment effects from direct and indirect evidence are in agreement [19], where as evidence ‘inconsistency’ is the discrepancy between direct and indirect comparisons [17]. Our null hypothesis was that there was consistency between the direct and indirect evidence [19] and we would reject the null hypothesis if there was a statistically significant difference between the direct and indirect evidence comparison ($p < 0.05$).

The comparative efficacy of four antibiotics included in this review was assessed using penicillin as the reference treatment because it is the first choice antibiotic for treating leptospirosis. The probability that each antibiotic is the best among the given treatments was determined by evaluating the rank probabilities and surface under the cumulative ranking curve (SUCRA) for the efficacy results of the NMA [20, 21]. A higher probability of achieving rank 1 indicates a higher probability that treated patients will experience a greater improvement in terms of mortality outcome (i.e. more likely to survive).

The heterogeneity of the indirect comparison was assessed using $\tau^2$, which examines heterogeneity because of study and study drug interaction (smaller values indicate a better model). For each outcome, one common heterogeneity parameter, $\tau^2$, which is the estimated standard deviation of underlying effects across studies [15] was assumed across comparisons, which corresponded to the variance of the underlying distribution. A $\tau^2$ value $\geq 1$ is considered to indicate relatively high intra-study variability [17]. All analyses were conducted using Stata 14.0 (Stata Corp, Tex).

**Results**

**Feasibility of a network meta-analysis**

Figure 1 shows the study selection process for the systematic review of antibiotic treatment of leptospirosis. We found four RCTs compared penicillin to a placebo [22–25], two RCTs comparing penicillin to a cephalosporin [2, 26], one RCT comparing doxycycline and a placebo [27], and further RCT comparing penicillin to doxycycline [2]. These seven RCTs [2, 22–27] were sufficient to allow the creation of a network for the NMA. Figure 2 shows a closed loop in which three comparator antibiotics were connected to each other through a polygon. Treatments penicillin, doxycycline, and cephalosporin (ceftiraxone or cefotaxime) were compared against each other in these trials and thus each comparison in the closed loop is informed by both direct and indirect evidence in the present leptospirosis network.

The network map shows all the available comparisons in the network using weighted nodes and the RoB level (for blinding in this case) for each comparison using colored edges. Each line joining two treatments represents a direct head-to-head comparison, providing efficacy in terms of mortality outcome. The size of the nodes is proportional to the number of studies evaluating each intervention and the thickness of the edges is proportional to the precision of each direct comparison.

**Systematic review results**

The characteristics of the seven trials included in this analysis are presented in Additional file 2. RCTs identified for the current network were generally single centre, open label trials evaluating the efficacy of antibiotics in treating patients diagnosed with leptospirosis. With regard to the methodological quality of RCTs in this analysis, only one trial [26] had low RoB with regards the adequacy of blinding (Table 1).

In the direct comparison using a pairwise meta-analysis, showed that there were comparable efficacies of antibiotics for the treatment of leptospirosis based on the mortality outcome. With regard to head-to-head comparison, four studies [22–25] provided data on mortality in the penicillin group (17/202, 84.16%) and the placebo group (11/207, 53%); a pooled analysis showed a comparable efficacy on mortality outcome between penicillin and placebo (OR: 1.65, 95% CI: 0.76-3.52, $I^2$:11.2%). Two studies [2, 26] reported data on mortality in the cephalosporin group (9/173, 52%) and the penicillin group (6/175, 34.3%) and a pooled analysis showed a comparable efficacy on mortality outcome between these two drugs (OR: 1.55, 95% CI: 0.54-4.48, $I^2$:17%). One each study compared penicillin and doxycycline (4/87 vs 2/81, OR: 1.9, 95% CI: 0.34-10.69) [2], doxycycline and cephalosporin (2/81 vs 1/88, OR: 2.2, 95% CI: 0.34-10.69) [26] or doxycycline and placebo (0/14 vs 0/15) [27], showing no differences in mortality outcome among the drugs of interest (Fig. 3). Overall, the absence of heterogeneity reflects the small number of included studies for pairwise comparison.

**The leptospirosis network**

The input data for the current NMA is shown in Table 2. Figure 4 shows the contribution of each direct comparison in the network estimates. The comparison of penicillin versus the placebo (A vs B) has the largest contribution to the entire network (31.8%).

A multivariate meta-analysis showed that there was no evidence of inconsistency ($\text{Chi}^2$: 1.11; $\text{Prob} > \text{Chi}^2$: 0.29). $\tau^2$ values also showed an ‘agreement’ between the direct and indirect evidence (0.0031). The predictive interval plot (Fig. 5) indicates that for these comparisons (penicillin vs placebo, cephalosporin vs placebo) are wide enough compared with the CIs; this suggests that in a future study the active treatment can appear more effective than placebo.

The assessment of rank probabilities using SUCRA plots indicated that penicillin presented the greatest likelihood
of improving efficacy, among the evaluated antibiotics for treating leptospirosis (Fig. 6).

**Discussion**

Meta-analyses comparing multiple treatments are feasible and should be considered as the bedrock for decisions when several treatments are available [2, 4]. NMA in its standard form makes an assumption of ‘consistency’ [19] that estimates of treatment effects from direct and indirect evidence are in agreement [17, 19]. The current NMA could hold the key assumption of consistency.

The results of this NMA showed that it is possible to assess the efficacy of cephalosporin compared to a placebo even though this direct comparison was not
performed in any of the included trials. Our results predicted that a cephalosporin antibiotic would have comparable efficacy to penicillin in reducing mortality in human leptospirosis. Indications for the use of cephalosporin antibiotics for the treatment of leptospirosis are included in the WHO guideline for management of leptospirosis [28] as well as some national guidelines for management of leptospirosis in some countries such as Malaysia, as an example [29].

A Cochrane review on seven RCTs [30] as well as a non-Cochrane review on ten RCTs [31] performed pairwise analyses of the efficacy of antibiotics for the treatment of human leptospirosis. Both reviews reported comparable efficacy of antibiotics in preventing mortality as an outcome as well as an effect on the duration of illness. The Cochrane systematic review concluded that there were insufficient evidence to advocate for or against the use of antibiotics for the treatment of treating leptospirosis [30] and the review by Charan and associates [31] showed that there was no significant difference between mortality in groups given penicillin compared to control groups.

The WHO treatment guidelines still recommend administration of antibiotics for leptospirosis regardless of the stage or severity of the disease [28]. The optimal treatment of leptospirosis remains a major clinical dilemma, for which limited data from clinical studies exist [14]. Penicillin G sodium (penicillin G) is generally recommended as the first choice treatment for severe leptospirosis. It is important to evaluate alternatives to penicillin G because its use has potential drawbacks. Antibiotic resistance has compromised the efficacy of

| Study, year [ref] | Random sequences generation | Allocation concealment | Blinding of outcome assessment |
|-------------------|-----------------------------|-----------------------|-------------------------------|
| Suputtamongkol, 2004 [2] | low risk | low risk | high risk |
| Edwards, 1988 [22] | low risk | unclear | unclear |
| Watt, 1988 [23] | high risk | high risk | high risk |
| Dahler, 2000 [24] | high risk | high risk | high risk |
| Costa, 2003 [25] | unclear | unclear | unclear risk |
| Panaphut, 2003 [26] | low risk | low risk | low risk |
| McClain, 1984 [27] | low risk | low risk | unclear |

Fig. 3 Forest plot showing the efficacy of antibiotics for the treatment of leptospirosis in a pairwise meta-analysis
penicillin G against many important bacterial pathogens, and it is intrinsically inactive against coinfecting Rickettsiosis that are common in tropical areas such as Thailand [26]. In addition, Jarisch-Herxheimer Reaction (JHR) is a known complication associated with the use of penicillin G for the treatment of leptospirosis [32, 33]. Therefore, penicillin G administration might pose a great burden in critically ill patients [33]. Of note is that the small number of included studies and these being not recent is a reflection of the limited scientific interest in performing clinical trials in this field. There may be a number of reasons for this. For instance, the lack of a widely available, sensitive and rapid method of laboratory confirmation of leptospirosis has been an important impediment [2] and this compromises the recruitment of patients for the clinical trials. Moreover, there may be a concern whether the clinical manifestation of leptospirosis would become worse after the initiation of antibiotic therapy due to the development of JHR. A systematic review of 27 studies in JHR had reported the development of JHR in 92 of 976 leptospirosis patients within 1 to 48 h after administration of the first dose of antibiotic [32]. It is also noted that a higher proportion of JHR occurred in early stage leptospirosis, suggesting a higher probability of the (adverse) event before the natural clearance of spirochetes [32].

Other classes of antibiotic may provide better alternatives to penicillin G. Doxycycline has the advantage that it can be administered orally but it is not suitable in pregnant women. Like penicillin, most cephalosporin act on the

Table 2 The matrix of source data used in a network meta-analysis of antibiotic treatment of leptospirosis

| Study, year [ref]   | dA | nA | dB | nB | dC | nC | dD | nD |
|---------------------|----|----|----|----|----|----|----|----|
| Suputtamongkol, 2004 [2] | 4  | 87 | 2  | 81 | 1  | 88 |
| Edwards, 1988 [22]   | 1  | 38 | 3  | 41 |
| Watt, 1988 [23]      | 05 | 23 | 0  | 19 |
| Daher, 2000 [24]     | 1  | 16 | 0  | 19 |
| Costa, 2003 [25]     | 15 | 125| 8  | 128|
| Panaphut, 2003 [26]  | 5  | 86 | 5  | 87 |
| McClain, 1984 [27]   | 0  | 15 | 0  | 14 |

\(d\) number of deaths, \(n\) total number of patients with leptospirosis, \(A\) penicillin, \(B\) placebo, \(C\) doxycycline, \(D\) cephalosporin

![Controlled comparisons in the network](image)
bacterial cell wall synthesis, with some exceptions that act on protein synthesis [34]. Ceftriaxone can be administered once daily, which is an advantage over another third generation cephalosporin such as cefotaxime [2] and no dosage adjustment was required for renal failure. In addition, there is no reported evidence of JHR in patients with leptospirosis. Moreover, ceftriaxone can give extra benefit of being an excellent empirical therapy for other infections (e.g. *Streptococcus pneumonia*) which mimic the clinical presentation of leptospirosis [14].

This is the first time that an indirect evaluation of the efficacy of an antibiotic treatment for leptospirosis using NMA has been performed. This is an important additional work because the evaluation of antibiotic treatments for leptospirosis using double-blind RCTs is complicated by ethical considerations associated with the provision of a

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**Fig. 5** Predictive intervals plot for the antibiotic network from seven randomised controlled trials of the treatment of leptospirosis

**Fig. 6** Plots of the surface under the cumulative ranking curves for all treatments in leptospirosis
placebo to severely affected patients [26]. Therefore, study designs that permit the use of indirect analyses of efficacy such as the NMA would allow an assessment of cephalosporin (ceftriaxone in this case) compared to a placebo control.

The indirect comparisons in the current review revealed that the antibiotics did not differ from each other with regards to their ability to reduce mortality, supporting the findings of earlier reviews [30, 31]. However, the NMA provided slightly different results compared to the more simplistic direct comparison using conventional pairwise meta-analysis efficacy estimates. This shows the potential advantage of NMA because it can incorporate both direct and indirect comparisons, decreasing the risk for possible sponsorship bias [35], which often is an issue for drug trials.

There are some limitations that needed to acknowledge. We did not find evidence of inconsistency in the results from our indirect comparison analysis. However, these findings should be interpreted with caution as only a small number of trials could be identified for inclusion in the current analysis. Nevertheless, our findings agree with the earlier reviews, indicating no significant difference between the antibiotics for mortality as an end point. The current network meta-analysis could hold the key assumption of consistency. The indirect comparisons presented in this study add to the current body of evidence in literature.

Conclusions
Findings suggest that network meta-analysis, a meta-analysis comparing multiple treatments, is feasible and should be considered as better precision of effect estimates for decisions when several antibiotic options are available for the treatment of leptospirosis.

Additional files

Additional file 1: Table S1. Citations and Ovid MEDLINE (R) <1946 to Present>. (DOC 47 kb)
Additional file 2: Table Characteristics of the clinical trials included in meta-analysis. (DOC 39 kb)

Abbreviations
CENTRAL: Cochrane Central Register of Controlled Trials; JHR: Jarisch-Henoch reaction; NMA: Network meta-analysis; RCT: Randomized controlled trial; Rob: Risk of bias; SUCRA: Surface under the cumulative ranking curve

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Availability of data and materials
The data supporting the findings can be found in the main paper and an additional supporting file.

Authors’ contributions
CN conceptualized, participated in its design, carried out the statistical analysis and wrote the first draft and revised the manuscript. SR conceptualized, participated in its design, analysis, writing and revising the manuscript. KA participated in data extraction, interpretation and revising. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The need for approval was waived as this study solely used published human data.

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