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APPENDIX 1

Search Terms and Protocol

There were no restrictions on the basis of date or language of publication for the following searches:

PUBMED on 29 March 2018 was searched using the following keywords, MeSH headings, MeSH terms, and filters:

#1 ('surgical antimicrobial prophylaxis orthopedic' OR (surgical AND ('antimicrobial'/exp OR antimicrobial) AND ('prophylaxis'/exp OR prophylaxis) AND orthopedic))
- MeSH subheading: prevention and control
- MeSH terms: orthopedics; orthopaedics; surgical procedures operative; anti infective agents; anti infective; operative surgical procedures; antimicrobial; control; procedures; surgical; prevention, operative; prevention and control
- Filter: Clinical Trials + Meta-Analysis + Randomized Controlled Trial + Systematic Reviews

#2 ('surgical antimicrobial prophylaxis orthopaedic' OR (surgical AND ('antimicrobial'/exp OR antimicrobial) AND ('prophylaxis'/exp OR prophylaxis) AND orthopaedic))
- MeSH subheading: prevention and control
- MeSH terms: orthopedics; orthopaedics; surgical procedures operative; anti infective agents; anti infective; operative surgical procedures; antimicrobial; control; procedures; surgical; prevention, operative; prevention and control
- Filter: Clinical Trials + Meta-Analysis + Randomized Controlled Trial + Systematic Reviews

Ovid MEDLINE 1946 to March WEEK 4 2018 on 29 March 2018 was searched using the following keywords and filters:

#3 Surgical antimicrobial prophylaxis orthopedics OR (prophylaxis AND orthopedics) OR (antimicrobial AND orthopedics)
- Filter: Basic Search; Relevancy (4 or more stars); Years (All years)

#4 Surgical antimicrobial prophylaxis orthopedics OR (prophylaxis AND orthopedics) OR (antimicrobial AND orthopedics)
- Filter: Basic Search; Relevancy (4 or more stars); Years (All years)

Ovid EMBASE on 29 March 2018 was searched using the following keywords and filters:

#5 ('surgical antimicrobial prophylaxis orthopedic' OR (surgical AND ('antimicrobial'/exp OR antimicrobial) AND ('prophylaxis'/exp OR prophylaxis) AND orthopedic)) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)

#6 ('surgical antimicrobial prophylaxis orthopaedic' OR (surgical AND ('antimicrobial'/exp OR antimicrobial) AND ('prophylaxis'/exp OR prophylaxis) AND orthopaedic)) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)

The Cochrane Collaboration's tool for assessing risk of bias for RCTs[21]

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		

Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.	

Risk of bias assessment (cohort-type studies)

More recent versions of this tool appear under the name 'Risk of Bias In Non-randomized Studies of Interventions' (ROBINS-I) tool [Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.], available from http://www.riskofbias.info.

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Y / PY / PN / N	[Description]
	If N or PN to 1.1:		
	1.2. Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding	NA / Y / PY / PN / N / NI	[Description]
	1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer questions 1.7 and 1.8, which relate to time-varying confounding	NA / Y / PY / PN / N / NI	[Description]
	If Y or PY to 1.2, or Y or PY to 1.3		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	NA / Y / PY / PN / N / NI	[Description]

	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI	[Description]
	1.6. Did the authors avoid adjusting for post-intervention variables?	NA / Y / PY / PN / N / NI	[Description]
	If N or PN to 1.2 and 1.3		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding?	NA / Y / PY / PN / N / NI	[Description]
	1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to confounding?	Favours experimental / Favours comparator / Unpredictable	[Rationale]
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	Y / PY / PN / N / NI	[Description]
	2.2. Do start of follow-up and start of intervention coincide for most subjects?	Y / PY / PN / N / NI	[Description]
	2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable	[Rationale]
Bias in measurement of interventions	3.1 Is intervention status well defined?	Y / PY / PN / N / NI	[Description]
	3.2 Was information on intervention status recorded at the time of intervention?	Y / PY / PN / N / NI	[Description]
	3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]

	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours experimental / Favours comparator / Towards null /Away from null/Unpredictable	[Rationale]
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups?	Y / PY / PN / N / NI	[Description]
	4.2. Were numbers of switches to other interventions low?	Y / PY / PN / N / NI	[Description]
	4.3. Was implementation failure minor?	Y / PY / PN / N / NI	[Description]
	4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these issues?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to departures from the intended interventions?	Favours experimental / Favours comparator / Towards null /Away from null/Unpredictable	[Rationale]
Bias due to missing data	5.1 Are outcome data reasonably complete?	Y / PY / PN / N / NI	[Description]
	5.2 Was intervention status reasonably complete for those in whom it was sought?	Y / PY / PN / N / NI	[Description]
	5.3 Are data reasonably complete for other variables in the analysis?	Y / PY / PN / N / NI	[Description]
	5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA / Y / PY / PN / N / NI	[Description]
	5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low /Moderate/Serious/ Critical /NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to missing data?	Favours experimental / Favours comparator / Towards null /Away from null/Unpredictable	[Rationale]
Bias in measurement of outcomes	6.1 Was the outcome measure objective?	Y / PY / PN / N / NI	[Description]
	6.2 Were outcome assessors unaware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y / PY / PN / N / NI	[Description]
	6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	Y / PY / PN / N / NI	[Description]

	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Favours experimental / Favours comparator / Towards null /Away from null/Unpredictable	[Rationale]
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain?	Y / PY / PN / N / NI	[Description]
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Y / PY / PN / N / NI	[Description]
	7.3 ... different *subgroups*?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null /Away from null/Unpredictable	[Rationale]
Overall bias	**Risk of bias judgement**	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the overall predicted direction of bias for this outcome?	Favours experimental / Favours comparator / Towards null /Away from null/Unpredictable	[Rationale]

Risk of bias assessment (case-control studies).

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Y / PY / PN / N	[Description]
	If N or PN to 1.1:		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	NA / Y / PY / PN / N / NI	[Description]
	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI	[Description]
	1.6. Did the authors avoid adjusting for post-intervention variables?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to confounding?	Favours experimental / Favours comparator / Unpredictable	[Rationale]
Bias in selection of participants into the study	2.4 Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable	[Rationale]
Bias in measurement of interventions	3.1 Is intervention status well defined? 3.2 Was information on intervention status recorded at the time of intervention? 3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome? **Risk of bias judgement**	Y / PY / PN / N / NI Y / PY / PN / N / NI Y / PY / PN / N / NI Low / Moderate / Serious / Critical / NI	[Description] [Description] [Description] [Support for judgement]

	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours experimental / Favours comparator / Towards null /Away from null /Unpredictable	[Rationale]
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups? 4.2. Were numbers of switches to other interventions low? 4.3. Was implementation failure minor? **Risk of bias judgement** Optional: What is the predicted direction of bias due to departures from the intended interventions?	Y / PY / PN / N / NI Y / PY / PN / N / NI Y / PY / PN / N / NI Low /Moderate /Serious / Critical /NI Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Description] [Description] [Description] [Support for judgement] [Rationale]
Bias due to missing data	5.1 Was outcome status reasonably complete for those in whom it was sought? 5.2 Were data on intervention status reasonably complete? 5.3 Are data reasonably complete for other variables in the analysis? 5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across cases and controls? 5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data? **Risk of bias judgement** Optional: What is the predicted direction of bias due to missing data?	Y / PY / PN / N / NI Y / PY / PN / N / NI Y / PY / PN / N / NI NA / Y / PY / PN / N / NI NA / Y / PY / PN / N / NI Low /Moderate /Serious / Critical /NI Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Description] [Description] [Description] [Description] [Description] [Support for judgement] [Rationale]
Bias in measurement of outcomes	6.1 Was the definition of case status (and control status, if applicable) based on objective criteria? 6.2 Was the definition of case status (and control status, if applicable) applied without knowledge of the intervention received? **Risk of bias judgement**	Y / PY / PN / N / NI Y / PY / PN / N / NI Low /Moderate /Serious / Critical /NI	[Description] [Description] [Support for judgement]

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	Optional: What is the predicted direction of bias due to definitions of case and control status?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		
	7.1. ... multiple *definitions of the intervention*?	Y / PY / PN / N / NI Y / PY	[Description]
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	/ PN / N / NI Y / PY / PN / N	[Description]
	7.3 ... different *subgroups*?	/ NI	[Description]
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	[Support for judgement]
	Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	[Rationale]
Overall bias	**Risk of bias judgement**	Low / Moderate / Serious / Critical / NI	[Support for judgement] [Rationale]
	Optional: What is the overall predicted direction of bias?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	