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The effects of adding quinolones to beta-lactam antibiotics for sepsis.

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Abstract

Background
Sepsis is common, deadly, and a major challenge to treat. Quinolones added to beta-lactam antibiotics are currently recommended as a second-line empiric regimen in sepsis, but the evidence regarding their benefits and harms is unclear.

Objective
To assess the benefits and harms of adding quinolones to standard care for sepsis.

Data sources
We conducted a systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis. We searched CENTRAL, MEDLINE, Embase, LILACS, SCI-Expanded, and BIOSIS.

Study selection
Randomized clinical trials assessing the effects of adding any quinolone to standard care for children and adults with sepsis.

Data extraction and synthesis
Two independent reviewers screened studies and extracted data. The certainty of the evidence was assessed by GRADE.

Results
We included three trials randomizing 995 adults. All trials were at overall ‘high risk of bias’. All trials compared a quinolone (moxifloxacin, levofloxacin, or ciprofloxacin) and a beta-
lactam antibiotic versus the same beta-lactam antibiotic. We found no evidence of an effect
of adding quinolones to beta-lactam antibiotics when assessing all-cause mortality (RR 1.07,
95% CI 0.86 to 1.33; 2 trials; 915 participants; very low certainty of evidence) and serious
adverse events (RR 1.00, 95% CI 0.67 to 1.50; 977 participants; 2 trials; very low certainty of
evidence). No trials reported on quality of life.

Conclusions

The effects of adding quinolones to beta-lactam antibiotics for the treatment of sepsis were
unclear for all outcomes. Additional trial data are warranted to support the recommendation
of empirical use of quinolones for sepsis.

Keywords

Sepsis, adults, quinolones, septic shock, systematic review, Trial Sequential Analysis.

Editorial Comment

Early and aggressive antibiotic treatment for sepsis patients is generally accepted as an
important aspect of therapy. Until relevant microbiological data is available for individual
sepsis patients, an empirical broad-spectrum antibiotic treatment program must be
chosen. This systematic review and meta-analysis assesses the current evidence concerning
this antibiotic combination for initial sepsis therapy.

Background

Sepsis is a common and deadly condition that comprises a major challenge to health care
systems globally. Quinolones are often used empirically in combination with beta-lactam
antibiotics in patients with sepsis (1,2). The combination broadens the coverage towards the
possible pathogen (1,3,4). Several prospective cohort studies show that timely and adequate
antibiotic coverage improves clinical outcomes such as mortality (5–9). Antibiotic
combination therapy may on the other hand also enhance drug toxicity (10,11). A Cochrane
systematic review from 2014, including 46 trials (5269 participants), showed that the addition
of aminoglycosides to beta-lactam antibiotics lead to an increased nephrotoxicity, without
any beneficial effect on mortality or other important outcomes (10). Also, antibiotic
combination versus mono-therapy was not observed to benefit adults with sepsis (12). We
planned to investigate whether adding quinolones to the empirical antibiotic regimen for
sepsis improve clinical outcomes. Appropriate use of antibiotics in patients with sepsis is also
important to minimize the increasing antibiotic resistance seen worldwide (8). No prior systematic review of randomized clinical trials with meta-analysis has assessed the benefits and harms of quinolones in patients with sepsis.

**Methods**

We conducted this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) (13) and the Cochrane Handbook for Systematic Reviews of Interventions (14). Our predefined methodology is described in detail in our published protocol (15).

**Eligibility criteria**

We searched for trials assessing the effects of adding any quinolone to standard care in children and adults suspected of or having sepsis. We would include trials adding quinolones to any other antibiotic regimen such as a beta-lactam antibiotic, an aminoglycoside or a glycopeptide (15).

**Search and study selection**

We searched for eligible trials published before December 2020 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded on Web of Science, BIOSIS, Google Scholar, clinicaltrials.gov, Trip Medical Database (TRIP), EU Clinical Trial Register (EUCTR), and WHO International Clinical Trials Registry Platform (ICTRP). The search strategy can be found in (Supplementary material). Additionally, we checked the reference lists of relevant publications for any unidentified trials. Trials were included irrespective of trial design, setting, publication status, year or language, and the reporting of one of our outcomes.

Two authors (SKK and MM) independently selected relevant trials, extracted data using a standardized data extraction sheet, and systematically assessed risks of bias (11–13). We contacted trial authors if relevant data were unclear or missing. A detailed description of the data collection process is found in our protocol (15).
Risk of bias assessment

We assessed risk of bias according to the Cochrane Handbook 5.1 and our protocol evaluating the following domains: generation of allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, for-profit bias, and other bias sources (15,16).

Outcomes and subgroup analyses

Our primary outcomes were all-cause mortality, serious adverse events, and quality of life. Our secondary outcomes were treatment failure (defined as recurrence or worsening of clinical signs leading to any modification of the assigned empirical antibiotic treatment) and non-serious adverse events (12). Our exploratory outcomes were individual serious adverse events, individual adverse events considered not to be serious, and persistent blood cultures (as defined by trialists).

We calculated risk ratios (RRs) with 95% confidence interval (CI) and trial sequential analysis-adjusted CI for dichotomous outcomes. We planned to calculate the mean differences (MDs) and the standardized mean difference (SMD) with 95% CI and trial sequential analysis-adjusted CI for continuous outcomes (15). For all outcomes, we used the trial results reported at maximal follow-up. In our protocol published before the literature search began, we planned the following subgroup analyses: risk of bias (low/high risk), age (infants, children, adolescents, adults, and elderly), type of standard care (e.g. beta-lactam antibiotics, aminoglycosides, glycosides), country, focus of infection (e.g. urinary system, lungs, skin, blood, nervous system, unknown and mixed), and type of quinolones (e.g. ciprofloxacin, garenoxacin, gatifloxacin, grepafloxacin, sparflloxacin, levofloxacin and moxifloxacin) (see ‘Results’) (15).

Data synthesis

We performed our meta-analyses according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions (14), Keus et al. (17), and the eight-step assessment suggested by Jakobsen et al. (18) for better validation of meta-analytic results in systematic reviews. Review Manager 5.4.1 was used for all meta-analyses (19). We used risk ratios (RR) for dichotomous outcomes. We performed both random-effects (Der Simonian-Laird model) (20) and fixed-effect (Mantel-Haenszel model) (21) meta-analyses and chose
the most conservative result as our primary result (15,18). The alternative method (less conservative) is presented under (Supplementary material). We used Trial Sequential Analysis (TSA) to control for random errors and reported TSA-adjusted CI if the cumulative Z-curves did not reach the futility area, crossed the boundaries of benefit and harm, or passed the diversity-adjusted required information size (DARIS) (18,22–29). We assessed three primary outcomes and, hence, considered a P-value of 0.025 as threshold for statistical significance for the primary outcomes (15,18). For all the remaining outcomes, we considered a P-value of 0.05 as threshold for statistical significance, as we considered these outcomes hypothesis generating only. The assumptions for our TSA were an alpha of 2.5% or 5%, a beta of 10%, a relative risk reduction of 20%, and the observed proportion in the control group and the observed diversity (15). We used ‘best-worst case’ and ‘worst-best case’ analyses to assess the potential impact of missing data (15). We calculated the Bayes factor to show if the meta-analysis results fitted better with the null hypothesis or the anticipated intervention effects (15). We used the GRADE approach to appraise the certainty of the evidence, taking into consideration study limitations, consistency of effect, imprecision, indirectness and publication bias (14,30,31–35).

Results

Included trials

The literature search identified a total of 7373 potential studies. A total of 5452 studies were excluded based on the title or abstract, and nine were excluded based on the full publication due to wrong comparisons (36–40), participants not having sepsis (41), or not reporting randomized clinical trials (42–44). In total, three trials randomizing a total of 995 participants met the inclusion criteria and were included.

See ‘PRISMA flowchart (figure 1)’ for details regarding the literature search and the selection of trials.

All three trials were at overall high risk of bias (see figure 2) and all were multicenter trials (conducted in Finland (45), Germany (46), and the US (47)). The randomized participants were all hospitalized adults diagnosed with sepsis with a mix of different infection foci. The
mean age of the participant was similar in the three trials (64.6 years (SD±14.5), 58 years (SD±19), and 57 years (SD±19), respectively. All three trials assessed quinolones as an add on therapy to beta-lactam antibiotics. The quinolones included moxifloxacin (added to meropenem) (47), levofloxacin (added to penicillin/standard therapy) (45), and ciprofloxacin (added to a beta lactam /standard therapy) (46). The two latter trials administered different antibiotic regimens as their standard therapy. The duration of the antibiotic treatment lasted from 4.5 to 86 days. See Table 1 for characteristics of included trials. The diversity-adjusted required information size (DARIS) and GRADE assessment are shown in Table 2 (Summary of findings table).

**Effects of interventions**

**Primary outcomes**

**All-cause mortality**

Two trials randomizing 915 participants reported on all-cause mortality; 122/463 (26%) participants allocated to quinolone died as compared with 111/452 (24.6%) allocated to control. Meta-analysis showed no evidence of a difference on all-cause mortality (RR 1.07, 95% CI 0.86 to 1.33; P = 0.52; I² = 0%; 915 participants; 2 trials; very low certainty of evidence; Figure 3). Visual inspection of the forest plot and tests for statistical heterogeneity (I² = 0%; P = 0.62) showed no clear signs of heterogeneity. TSA showed that we did not have sufficient information to reject or detect that adding quinolones to beta-lactam antibiotics reduced the risk ratio of death by 20% and that the accrued information was compatible with either a reduced risk of death by 36% or an increased risk of death by 81% (TSA-adjusted CI 0.64 to 1.81) (Figure 4). Bayes factor (11.9) was above the Bayes factor threshold for significance of 0.1. Hence, the Bayes factor result confirmed the meta-analysis result of no evidence of a difference. We assessed this result to be at ‘high risk of bias.’

**Sensitivity and subgroup analyses**

We did not perform sensitivity analyses or subgroup analyses as planned due to lack of relevant data.
Serious adverse events

Two trials randomizing 977 participants reported on serious adverse events; 43/494 (9%) of participants allocated to quinolone had a serious adverse event as compared with 42/483 (8.7%) allocated to control. Meta-analysis showed no evidence of a difference on serious adverse events (RR 1.00, 95% CI 0.67 to 1.50; P = 0.98; I² = 0%; 977 participants; 2 trials; very low certainty of evidence; Figure 5).

Visual inspection of the forest plot and tests for statistical heterogeneity (I² = 0%; P = 0.75) showed no clear signs of heterogeneity. TSA showed that we did not have sufficient data to reject or detect that adding quinolones to beta-lactam antibiotics reduce the relative risk of having one or more serious adverse event by 20% and that the accrued information was compatible with either a decrease of serious adverse events by 81% or an increase of serious adverse events by 418% (TSA-adjusted CI 0.19 to 5.18) (Figure 6). Bayes factor (1.8) was above the Bayes factor threshold for significance of 0.1. Hence, the Bayes factor result confirmed the meta-analysis result of no evidence of a difference. We assessed the risk of bias of this result at high risk of bias.

Sensitivity and subgroup analyses

We did not perform sensitivity analyses or subgroup analyses as planned due to lack of relevant data.

Quality of life

No trials reported quality of life.

Secondary outcomes

Treatment failure

Two trials randomizing 424 participants reported on treatment failure; 105/209 (50.2%) of participants allocated to quinolone had treatment failure as compared with 108/215 (50.2%) control participants. Meta-analysis showed no evidence of a difference on treatment failure (RR 0.98, 95% CI 0.81 to 1.18; P = 0.82; I² = 0%; 424 participants; 2 trials; very low certainty of evidence; Figure 5).
certainty of evidence; Figure 7). Visual inspection of the forest plot and tests for statistical heterogeneity ($I^2 = 0 \% ; P = 0.59$) showed no clear signs of heterogeneity. TSA showed that we did not have sufficient data to reject or detect that adding quinolones to beta-lactam antibiotics reduce the relative risk of having treatment failure by 20% and that the accrued information was compatible with either a decrease of treatment failure by 29% or an increase of treatment failure by 34% (TSA-adjusted CI 0.71 to 1.34) (Figure 8).

Non-serious adverse events

One trial reported on adverse events. Therefore, no meta-analysis was performed. 85/303 (28.1%) quinolone participants had a non-serious adverse event compared with 71/293 (24.2%) control participants. The trial found no evidence of an effect of adding moxifloxacin to meropenem when assessing adverse events.

Exploratory outcomes

We planned to assess individual serious adverse events and individual adverse event (considered not serious). As trials did not report individual adverse events, neither of these two exploratory outcomes were possible to assess.

Persistent positive blood cultures

Only one trial reported persistent positive blood cultures. Therefore, no meta-analysis was performed. 19/201 (9.5%) quinolone participants had persistent positive blood cultures compared with 21/203 (10.3%) control.

Discussion

We included three trials randomizing a total of 995 adults with sepsis. The types of quinolones were moxifloxacin (47), ciprofloxacin (46), and levofloxacin (45) and they were all combined with a beta-lactam antibiotic. Control interventions were beta-lactam antibiotics in all trials. Meta-analyses and TSAs showed that we did not have sufficient information to reject or detect that adding quinolones to beta-lactam antibiotics reduced the risk of death, serious adverse events, or treatment failure. No trials reported on quality of life. Only one trial assessed non-serious adverse events and persistent blood cultures. Therefore, we were unable to perform meta-analyses of these outcomes.
Our review has several strengths. First, our methodology is described in detail in a protocol that was published before the literature search was initiated (15). Second, we did not observe any clear signs of statistical heterogeneity which indicates that it was valid to perform meta-analysis. Third, we systematically assessed the risks of systematic errors via bias risk assessments. Fourth, we conducted TSAs and adjusted our thresholds for statistical significance to control the risks of random errors (18).

Our review also has some limitations. We were only able to include three trials with a total of 995 participants assessing the effects of different quinolones and did not reach a sufficient information size to conclude whether quinolones impose a beneficial or harmful effect when added to standard care or another antibiotic regimen. The trials were conducted in Europe and the US; other results may have been obtained in areas where there are different patterns of antimicrobial resistance. Moreover, all trials were at high risk of bias. Extensive meta-epidemiological studies have repeatably shown that high risks of bias trials tend to overestimate benefits and underestimate harms of experimental interventions (48–50).

The latest updated version of the Surviving Sepsis Campaign guidelines recommend quinolones (fluoroquinolones) as a possible addition to a beta-lactam antibiotic for combination therapy, when treating sepsis empirically (1). This recommendation is supported by a meta-analysis/meta-regression analysis and a propensity-matched analysis showing improved survival with combination therapy (1,51,52). A previous systematic review found no evidence of this benefit, when assessing the addition of quinolones and aminoglycosides to beta-lactam antibiotics for sepsis caused by Pseudomonas aeruginosa (53). As they only assessed Pseudomonas aeruginosa infections, they did not include all the trials included in this review.

Conclusions

The effects of adding quinolones to beta-lactam antibiotics for the treatment of sepsis were unclear for all outcomes due to insufficient information. As for all empirical use of antibiotic, the choice of specific agents may be informed by local patterns of sensitivity among target microbes. Additional data from randomized trials are warranted to support the recommendation of adding quinolones for the empirical treatment of sepsis.

Availability of data and materials
All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The datasets used are based on publicly available data from the published included studies.

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

Funding
None of the authors received any specific funding related to the review.

Authors' contributions
Dr. Korang: Drafted the protocol, extracted data, co-ordinated the review, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological and clinical view, and revised the review.

Dr. Maagaard: Revised the protocol, extracted data, analyzed the data, interpreted the data, commented on, and revised the review.

Dr. Feinberg and Prof. Perner: Revised the protocol, analyzed the data, interpreted the data, commented on and revised the review.

Prof. Gluud: Revised the protocol, analyzed the data, interpreted the data providing a methodological view, commented on and revised the review.

Prof. Jakobsen: Drafted the protocol, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological view, and revised the review.
Acknowledgement

The review author team would like to acknowledge the information specialist Sarah Klingenberg (from the Cochrane Hepato-Biliary Group) for the development of our search strategy and searches.

Legends

**Figure 1:** PRISMA flowchart.

**Figure 2:** Risk of bias assessment.

**Figure 3:** Forest plot of all-cause mortality

**Figure 4:** TSA all-cause mortality

**Figure 5:** Forest plot of serious adverse events.

**Figure 6:** TSA serious adverse events.

**Figure 7:** Forest plot of treatment failure.

**Figure 8:** TSA treatment failure.

**Table 1:** Characteristics of included trials.

**Table 2:** Summary of findings table.

**Supplementary Material**

- Search Strategies
- Alternative meta-analyses (less conservative)
References


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440 Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol. 2011
443 versus a tobramycin/cefuroxime combination in the treatment of serious systemic infections: a 
444 prospective, randomized and controlled study of efficacy and safety. Scand J Infect Dis.
447 empirical treatment of patients with suspected bacteraemia/sepsis: comparison with 
449 810.
451 of ciprofloxacin and ceftazidime on cytokine production in patients with severe sepsis caused by 
454 Randomized trial of combination versus monotherapy for the empiric treatment of suspected 
457 clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment 
459 41. Burki TK. β-lactam monotherapy is non-inferior to combination treatment for community-acquired 
461 42. Bliziotis IA, Petrosillo N, Michalopoulos A, Samonis G, Falagas ME. Impact of definitive therapy 
462 with beta-lactam monotherapy or combination with an aminoglycoside or a quinolone for 
464 43. Kolditz M, Halank M, Höffken G. Monotherapy versus combination therapy in patients 
468 D:115–21.
decrease mortality in Staphylococcus aureus bacteraemia when added to the standard
Feb; 259(2):179–90.

mono- or combination-therapy in the treatment of severe infections: ciprofloxacin versus standard

treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction

methodological quality associated with estimates of treatment effects in controlled trials. JAMA.


treatment effect estimates in controlled trials with different interventions and outcomes: meta-

475 51. Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic
therapy for serious infections associated with sepsis and septic shock is contingent only on the risk

therapy yields improved survival compared with monotherapy in septic shock: a propensity-

477 53. Vardakas KZ, Tansarli GS, Bliziotis IA, Falagas ME. β-Lactam plus aminoglycoside or
fluoroquinolone combination versus β-lactam monotherapy for Pseudomonas aeruginosa
<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of quinolone/Beta-lactam</th>
<th>Focus of infection</th>
<th>Septic shock</th>
<th>Country (income)</th>
<th>Setting (center)</th>
<th>Age group</th>
<th>Duration in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krumpe 1999</td>
<td>Ciprofloxacin / standard therapy (aztreonam, ceftazidime, ticarcillin/clavulanate, or piperacillin)</td>
<td>Bacteraemia</td>
<td>No</td>
<td>USA (high income)</td>
<td>Hospital (41)</td>
<td>Adults</td>
<td>Control: 9.8-17.1 Intervention: 4.5-16.5</td>
</tr>
<tr>
<td>Ruotsalainen 2006</td>
<td>Levofloxacin / standard therapy (penicillin, cloxacillin or dicloxacillin)</td>
<td>Bacteraemia</td>
<td>No</td>
<td>Finland (high income)</td>
<td>Hospital (12)</td>
<td>Adults</td>
<td>Control: 42-84 (IQR) Intervention: 45–85 (IQR)</td>
</tr>
<tr>
<td>Brunkhorst 2012</td>
<td>Moxifloxacin / Meropenem</td>
<td>mixed</td>
<td>No</td>
<td>Germany (high income)</td>
<td>ICU (44)</td>
<td>Adults</td>
<td>Control: 8 (median) Intervention: 7 (median)</td>
</tr>
</tbody>
</table>
Table 2: Summary of findings table.

Quinolones plus beta-lactam antibiotic compared with beta-lactam antibiotic for sepsis

Patient or population: Adults with sepsis

Settings: Hospital

Intervention: Quinolones + beta-lactam antibiotic

Comparison: Beta-lactam antibiotic

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality maximum follow-up</td>
<td>Study population</td>
<td>RR 1.07, (95% CI 0.86 to 1.33)</td>
<td>915 (2)</td>
<td>⊕⊝⊝⊝</td>
<td>Very low</td>
</tr>
<tr>
<td>Serious</td>
<td>Study population</td>
<td>RR 1.00</td>
<td>977</td>
<td>⊕⊕⊕⊕</td>
<td></td>
</tr>
</tbody>
</table>

*Illustrative comparative risks are calculated as the number of events in the control divided by the number of events in the quinolones group.
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Study Population</th>
<th>RR</th>
<th>95% CI</th>
<th>424</th>
<th>Very Low</th>
<th>Downgraded one level due to serious risk of bias and two levels for imprecision due to small information size (two levels).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.67 to 1.50)</td>
<td></td>
<td></td>
<td>DARIS: 11834 (RRR 20; alpha 2.5%; beta 10%; Pc 8.7% diversity 0.0%)</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td></td>
<td>RR 0.98</td>
<td>(0.81 to 1.18)</td>
<td>424</td>
<td>Very Low</td>
<td>Downgraded one level due to serious risk of bias, one level for imprecision due to small information size, and one level for indirectness due to different ways of measuring treatment failure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DARIS: 1033 (RRR 20; alpha 5%; beta 10%; Pc 50.2% diversity 0.0%)</td>
</tr>
</tbody>
</table>
The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk Ratio **DARIS:** diversity-adjusted required information size

---

**GRADE Working Group grades of evidence**

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.
Figure 1: PRISMA flowchart

7373 studies identified through database searching

5464 records after duplicates removed

5464 studies screened

5452 records excluded based on title and abstract

12 full-text articles assessed for eligibility

9 full-text articles excluded based on full text

3 studies included in qualitative synthesis

3 studies included in quantitative synthesis (meta-analysis)
Figure 2: Risk of bias assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>For-profit bias</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunner et al. 2012</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Krumpe 1999</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Ruotsalainen 2006</td>
<td>?</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>
Figure 3: Forest plot of all-cause mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Quinolones</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunkehorst 2012</td>
<td>96</td>
<td>272</td>
<td>1.10 [0.87, 1.40]</td>
</tr>
<tr>
<td>Rautala et al. 2006</td>
<td>26</td>
<td>191</td>
<td>0.96 [0.68, 1.38]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>462</strong></td>
<td><strong>452</strong></td>
<td><strong>1.07 [0.86, 1.33]</strong></td>
</tr>
</tbody>
</table>

Total events: 111
Heterogeneity: Tau² = 0.00, Chi² = 1, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.32)
Figure 4: Trial Sequential Analysis of quinolones versus placebo or no intervention on all-cause mortality

DARIS: Pc 24.6%; RRR 20%; alpha 2.5%; beta 10%; div 0.0% is a Two-sided graph

Author Manuscript
**Figure 5: Forest plot of serious adverse events**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Quinolones</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunnhorst 2012</td>
<td>17</td>
<td>303</td>
<td>1.10 [0.56; 2.15]</td>
</tr>
<tr>
<td>Ruottalainen 2006</td>
<td>26</td>
<td>191</td>
<td>0.98 [0.56; 1.50]</td>
</tr>
</tbody>
</table>

Total (95% CI) 494 483 100.0% 1.00 [0.87; 1.50]

Heterogeneity: \( \tau^2 = 0.008 \), \( \chi^2 = 1, \text{df} = 1 \) (\( \rho = 0.75 \)), \( I^2 = 0 \%

Test for overall effect: \( z = 0.02 \) (\( \rho = 0.98 \))

![Forest plot image]
Figure 6: Trial Sequential Analysis of quinolones versus placebo or no intervention on serious adverse events
Figure 7: Forest plot of treatment failure
Figure 8: Trial Sequential Analysis of quinolones versus placebo or no intervention on treatment failure

DARIS: Pe 50.2%; RRR 20%; alpha 5%; beta 10%; div 0.0% is a Two-sided graph