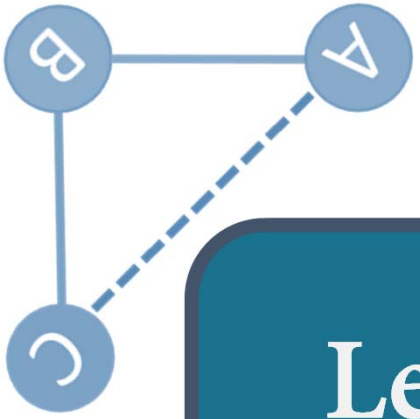

Learning from Systematic Review and Network meta-analysis (NMA)

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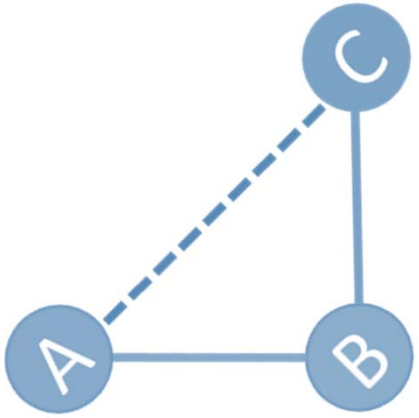
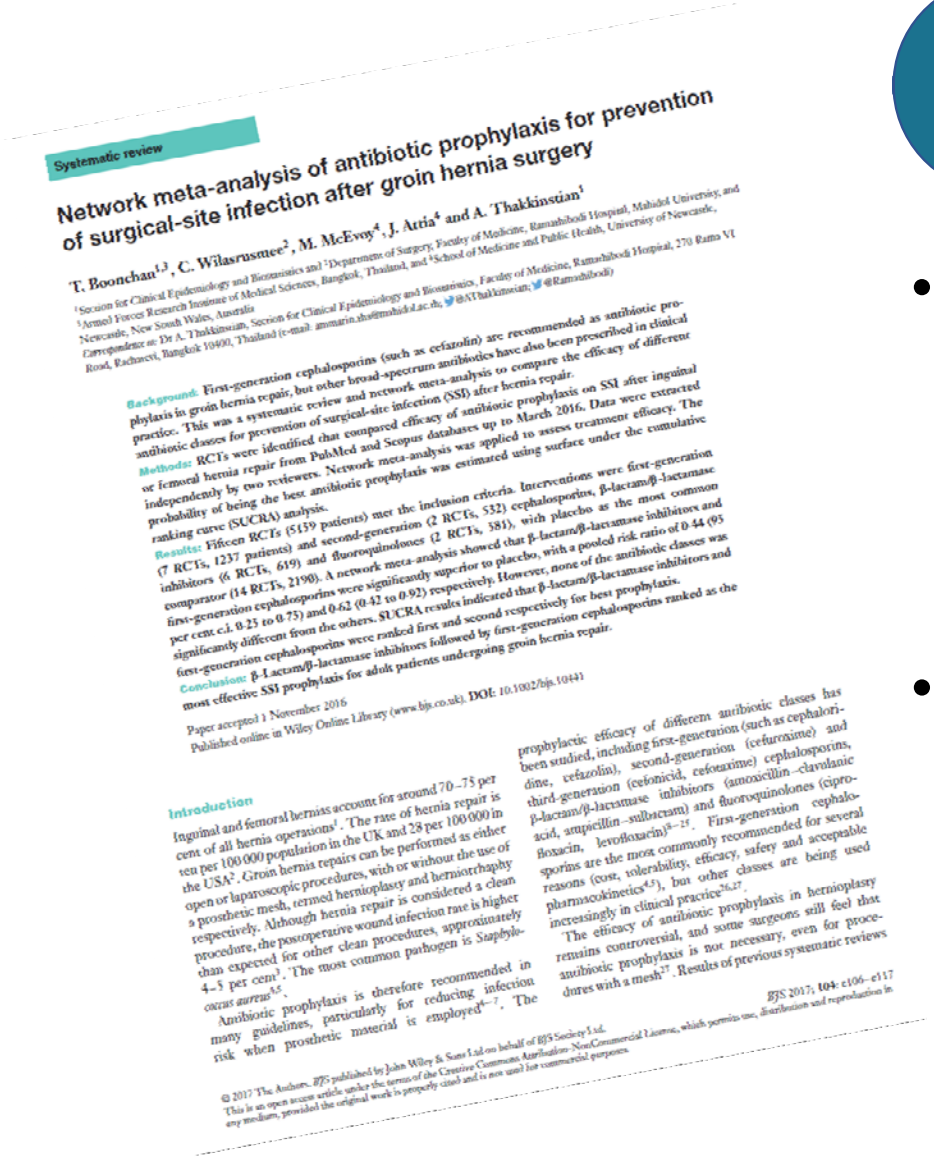
Ramathibodi International Academic Conference (RIAC) 2018
4 September, 2018
At Marriott Marquis Bangkok Queen's Park





Systematic review

Network meta-analysis of antibiotic prophylaxis for prevention of surgical-site infection after groin hernia surgery

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Background: First-generation cephalosporins (such as cefazolin) are recommended as antibiotic prophylaxis in groin hernia repair, but other broad-spectrum antibiotics have also been prescribed in clinical practice. This was a systematic review and network meta-analysis to compare the efficacy of different antibiotic classes for prevention of surgical-site infection (SSI) after hernia repair.

Methods: RCTs were identified that compared efficacy of antibiotic prophylaxis on SSI after inguinal or femoral hernia repair from PubMed and Scopus databases up to March 2016. Data were extracted independently by two reviewers. Network meta-analysis was applied to assess treatment efficacy. The probability of being the best antibiotic prophylaxis was estimated using surface under the cumulative ranking curve (SUCRA) analysis.

Results: Fifteen RCTs (5139 patients) met the inclusion criteria. Interventions were first-generation (7 RCTs, 1237 patients) and second-generation (2 RCTs, 532) cephalosporins, β-lactam/β-lactamase inhibitors (6 RCTs, 619) and fluoroquinolones (2 RCTs, 581), with placebo as the most common comparator (14 RCTs, 2190). A network meta-analysis showed that β-lactam/β-lactamase inhibitors and first-generation cephalosporins were significantly superior to placebo, with a pooled risk ratio of 0·44 (95 per cent c.i. 0·25 to 0·75) and 0·62 (0·42 to 0·92) respectively. However, none of the antibiotic classes was significantly different from the others. SUCRA results indicated that β-lactam/β-lactamase inhibitors and first-generation cephalosporins were ranked first and second respectively for best prophylaxis.

Conclusion: β-Lactam/β-lactamase inhibitors followed by first-generation cephalosporins ranked as the most effective SSI prophylaxis for adult patients undergoing groin hernia repair.

Paper accepted 1 November 2016

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.10443

Introduction

Inguinal and femoral hernias account for around 70–75 per cent of all hernia operations[1]. The rate of hernia repair is ten per 100 000 population in the UK and 28 per 100 000 in the USA[2]. Groin hernia repairs can be performed as either open or laparoscopic procedures, with or without the use of a prosthetic mesh, termed herniaplasty and herniorrhaphy respectively. Although hernia repair is considered a clean procedure, the postoperative wound infection rate is higher than expected for other clean procedures, approximately 4–5 per cent[3]. The most common pathogen is *Staphylococcus aureus*[4,5].

Antibiotic prophylaxis is therefore recommended in many guidelines, particularly for reducing infection risk when prosthetic material is employed[6–7]. The prophylactic efficacy of different antibiotic classes has been studied, including first-generation (such as cephalordine, cefazolin), second-generation (cefuroxime) and third-generation (cefonicid, ceftriaxime) cephalosporins, β-lactam/β-lactamase inhibitors (amoxicillin–clavulanic acid, ampicillin–sulbactam) and fluoroquinolones (ciprofloxacin, levofloxacin)[8–25]. First-generation cephalosporins are the most commonly recommended for several reasons (cost, tolerability, efficacy, safety and acceptable pharmacokinetics[4,5]), but other classes are being used increasingly in clinical practice[26,27].

The efficacy of antibiotic prophylaxis in herniaplasty remains controversial, and some surgeons still feel that antibiotic prophylaxis is not necessary, even for procedures with a mesh[27]. Results of previous systematic reviews

BJS 2017; **104**: e106–e117

Our NMA

- **Network meta-analysis of antibiotic prophylaxis for prevention of surgical-site infection after groin hernia surgery. BJS 2017;104(2):e106-e17.**

- **CRD42015025398**

Evidence Appraisal Score: I B

A score of I B:

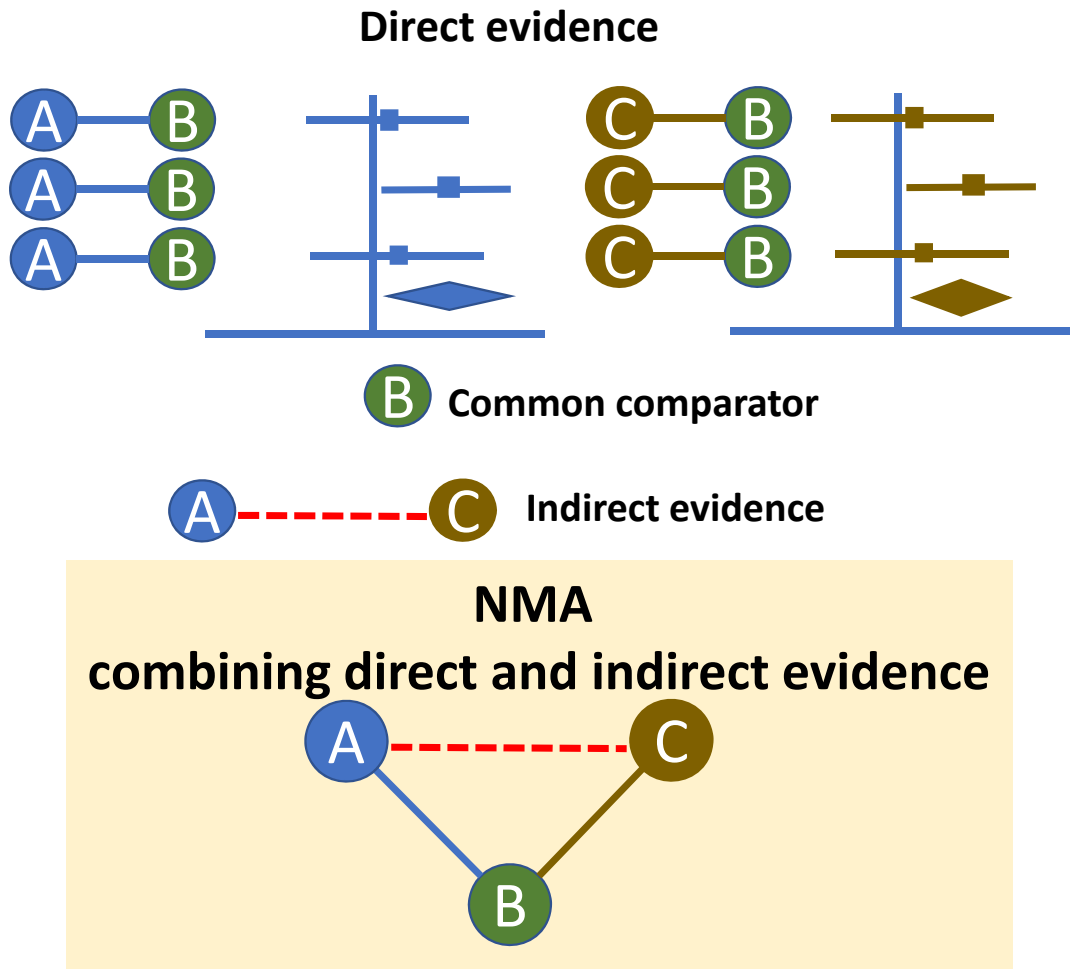
The results of this meta-analysis are appropriate for perioperative nurses to use in guiding their practice.

https://aornjournal.onlinelibrary.wiley.com/doi/epdf/10.1002/aorn.12011

Why NMA?

NMA

- To make treatment estimates for an entire treatment **network** instead of scanning each individual pair-wise comparison
- To give the "**full picture**" to clinicians
- **Gain precision by considering all available evidence**, not just A vs. B or B vs C comparisons.
- Potential to more explicitly **"rank"** treatments using summary outputs



Why NMA?

PRISMA Extension for NMA# 3 Rationale

"Mention of why a network meta-analysis has been conducted"

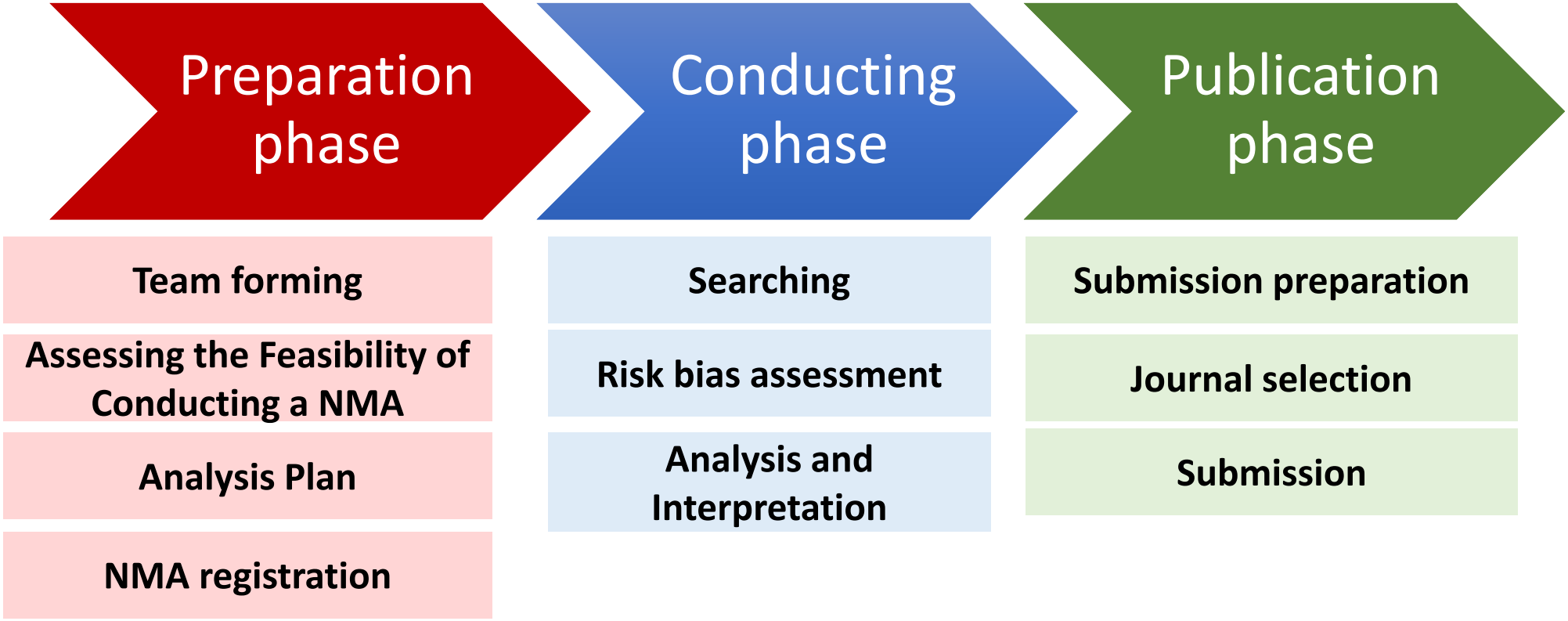
First-generation cephalosporins (Cefazolin) are the most commonly recommended

But higher generation of antibiotics are being used increasingly in clinical practice.

No direct evidences of RCTs that compared between different antibiotics.

Conventional meta-analyses was unable to answer which antibiotic class is the best.

Learning from NMA



Team forming

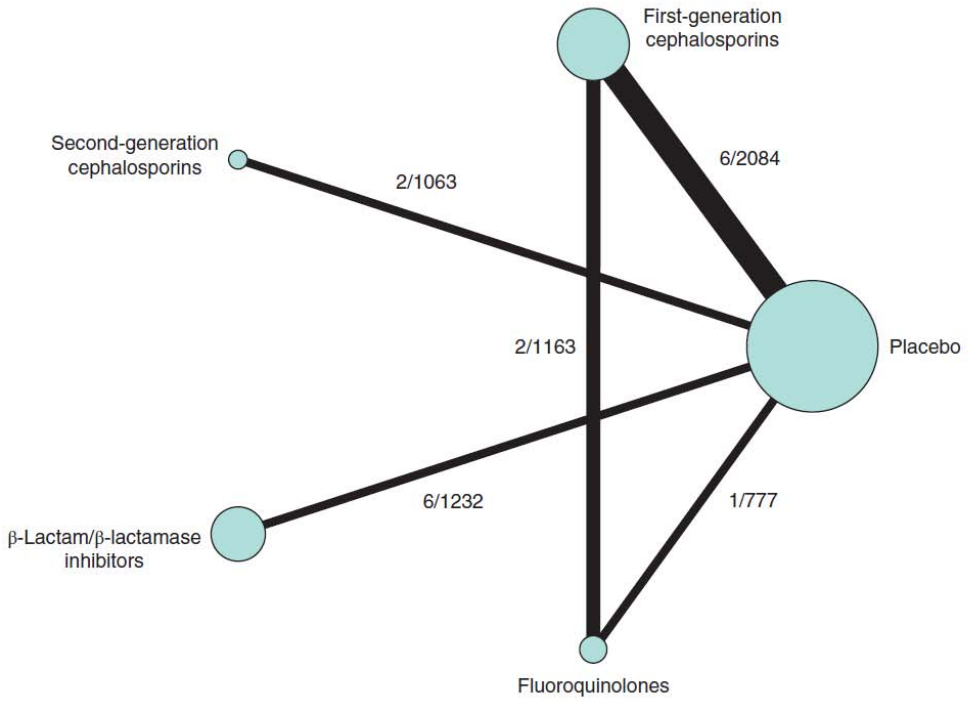
- ☑ Both experts in clinical therapeutic and statistic fields
- ☑ Risk bias assessment/data extraction should be performed independently by 2 individuals who expertise the clinical therapeutic
- ☑ To make unbiased consensus by the third party, the third party should be blinded from the differences results assessed by the 2 individuals.
- ☑ Clearly discuss role and responsibilities
- ☑ Clearly discuss timeline

Assessing the Feasibility of Conducting a NMA

Should be performed

- to determine whether the **NMA is feasible.**

- to **identify the clinical and statistical assumptions required** **to conduct the NMA.**



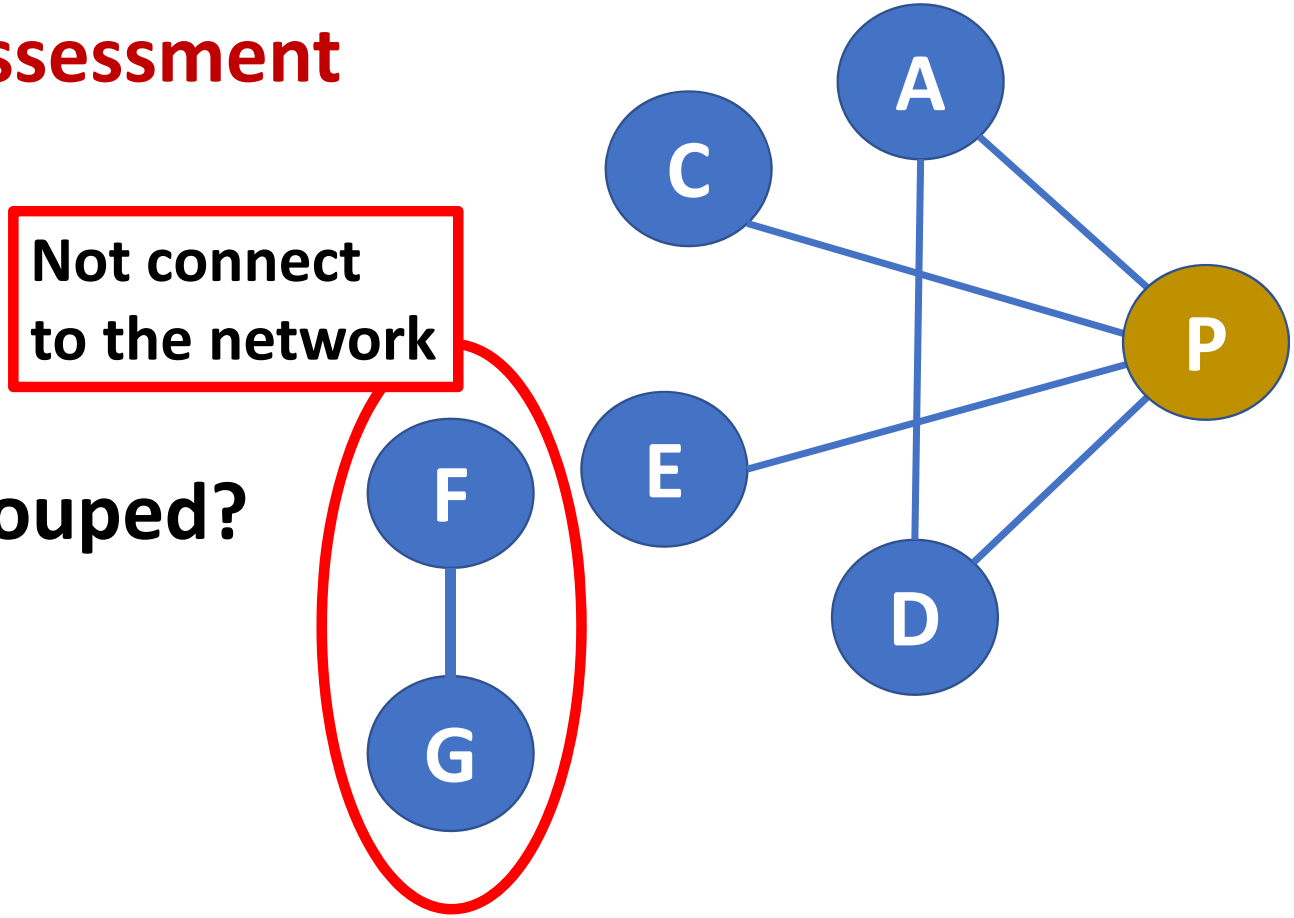
Assessing the Feasibility of Conducting a NMA

Key

- A connected network
- The RCT are suitable for comparison : Homogeneous to facilitate reliable comparison
- Report data on common outcome
- Interested outcome was available in each RCT
- Sufficient data for comparison

Assessing the Feasibility of Conducting a NMA

A connected network assessment



Resolution plan

Can the antibiotic be grouped?

Grouped by ATB classes

Assessing the Feasibility of Conducting a NMA

Key of NMA: the studies do not differ in any characteristics that may influence the size of prophylaxis effect.

Similarity of the studies assessment: 4 elements

- ☑ Quality of methods employed to conducting RCT
  Risk/Bias Assessment and Sensitivities analysis
- ☑ Confounding factors in relation to participant population
  Get clinical input to determine inclusion/exclusion, data extraction
- ☑ Similarity of prophylaxis (common reference and intervention)
  Frequency, dose
- ☑ Similarity of outcomes and outcome measures

Assessing the Feasibility of Conducting a NMA

Key of NMA: **Useable data for the interested outcome**

Data required for binary outcomes

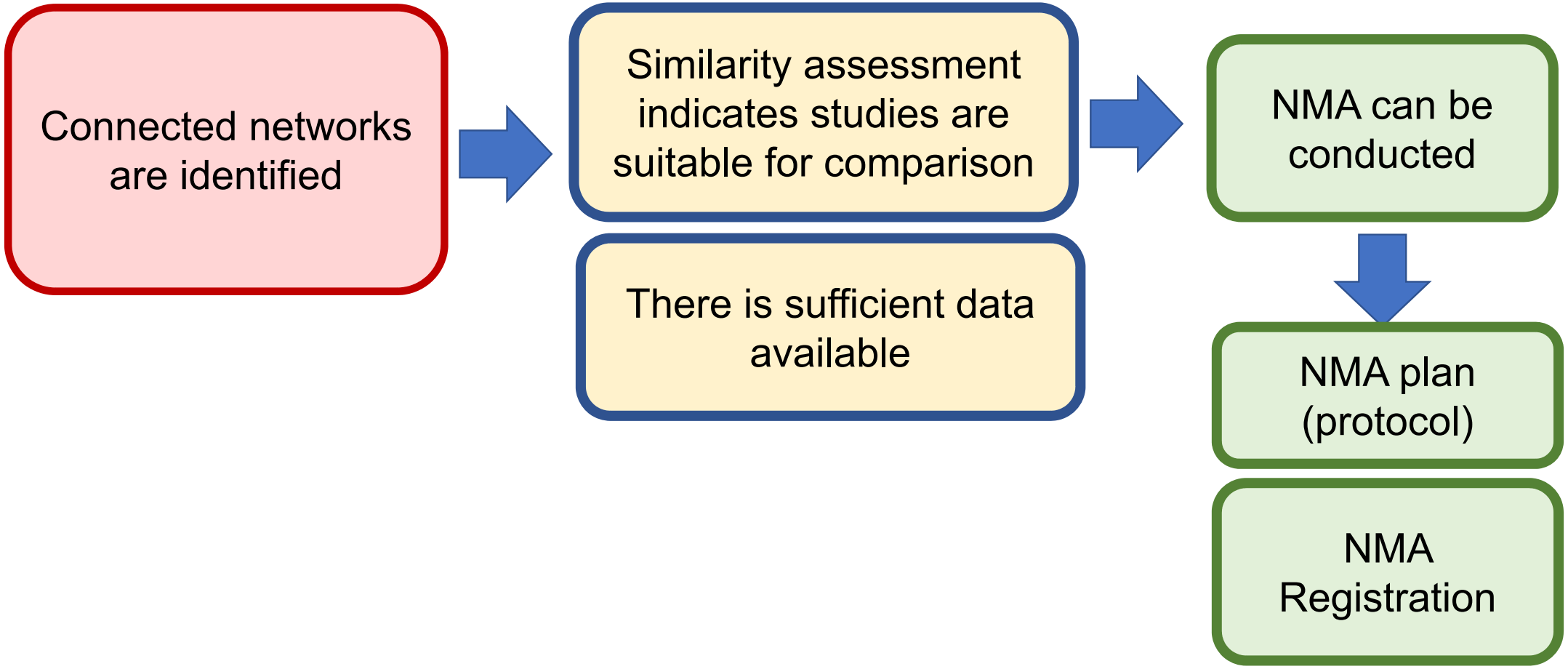
☑ **Number of patients in each prophylaxis treatment arm**

☑ **Number of patients or proportion of patients experiencing the "event of interest"**

Example: Some studies were not clearly reported "number of interested event" but report in percent (%) without statement what is the denominator.

Number of patients randomized into the treatment arm at beginning
OR number of patient at the end of the RCT flow chart

Can we conduct an NMA? ……..



NMA registration ……..

Registration of systematic reviews: PROSPERO

Why

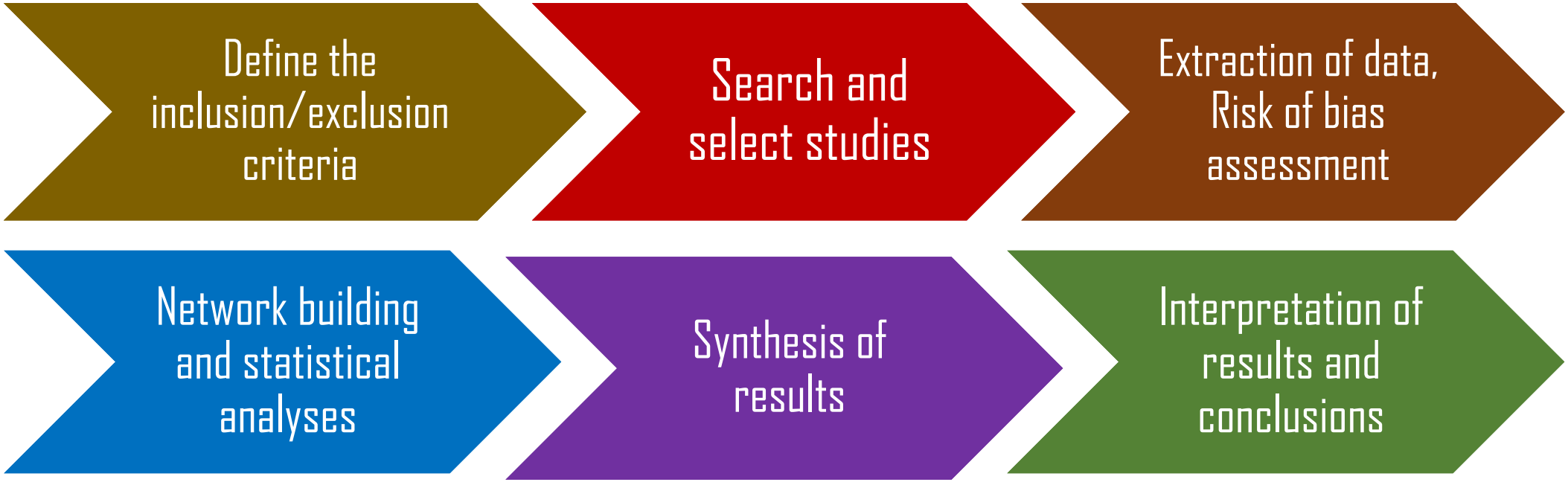
- **Helps minimize bias** in the conduct and reporting of the review –
- **Reduce duplication** of effort between groups
- **Keep systematic reviews updated**
- **To comply with the PRISMA-NMA #5**
- **Supported by PLoS journals, BMJ and BMJ Open, BioMed Central Cochrane Collaboration, and BJOG journals' Editorial Board.**

NMA registration ……..

Trick and Tips

Check the standard PROSPERO eligibility criteria before submission to get the fast acceptance.

Performing NMA



Define the inclusion/exclusion criteria

"Study question" is important for successful publication

Key: Not able to answer by the previous available publication or conventional meta-analysis

Treatments (antibiotic classes) of the network (nodes) should be precisely defined.

Key: Ensure that the grouping is acceptable.

Follow PRISMA-NMA extension guide and recommendations (e.g. Cochrane Collaboration) to conduct the NMA.

Key: Read the guideline and recommendation before performing

Define the inclusion/exclusion criteria

PICOS – inclusion

Any RCT regardless of sample size was included if it met the following criteria: included adult patients who underwent groin hernia repair (inguinal or femoral hernia, laparoscopic or open repair) with, or without using prosthetic material; compared any systemic administration of antibiotic with antibiotic, placebo or no treatment; prophylactic antibiotics included any generation of cephalosporins, β-lactam antibiotics combined with β-lactamase inhibitors, or fluoroquinolones; and had SSI as the outcome. Studies were excluded if there were insufficient data for pooling after three failed attempts to contact the authors regarding data provision, or if they compared different doses of the same antibiotic class.

S: Study design

P: Patients with groin hernia

I vs C

Antibiotic vs Placebo -- or
Antibiotic vs Antibiotic

- For prophylaxis
- Systemic ATB

O: SSI

Define the inclusion/exclusion criteria

Exclusion – (limitation)

as the outcome. Studies were excluded if there were insufficient data for pooling after three failed attempts to contact the authors regarding data provision, or if they compared different doses of the same antibiotic class.

Search and select studies

Ensure that the search is broad enough.

Search terms for the PICO.

- **Patient:** herni*;
- **Intervention:** antibiotic*, antimicrob*, Cephalosporins, Cefazolin, Cefuroxime, Cefotaxime, Cefoxitin, Cefotetan, Ceftriaxone, Penicillins, Beta-lactams, Amoxicillin, Ampicillin, Piperacillin, Beta-lactamase Inhibitors, Sulbactam, Clavulan*, Tazobactam, Sultamicillin, Amoxicillin–potassium clavulanate combination, Fluoroquinolones, Levofloxacin, Ciprofloxacin, Moxifloxacin;
- **Comparator:** placebo, no treatment;
- **Outcome:** prophyla*, prevent*, surgical wound infection, wound infection

Clearly define cutoff date (up to 23 March 2016)

Clearly define Databases (PubMed, Scopus)

Search and select studies

Tricks and Tips

- Don’t forget to save final “search query” for publication

Database:
PubMed
User query:
((((herni*) AND ((antibiotic*) OR (antimicrob*) OR (cephalosporins) OR (cefazolin) OR (cefuroxime) OR (cefotaxime) OR (cefoxitin) OR (cefotetan) OR (ceftriaxone) OR (penicillins) OR (beta-lactams) OR (amoxicillin) OR (ampicillin) OR (piperacillin) OR (beta-lactamase Inhibitors) OR (sulbactam) OR (clavulan*) OR (tazobactam) OR (sultamicillin) OR (amoxicillin-potassium clavulanate combination) OR (fluoroquinolones) OR (levofloxacin) OR (ciprofloxacin) OR (moxifloxacin))) AND (((antibiotic*) OR (antimicrob*) OR (cephalosporins) OR (cefazolin) OR (cefuroxime) OR (cefotaxime) OR (cefoxitin) OR (cefotetan) OR (ceftriaxone) OR (penicillins) OR (beta-lactams) OR (amoxicillin) OR (ampicillin) OR (piperacillin) OR (beta-lactamase Inhibitors) OR (sulbactam) OR (clavulan*) OR (tazobactam) OR (sultamicillin) OR (amoxicillin-potassium clavulanate combination) OR (fluoroquinolones) OR (levofloxacin) OR (ciprofloxacin) OR (moxifloxacin)) OR (placebo) OR (no treatment))) AND (((prophyla*) OR (prevent*)) AND ((surgical wound infection) OR (wound infection)))) AND (English[lang])

Scopus

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2,155 document results

View secondary documents View 4872 patent results View 23 Mendeley Data

(((herni*) AND (((antibiotic*) OR (antimicrob*)) OR ((cephalosporins) OR (cefazolin) OR (cefuroxime) OR (cefotaxime) OR (cefoxitin) OR (cefotetan) OR (ceftriaxone)) OR ((penicillins) OR (beta-lactams) OR (amoxicillin) OR (ampicillin) OR (piperacillin)) OR ((beta-lactamase AND inhibitors) OR (sulbactam) OR (clavulan*) OR (tazobactam) OR (sultamicillin) OR (amoxicillin-potassium AND clavulanate AND combination)) OR ((fluoroquinolones) OR (levofloxacin) OR (ciprofloxacin) OR (moxifloxacin)))) AND ((((antibiotic*) OR (antimicrob*)) OR ((cephalosporins) OR (cefazolin) OR (cefuroxime) OR (cefotaxime) OR (cefoxitin) OR (cefotetan) OR (ceftriaxone)) OR ((penicillins) OR (beta-lactams) OR (amoxicillin) OR (ampicillin) OR (piperacillin)) OR ((beta-lactamase AND inhibitors) OR (sulbactam) OR (clavulan*) OR (tazobactam) OR (sultamicillin) OR (amoxicillin-potassium AND clavulanate AND combination)) OR ((fluoroquinolones) OR (levofloxacin) OR (ciprofloxacin) OR (moxifloxacin))) OR (placebo) OR (no AND treatment))) AND (((prophyla*) OR (prevent*)) AND ((surgical AND wound AND infection) OR (wound AND infection))) AND (LIMIT-TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (LANGUAGE, "English"))

Edit Save Set alert Set feed

Data extraction

Clearly describe method of data extraction

- **2 person, Independently**
- **3rd person-consensus for disagreement**

Clearly define what data will be extracted

Table 1 Characteristics of included RCTs

Reference	Antibiotic regimen	Class of antibiotic	Setting	SSI definition	Country	Follow-up (days)
Herniorrhaphy						
8	Cephaloridine 1 g single dose i.m. followed by 1 g i.m. × 2 doses *versus* no antibiotic	First-generation cephalosporins *versus* no antibiotic	Single	n.r.	UK	At least 28
9	Cefonicid 1 g i.v. *versus* placebo	Second-generation cephalosporins *versus* placebo	Multi	S/S	USA	At least 42
10	Amoxicillin–clavulanate 1·2 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Multi	S/S	UK	28–42
Hernioplasty						
11	Ampicillin–sulbactam 1·5 g i.v. *versus* placebo	β-Lactam/β-lactamase inhibitors *versus* placebo	Single	CDC	Turkey	365
12	Cefuroxime 1·5 g i.v. *versus* placebo	Second-generation cephalosporins *versus* placebo	Multi	CDC	The Netherlands	84

Table 2 Further details of included RCTs

Reference	No. of subjects	Mean age (years)	% men	Mean BMI (kg/m^2)	ASA grade (I/II/III/IV)	% ASA grade > II	% diabetes mellitus	% resident/non-certified surgeon	Mean duration of surgery (min)
Herniorrhaphy									
8	97	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
9	612	50	90·4	24·7	n.r.	n.r.	4·0	n.r.	n.r.
10	563	57	94·7	73*	n.r.	n.r.	n.r.	n.r.	50% > 35 min
Hernioplasty									
11	269	56	92·6	25·0	198/71/0/0	0	0	n.r.	63·5
12	1008	58	96·3	n.r.	n.r.	n.r.	0	43·4	39·9
13	99	58	90	26·1	I or II	0	18	24	64·5
14	360	61	98·1	n.r.	284/76/0/0	0	n.r.	n.r.	53·1

Risk of bias assessment

Clearly describe methodological quality and risk of bias assessment tool to preserve similarity and consistency.

Tool

Cochrane Collaboration's tool for assessing risk of bias in randomized trials

How

Two authors independently

Any disagreement was resolved by discussion.

Study	Authors	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting?
	Hernioplasty							
1	Yerdel MA	2001	+	+	+	+	+	+
2	Aufenacker TJ	2004	+	+	+	+	+	+
3	Celdrán A	2004	+	−	?	+	?	+
4	Perez AR	2005	+	+	+	+	+	+
5	Terzi C	2005	+	+	+	+	+	+
6	Tzovaras G	2007	+	+	+	+	+	+
7	Jain SK	2008	+	+	+	+	+	+
8	Shankar VG	2010	+	+	+	+	−	−
9	Thakur L	2010	+	?	+	+	?	?
10	Goyal A	2011	+	?	+	?	+	?
11	Othman I	2011	+	+	+	?	?	+
12	Ergul Z	2012	+	+	+	+	+	+
13	Ullah B	2013	+	?	?	?	?	?
14	Wang J	2013	+	+	+	+	+	+
15	Mazaki T	2014	+	+	+	+	+	+

+ Low risk ? Unclear − High risk

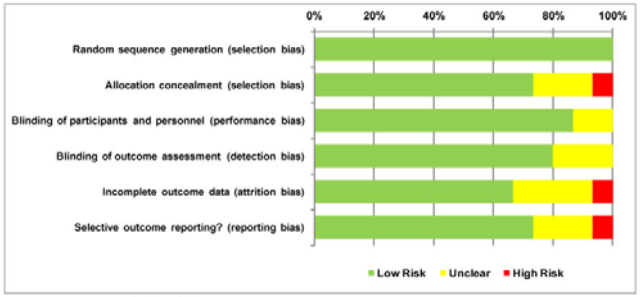


Fig. S2 Summary of risk-of-bias assessments

Network building

‘Network plot”

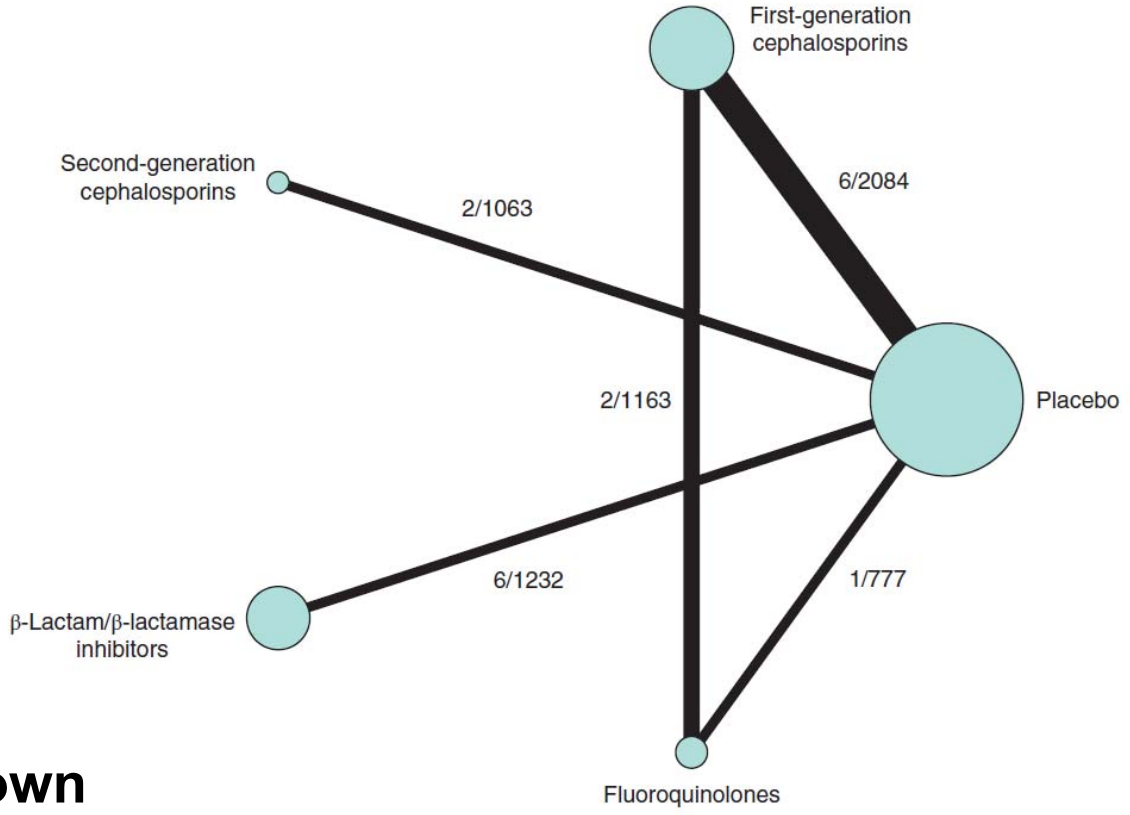
Nodes:

- **Interventions being compared**
- **Weighted by number of studies;**

Edges :

- **Available direct comparisons**
- **Weighted by numbers of included subjects**

Numbers of studies/subjects are shown



Network building

‘Contribution plot’ : presenting the influence of each direct piece of evidence

Direct comparisons in the network

Network meta-analysis estimates		PBvs1CEP	PBvs2CEP	PBvsB-LAC	PBvsQUIN	1CEPvsQUIN
Mixed estimates						
	PBvs1CEP	67.7			16.2	16.2
	PBvs2CEP		100.0			
	PBvsB-LAC			100.0		
	PBvsQUIN	29.5			41.0	29.5
	1CEPvsQUIN	28.0			28.0	44.0
Indirect estimates						
	1CEPvs2CEP	36.8	45.6		8.8	8.8
	1CEPvsB-LAC	36.8		45.6	8.8	8.8
	2CEPvsB-LAC		50.0	50.0		
	2CEPvsQUIN	17.3	41.4		24.1	17.3
	B-LACvsQUIN	17.3		41.4	24.1	17.3
Entire network		23.6	23.2	23.2	15.8	14.2
Included studies		6	2	6	1	2

Network building and statistical analyses

Clearly defined the method of analysis:

Direct comparison (conventional method)

Network meta-analysis- "consistent with details submitted to PROSPERO" - if not, amend PROSPERO with reason of changes

- One-stage approach
- Two-stage approach

Network building and statistical analyses

Network meta-analysis- Two-stage approach results were presented in **Table format**

Table 3 Comparisons of antibiotic prophylaxis effects on surgical-site infection in hernioplasty

	Risk ratio			
	First-generation cephalosporins	Second-generation cephalosporins	β-Lactam/ β-lactamase inhibitors	Fluoroquinolones
Reference antibiotic				
First-generation cephalosporins	0·62 (0·42, 0·92)* [65·5; 11·5]	1·32 (0·55, 3·16)	0·70 (0·36, 1·38)	1·23 (0·71, 2·15)
Second-generation cephalosporins	0·76 (0·32, 1·82)	0·82 (0·37, 1·79)* [40·7; 10·7]	0·54 (0·21, 1·39)	0·94 (0·36, 2·45)
β-Lactam/β-lactamase inhibitors	1·42 (0·73, 2·78)	1·87 (0·72, 4·84)	0·44 (0·25, 0·75)* [91·0; 74·4]	1·75 (0·80, 3·82)
Fluoroquinolones	0·81 (0·46, 1·42)	1·07 (0·41, 2·80)	0·57 (0·26, 1·25)	0·77 (0·44, 1·34)* [41·0; 3·4]

Values are the risk ratio, with 95 per cent confidence intervals in parentheses, of surgical-site infection with use of test antibiotic (in column heading) *versus* reference antibiotic or *placebo. Values below 1·00 show benefit for test antibiotic compared with reference antibiotic. Values in square brackets are surface under the cumulative ranking curve area; percentage probability of test antibiotic being best prophylaxis.

Network building and statistical analyses

Evaluate uncertainty - present using plots

- **Inconsistency -** Agreement between **direct and indirect treatment effects**, was assessed **using a design-by-treatment interaction model**.

- Predictive intervals were also estimated and plotted (**predictive interval plots**) to see the RRs after taking into account **uncertainty** from **both heterogeneity and inconsistency.**

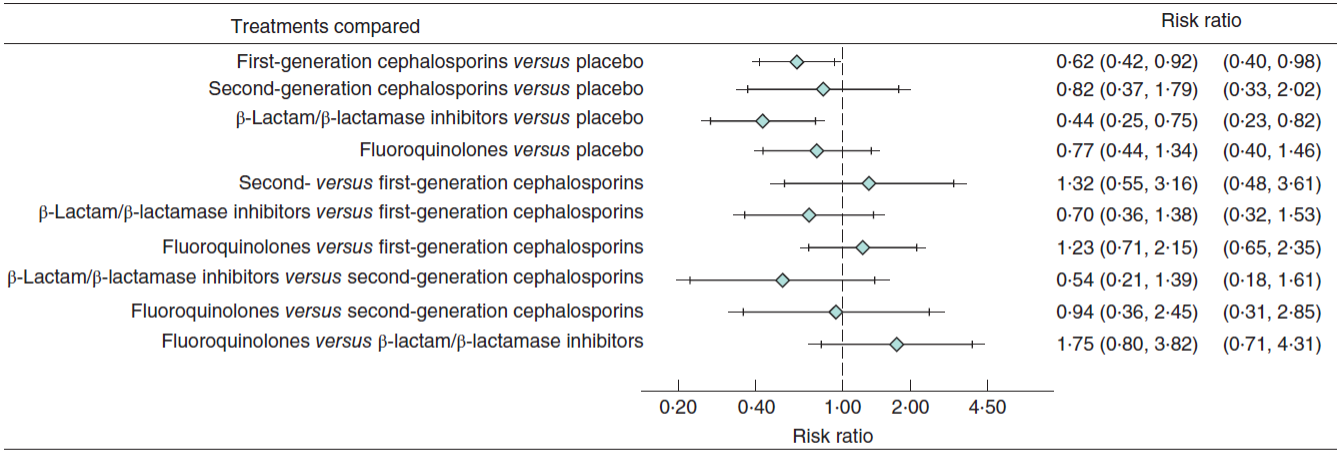


Fig. 4 Predictive interval plots for antibiotic prophylaxis network of groin hernioplasty. Values in parentheses are 95 per cent confidence intervals, followed by 95 per cent predictive intervals that take future uncertainty into account. These are also plotted as bold and extended lines respectively. The dashed line indicates no treatment effect (risk ratio = 1·00)

Network building and statistical analyses

Ranking method

Estimated probability of being best prophylaxis using the surface under the cumulative ranking curve (SUCRA) method.

Rankograms

Graphical presentations of the ranking

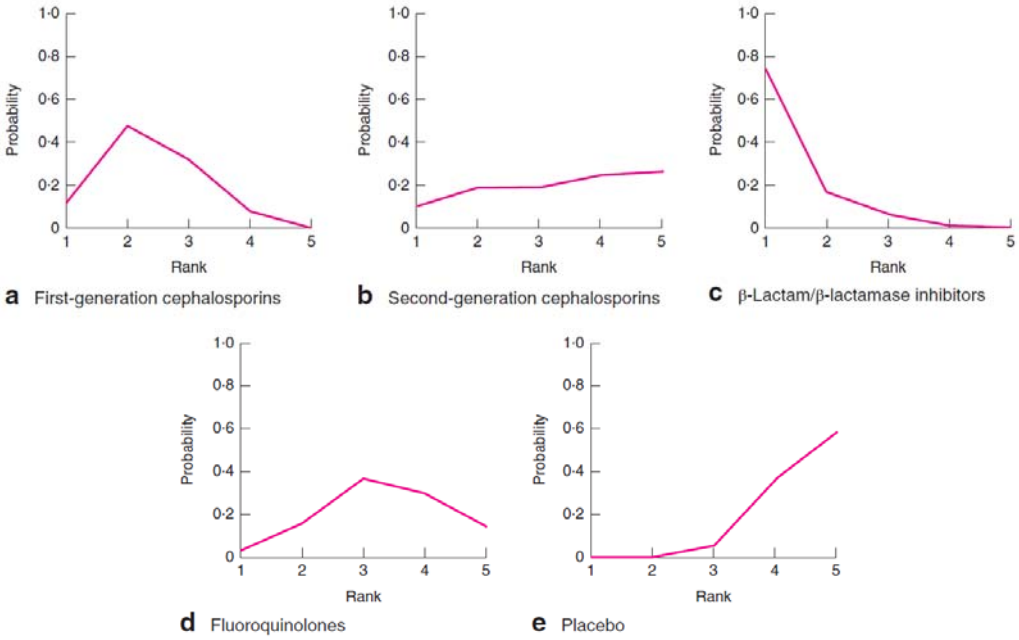


Fig. 3 Rankograms showing use of antibiotic prophylaxis for reducing surgical-site infection after hernioplasty: **a** first-generation cephalosporins, **b** second-generation cephalosporins, **c** β-lactam/β-lactamase inhibitors, **d** fluoroquinolones and **e** placebo

Network building and statistical analyses

A number needed to treat (NNT) was estimated

to more easy to understand by reader and to summary at the end.

$$\mathrm{NNT} = \frac{1}{I_{\mathrm{placebo}} \times (1 - \mathrm{pooled\ RR})}$$

The pooled SSI incidence in the placebo group was 6.1% (95% CI 4.2 to 8.1)

The estimated NNTs

1st Gen cephalosporins : 43 (95% CI 28 to 202)

β-lactam/β-lactamase inhibitors : 29 (95% CI 21 to 66)

Publication phase- Tricks and Tips

Read "SCOPE" of the journal - Is your topic in the journal scope?

Read author information in the interested journal

- **Word and reference limits**
- **Number of tables & figures for publication in print – Select the key table and Figures – See PRISMA-NMA**

Read previously NMA published in the journal to explore the format

Write: PRISMA for Network Meta-Analyses (PRISMA-NMA) – Follow the guideline step by step.


Q&A