Supplemental information

Comparative efficacy and safety of antibiotic prophylaxis for reducing recurrent urinary infection in children: A systematic review and network meta-analysis

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Content

Contenido

Supplemental information 1. Search strategies.

OVID MEDLINE

1. urinary tract infection$.mp. or exp Urinary Tract Infections/
2. vesico-ureteral reflux.mp. or exp Vesico-Ureteral Reflux/ or vesicoureteral reflux.mp.
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21. 18 and 19 and 20

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#8	MeSH descriptor: [Recurrence] explode all trees 14687
#9	MeSH descriptor: [Nitrofurantoin] explode all trees 186
#10	MeSH descriptor: [Cephalosporins] explode all trees 4786
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#13	MeSH descriptor: [Sulfamethoxazole] explode all trees 1254
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#22	#20 OR #21 408874
#23	#19 AND #22 in Trials 824

LILACS

(antibiotics or antibiotic prophylaxis or nitrofurantoin or trimethoprim or cotrimoxazole or trimethoprim sulfamethoxazole or cephalosporins) and (children or infant* or bab*) and (UTI or Urinary tract infection or pyelonephritis or cystitis)

Supplemental information 2. Definitions.

Definition of Antibiotic Prophylaxis

Synonyms: Continuous Antibiotic Prophylaxis (CAP), Long-Term Low-Dose Antibiotic Therapy

Antibiotic prophylaxis refers to the administration of long-term, low-dose antibiotics to prevent recurrent UTI. In this study, long-term is defined as a **minimum duration of two months, and the dosage is typically administered once daily**, resulting in a lower dose compared to standard treatment regimens.

A variety of antibiotic regimens have been described for long-term prophylaxis, including: trimethoprim/sulfamethoxazole (TMP/SMX, also known as co-trimoxazole) at 2 mg/kg/day of trimethoprim and 10 mg/kg/day of sulfamethoxazole, nitrofurantoin (1-2 mg/kg/day), cefadroxil (12.5-15 mg/kg/day), the fluoroquinolone nalidixic acid (30 mg/kg/day), and beta-lactams such as cefixime (2 mg/kg), cefadroxil (5 mg/kg), cefprozil (10 mg/kg), cefuroxime axetil (15 mg/kg), cefaclor (15 mg/kg), co-amoxiclav (15 mg/kg/day), and pivmecillinam (100-200 mg/day).

Definition of renal scarring

Following a febrile urinary tract infection (UTI) episode, parenchymal changes can occur within the kidney. These changes are identifiable on 99mTc-dimercaptosuccinic acid (DMSA) scans as photon-deficient areas, characterized by contraction and distortion of the renal cortex with loss of volume. These features often manifest 3 to 6 months after a pyelonephritis episode. However, it is crucial to differentiate renal scarring that precedes antibiotic prophylaxis (including the index infection in trials where a UTI was an inclusion criterion) and renal scarring that develops subsequently. Ideally, new kidney scars should be assessed with two DMSA scans: initially within the first 6 months of recruitment and again

during the late follow-up period (in the latter 6 months). However, this approach presents methodological challenges and is not commonly implemented in clinical trials. Therefore, in our study, new renal scarring was defined as a scar identified on a DMSA scan during late follow-up (defined by authors). DMSA scans were evaluated by experts in the field to ensure accurate identification and interpretation of scarring.

Urinary tract infection

A urinary tract infection is defined as the presence of clinical signs or symptoms (which may vary depending on age) consistent with a UTI, accompanied by confirmed bacterial growth in a urine culture.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the isolation of a significant quantity of bacteria in a urine culture from a patient who does not exhibit any signs or symptoms indicative of a urinary tract infection.

Antibacterial resistance

Antibacterial resistance is defined as the in vitro growth of a bacterial isolate in the presence of an antimicrobial agent at a concentration equal to or exceeding minimum inhibitory concentration (MIC) established by the Clinical and Laboratory Standards Institute (CLSI). For pragmatical purposes antibacterial resistance was defined by each author. Cultures derived from samples other than urine (e.g., urethral, perineal and fecal samples) were excluded from the analysis.

Adverse events

Adverse events were defined as any undesirable effect on health experienced by a participant during the clinical trial, whether considered directly related to the intervention or not. In our study, AEs were defined by the individual study authors, with the most frequently encountered being mild and transient in nature. These commonly included nausea, vomiting, skin rash, and diarrhea.

Supplemental Table 1. Excluded studies and reasons.

#	Author	Journal	Title	Reason to exclude
1	Ctri 2012	Clinical Trials.gov	A clinical trial to study the effectiveness of low dose antibiotic treatment and placebo for prevention of urinary infection in children with vesicoureteric reflux	RCT registry
2	Wang 2018	The Journal of Urology	A Reanalysis of the RIVUR Trial Using a Risk Classification System	Not an RCT, a reanalysis of RIVUR trial
3	Canning 2010	Pediatrics	Antibiotic prophylaxis and recurrent urinary tract infection in children	Already included
4	Zegers 2011	BJU International	Antibiotic prophylaxis for urinary tract infections in children with spina bifida on intermittent catheterization	Different population, only patients with neurogenic bladder on intermittent catheterization
5	Hari 2013	Indian Journal of Urology	Antibiotic prophylaxis in management of vesicoureteric reflux: a double-blind placebo controlled trial	Already included
6	Nelson 2016	The Journal of Urology	Antimicrobial Resistance and Urinary Tract Infection Recurrence	Not an RCT, a reanalysis of RIVUR trial
7	Clarke 2005	The Journal of Urology	Are prophylactic antibiotics necessary with clean intermittent catheterization? A randomized controlled trial	Different population, only patients with neurogenic bladder on intermittent catheterization

8	Tamminen-Mobius 1992	Journal of Urology	Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children	Not an RCT, a reanalysis of RIVUR trial
9	Akinci 2021	Urology Journal	Effect of continuous antibiotic prophylaxis in children with postoperative JJ stents: A prospective randomized study	Antibiotic only for 10 days
10	Irct20201112049368N 2020	Iranian Registry of Clinical Trials	Evaluation of various antibiotic regimens in recurrent urinary tract infections	RCT registry
11	Nadkarni 2020	The Journal of Urology	Laboratory Findings After Urinary Tract Infection and Antimicrobial Prophylaxis in Children With Vesicoureteral Reflux	Did not report outcomes of interest
12	Zegers 2010	Developmental Medicine & Child Neurology	Low-dose chemoprophylaxis and prevention of urinary tract infections in children with meningomyelocele and clean intermittent catheterization	Different population, only patients with neurogenic bladder on intermittent catheterization
13	Schlager 1998	The Journal of Urology	Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization	Different population, only patients with neurogenic bladder on intermittent catheterization
14	Yiee 2012	The Journal of Urology	Prospective blinded laboratory assessment of prophylactic antibiotic compliance in a pediatric outpatient setting	Not an RCT
15	Olbing1970	Current Therapeutic	Prospective comparison between nitrofurantoin and	Not an RCT

		Research, Clinical and Experimental	sulphamethoxydiazine in the long-term therapy of children suffering from severe chronic recurrent pyelonephritis	
16	Mattoo 2016	The Journal of Urology	Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial	Not an RCT, a reanalysis of RIVUR trial
17	Cara-Fuentes 2015	Pediatric Nephrology	The RIVUR study: a review of its findings	Not an RCT, a reanalysis of RIVUR trial
18	Mattoo 2015	Pediatric Nephrology	The RIVUR trial: a factual interpretation of our data	Not an RCT, commentary of RIVUR trial
19	Wang 2019	Pediatric Nephrology	Why Does Prevention of Recurrent Urinary Tract Infection not Result in Less Renal Scarring? A Deeper Dive into the RIVUR Trial	Not an RCT, a reanalysis of RIVUR trial
20	Johnson 1994	British Journal of Urology	A short-term study of nitrofurantoin prophylaxis in children managed with clean intermittent catheterization	Only patients with neurogenic bladder on intermittent catheterization
21	Nordenstrom 2015	The Journal of Urology	The swedish infant high grade reflux trial-UTI and renal damage	RCT comparing antibiotic prophylaxis to endoscopic treatment, did not include no treatment arm
22	Brandstrom 2010	The Journal of Urology	The Swedish reflux trial in children: I. Study design and study population characteristics	Already included
23	Holmdahl 2010	The Journal of Urology	The Swedish reflux trial in children: II. Vesicoureteral reflux outcome	Already included

24	Brandstrom 2010	The Journal of Urology	The Swedish reflux trial in children: III. Urinary tract infection pattern	Already included
25	Brandstrom 2010	The Journal of Urology	The Swedish reflux trial in children: IV. Renal damage	Already included
26	Rianthavorn 2020	Pediatric Nephrology	The role of antibiotic prophylaxis in mild to moderate isolated hydronephrosis detected in antenatal screening	Different population, only patients with prenatal hydronephrosis
27	Irct20201112049368N	Iranian Registry of Clinical Trials	Evaluation of various antibiotic regimens in recurrent urinary tract infections	RCT registry
28	Olbing 1970	Current Therapeutic Research, Clinical and Experimental	Prospective comparison between nitrofurantoin and sulphamethoxydiazine in the long-term therapy of children suffering from severe chronic recurrent pyelonephritis.	Not an RCT
29	Rianthavorn 2020	Pediatric Nephrology	The role of antibiotic prophylaxis in mild to moderate isolated hydronephrosis detected in antenatal screening	Different population, only patients with prenatal hydronephrosis
30	Lohr 1977	The Journal of Pediatrics	Prevention of Recurrent Urinary Tract Infections in Girls	Did not report outcomes of interest
31	Savage 1975	Lancet	Controlled Trial Of Therapy In Covert Bacteriuria Of Childhood	Did not report outcomes of interest
32	Carlsen 1985	Scandinavian Journal of Primary Health Care	Comparison of long-term, low-dose pivmecillinam and nitrofurantoin in the control of recurrent urinary tract infection in children. An open, randomized, cross-over study	Did not report outcomes of interest.
33	Braga 2014	Journal of Pediatric Urology	Pilot randomized, placebo controlled trial to investigate the effect of antibiotic prophylaxis on the rate of	Pilot RCT., did not report

			urinary tract infection in infants with prenatal hydronephrosis	outcomes of interest
34	Liern 2011	International Brazilian Journal of Urology	Recurrent urinary tract infections: Predisposing factors and antibiotic profilaxis	Did not report outcomes of interest.
35	Baciulis 2003	Medicina (Kaunas, Lithuania)	Long-term Cefadroxil prophylaxis in children with recurrent urinary tract infections	An RCT but compared cefadroxil every night versus alternate night.

Supplemental Table 2. List of articles full text could not be retrieved

#	Author/source	Year	Title
1	Actrn	2005	A placebo controlled randomized trial of long-term antibiotics to prevent recurrent urinary tract infection in children
2	Montini	2004	A randomised controlled trial of antibiotic prophylaxis in children with a previous documentated pyelonephritis
3	Nct	2006	A Randomized Controlled Trial on Antibiotic Prophylaxis in Children With Vesico-Ureteral Reflux
4	Euctr, E. S.	2014	Antibiotic Prophylaxis and Renal Damage In Congenital abnormalities of the kidney and urinary Tract
5	Nct	2013	Antibiotic Prophylaxis and Renal Damage In Congenital Abnormalities of the Kidney and Urinary Tract
6	Nct	2008	Antibiotic Prophylaxis in Children With Pyelonephritis
7	Hernandez, M. E	2014	Antibiotic prophylaxis in high degree vesicoureteral reflux clinical trial and prospective, observational and multicentric study
8	Isrctn	2007	Antibiotic prophylaxis in prevention of urinary tract infections caused by removal of a bladder catheter in children
9	Espino, M.	2012	Antibiotic prophylaxis inhighdegree vesicoureteral reflux. Prospective, randomized and multicentric study. Preliminary results
10	Reddy M.	1997	Antimicrobial prophylaxis in children with vesico-ureteral reflux: a randomized prospective study of continuous therapy vs intermittent therapy vs surveillance
11	Nct	2010	Effectiveness of Antibiotics Versus Placebo to Treat Antenatal Hydronephrosis
12	Tctr	2015	Efficacy of continuous prophylactic antibiotics in children having insignificant antenatal hydronephrosis
13	Nct	2005	Evaluation of the Effectiveness of Antibiotic Prophylaxis in Children With a Previous Urinary Tract Infection
14	Craig, J	2002	Long-term anitbiotics to prevent urinary tract infection in children with isolated vesicoureteric reflux: a placebo-controlled randomized trial
15	Euctr, I. T.	2009	Management of children following acute pyelonefritis or recurrent urinary tract infection episodes and prevention of renal scarring: a prospective randomised controlled clinical trial. - ND

16	Sureshkumar, P	2010	Recurrent urinary tract infections in children: Whom should we treat with prophylactic antibiotics?
17	Wald	2006	Urinary antibiotic prophylaxis may not be required in children with mild or moderate vesicoureteral reflux following acute pyelonephritis
18	Neto	1997	Use of ciprofloxacin as a prophylactic agent in urinary tract infections in renal transplant recipients
19	Nct	2005	Usefulness of Antimicrobial Prophylaxis in Children With Isolated Vesico-Ureteral Reflux
20	Umin	2009	Without antibiotic prophylaxis in children with mild vesicoureteral reflux (grade 0-2) after a first urinary tract infection. : a multicenter trial

Supplemental Table 3. Characteristics of Included studies

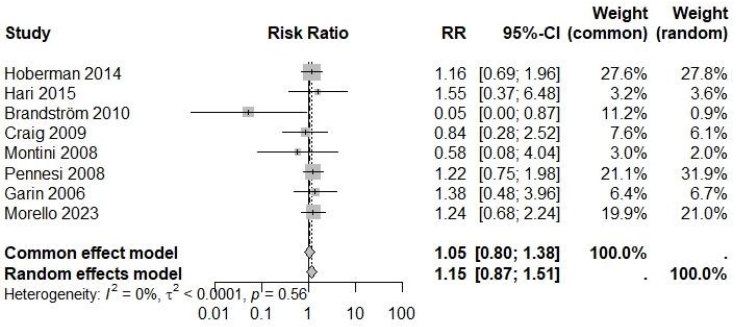
#	**Author**	**Country**	***Mean Age*** *months (SD)*	**% Previous UTI**	**% VUR**	**# patients**	**Interventions description**	**Classified in the grouped NMA as**	**Included outcomes**
1	Hoberman 2014	USA	16 (18,55)	8,7	100	607	TMP- SMX (3 mg of TMP plus 15 mg SMX per Kg) vs placebo	Fixed antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Kidney scars Antimicrobial resistance
2	Hari 2015	India	38,4 (32,4)	44	100	93	TMP- SMX (2 mg of TMP plus 10 mg of SMX per kg) vs no treatment	Fixed antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Kidney scars Asymptomatic bacteriuria Antimicrobial resistance
3	Brandström 2010	Sweden	21,6 (2,48)	98	100	137	TMP- SMX (0,5-1,0 mg/kg) as a first option, other allowed options	Pediatrician selected antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Kidney scars Antimicrobial resistance

							were nitrofurantoin (1 mg/kg) and cefadroxil (5 mg/kg) vs no treatment		
4	Craig 2009	Australia	14 (Not reported)	100	40	576	TMP- SMX (2 mg of TMP plus 10 mg of SMX per kg) vs placebo	Fixed antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Kidney scars Antimicrobial resistance
5	Roussey-Kesler 2008	France	11,2 (11,03)	Not reported	100	225	TMP- SMX (2 mg of TMP plus 10 mg of SMX per kg) vs no treatment	Fixed antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Antimicrobial resistance
6	Montini 2008	Italy	14,7 (15,48)	0	37	338	Amoxicillin clavulanate (15mg/kg)or TMP-SMX (15mg/kg) vs no treatment	Pediatrician selected antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Kidney scars Asymptomatic bacteriuria Antimicrobial resistance
7	Pennesi 2008	Italy	8,7 (5,64)	0	100	100	TMP- SMX (1-2 mg of TMP plus 5-10 mg of SMX per kg) vs no treatment	Fixed antibiotic	Incidence of UTI at 12 months Kidney scars Antimicrobial resistance
8	Garin 2006	USA, Chile and Spain	55,14 (218)	Not reported	51	218	TMP- SMX (1-2 mg of TMP plus 5-10 mg of SMX per kg) or nitrofuratoin (1.5 mg/Kg) vs no treatment	Pediatrician selected antibiotic	Incidence of UTI at 12 months Kidney scars Asymptomatic bacteriuria
9	Smellie 1978	UK	Not reported	52	Not reported	47	TMP- SMX (2 mg of TMP plus 10 mg of SMX per kg) or nitrofuratoin (1-2 mg/Kg) vs no treatment	Pediatrician selected antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Antimicrobial resistance
10	Morello 2023	Italy	3,3 (1,2)	0	100	292	Antibiotic agent was selected by Pediatricians. Amoxicillin	Pediatrician selected antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months Kidney scars Antimicrobial resistance

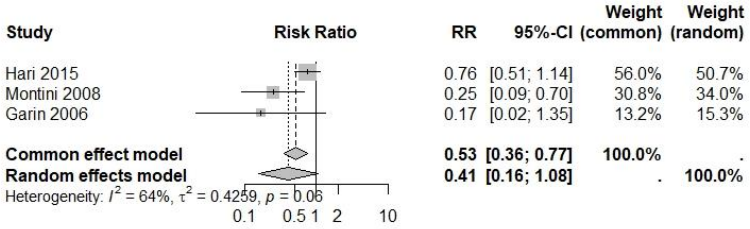
							clavulanate (15mg/kg), cefexime (2mg/kg),TMP-SMX (2,5 mg of TMP plus 5-10 mg of SMX per kg) or nitrofuratoin (1.5 mg/Kg) vs no treatment		
11	Antachopoulos 2016	Greece	25,75 (10,65)	0	Not reported	97	TMP- SMX (2 mg of TMP plus 10 mg of SMX per kg), axetil cefuroxime (10 mg/kg) , cefprozilo (10 mg/kg) vs cefaclor (15 mg/kg)	Fixed antibiotic	Incidence of UTI at 6 months
12	Falakaflaki 2007	Iran	45,6 (23,5)	100	43	132	TMP- SMX (based on 2 mg of TMP per kg) vs nitrofuratoin (2 mg/Kg)	Fixed antibiotic	Antimicrobial resistance
13	Belet 2004	Turkey	65,52 (50,64)	100	Not reported	80	TMP- SMX (based on 2 mg of TMP per kg) vs Cefadroxil (5 mg/kg) or cefprozil (5 mg/kg)	Fixed antibiotic	Incidence of UTI at 6 months Asymptomatic bacteriuria
14	Brendstrup 1990	Denmark	90 (30,11)	100	Not reported	130	TMP- SMX (based on 1-2 mg of TMP per kg) vs nitrofuratoin (1- 1,5 mg/Kg)	Fixed antibiotic	Incidence of UTI at 6 months Antimicrobial resistance
15	Lettgen 2002	Germany	61,6 (28,12)	100	Not reported	57	Cefexime (2mg/kg) or nitrofuratoin (1-1,5 mg/Kg)	Fixed antibiotic	Incidence of UTI at 6 months Incidence of UTI at 12 months

16	Beiraghi 2011	Iran	59,5 (38,62)	100	92	102	TMP- SMX (based on 1 mg of TMP per kg) or Nalidixic acid (20 mg/Kg)	Fixed antibiotic	Incidence of UTI at 6 months

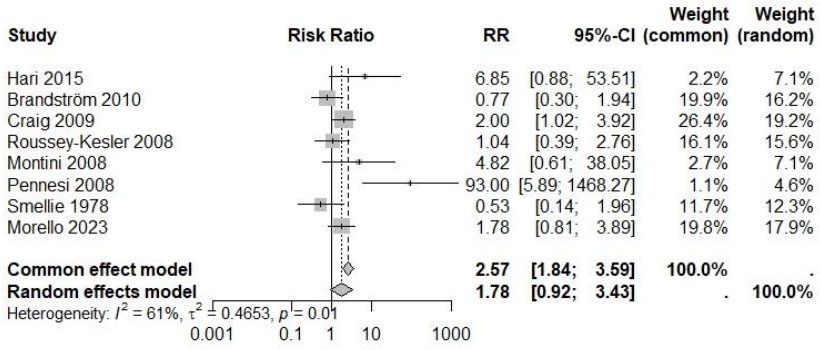
Supplemental Figure 1. Forest plot Pairwise meta-analysis comparing antibiotic prophylaxis to control for new kidney scars.



Supplemental Figure 2. Forest plot Pairwise meta-analysis comparing antibiotic prophylaxis to control for asymptomatic bacteriuria.

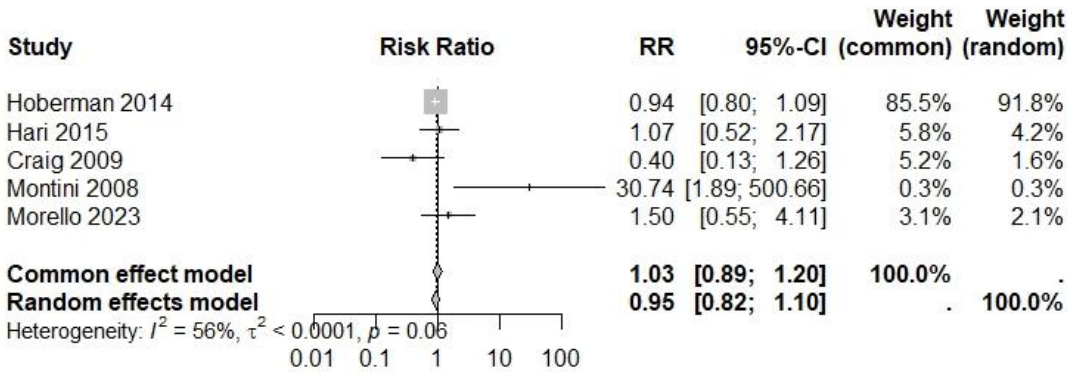


Supplemental Figure 3. Forest plot Pairwise meta-analysis comparing antibiotic prophylaxis to control for antimicrobial resistance.

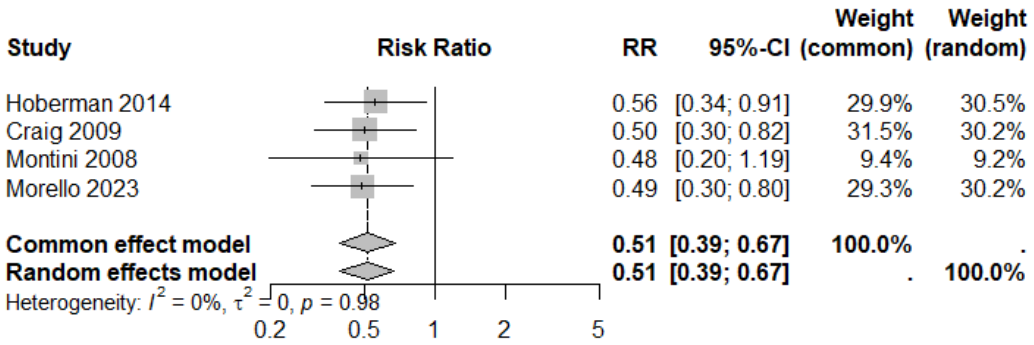


Supplemental Figure 4. Risk of bias assessment of included studies

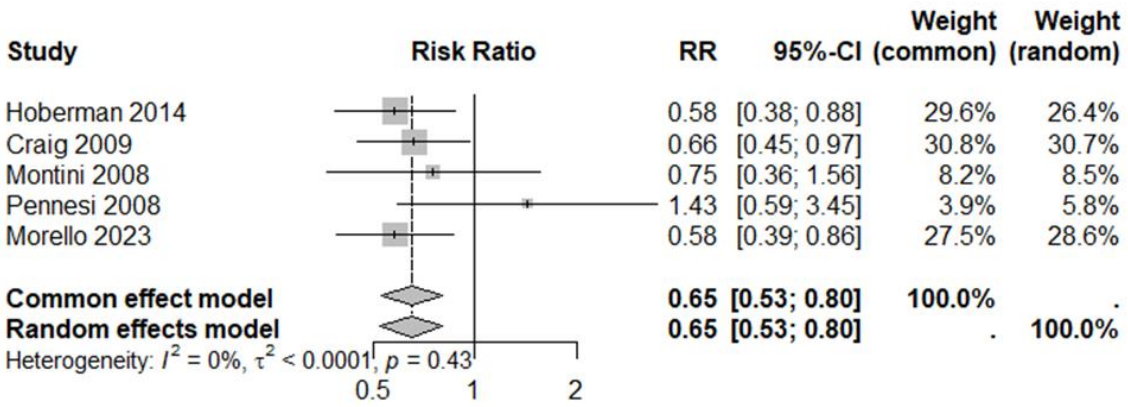
Supplemental Figure 5. Forest plot Pairwise meta-analysis comparing antibiotic prophylaxis to control for adverse events



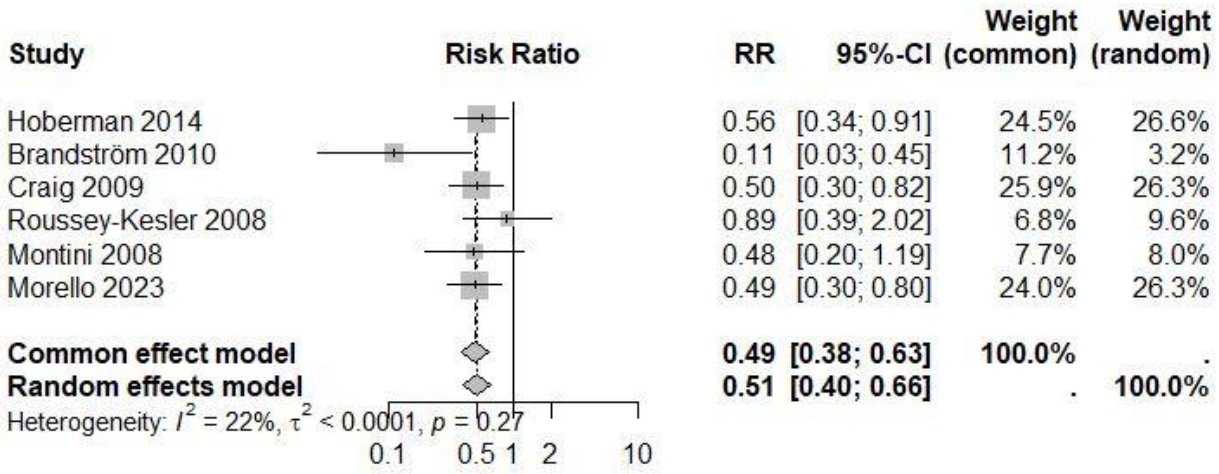
Supplemental Figure 6. Forest plot for sensitivity analysis of recurrence of UTI at 6 months including studies classified as low risk in 'overall domain'



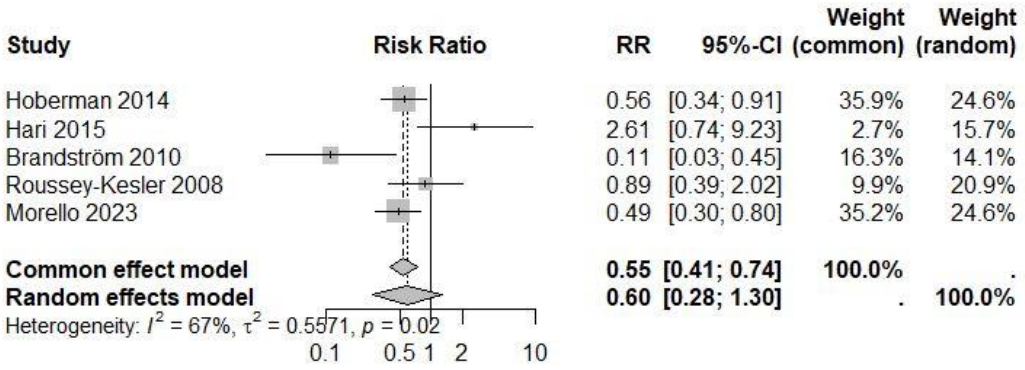
Supplemental Figure 7. Forest plot for sensitivity analysis of recurrence of UTI at 12 months including studies classified as low risk in 'overall domain'



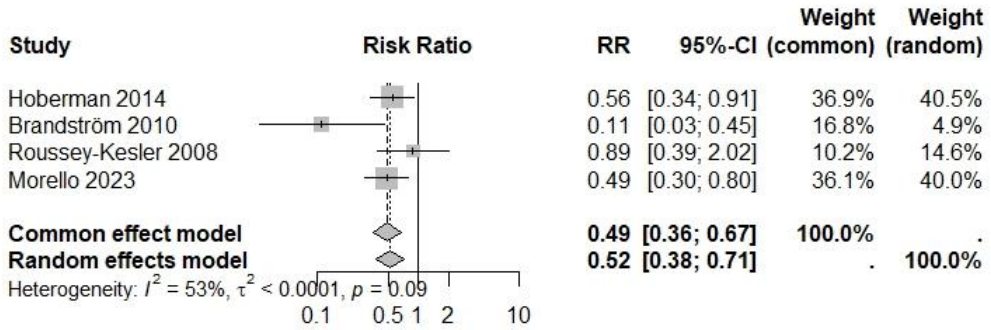
Supplemental Figure 8. Pairwise subgroup meta-analyses for incidence of UTI at 6 months. Subgroup younger than 2 years



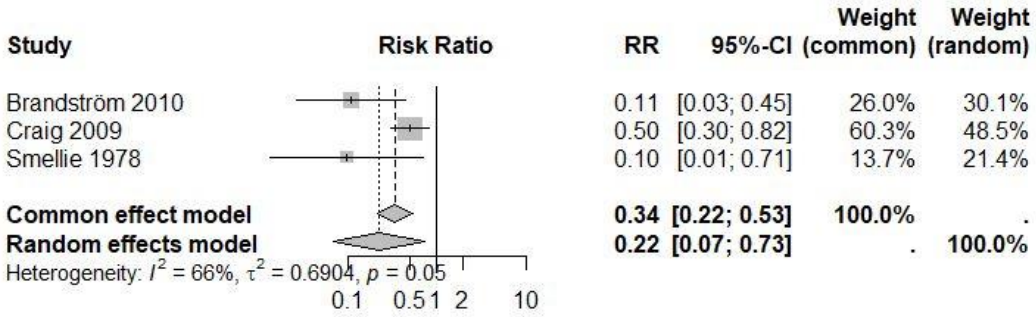
Supplemental Figure 9. Pairwise subgroup meta-analyses for incidence of UTI at 6 months. Subgroup VUR



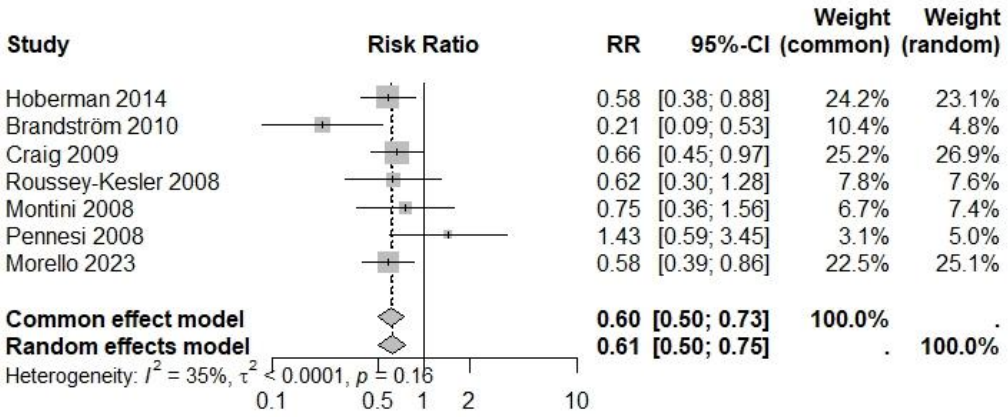
Supplemental Figure 10. Pairwise subgroup meta-analyses for incidence of UTI at 6 months. Subgroup VUR in younger than 2 years



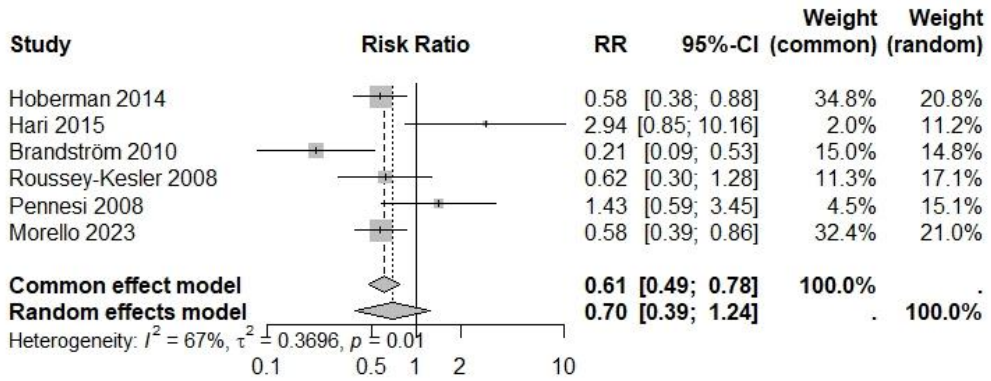
Supplemental Figure 11. Pairwise subgroup meta-analyses for incidence of UTI at 6 months. Subgroups Recurrent UTI



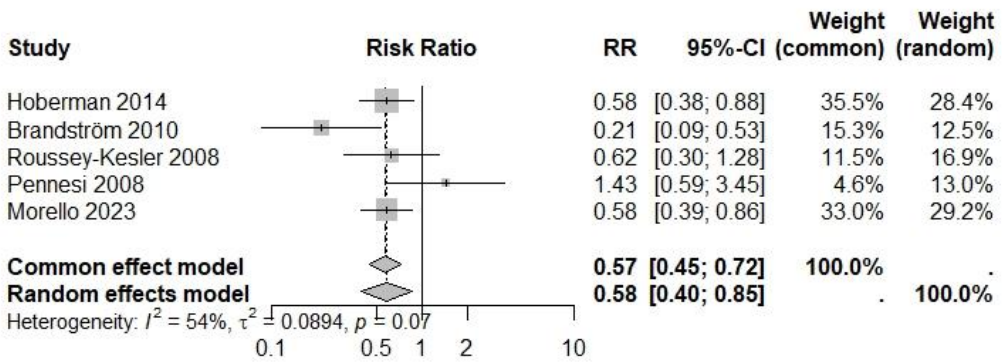
Supplemental Figure 12. Pairwise subgroup meta-analyses for incidence of UTI at 12 months. Subgroup younger than 2 years



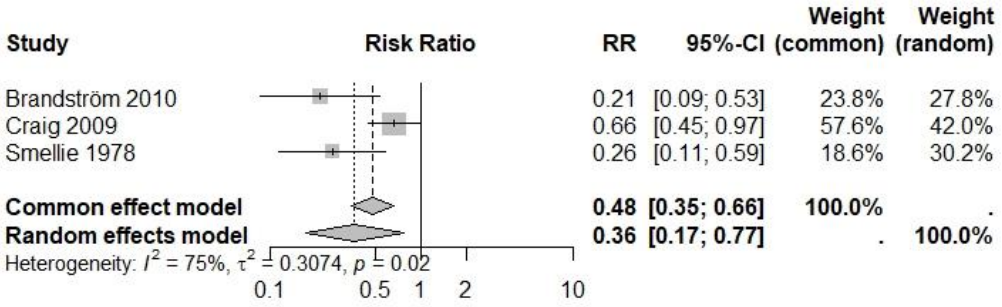
Supplemental Figure 13. Pairwise subgroup meta-analyses for incidence of UTI at 12 months. Subgroup VUR



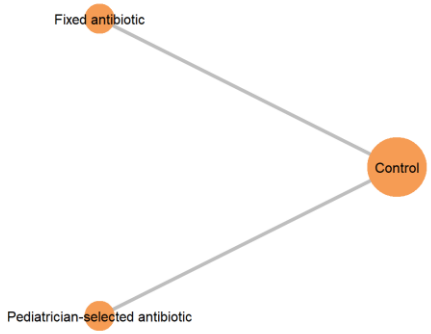
Supplemental Figure 14. Pairwise subgroup meta-analyses for incidence of UTI at 12 months. Subgroup VUR in younger than 2 years

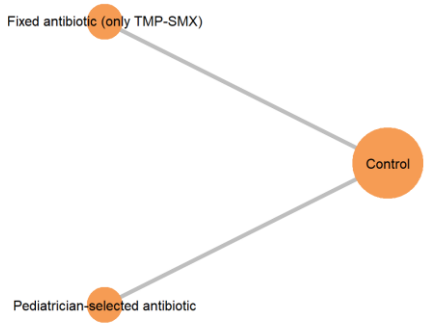


Supplemental Figure 15. Pairwise subgroup meta-analyses for incidence of UTI at 12 months. Subgroups Recurrent UTI

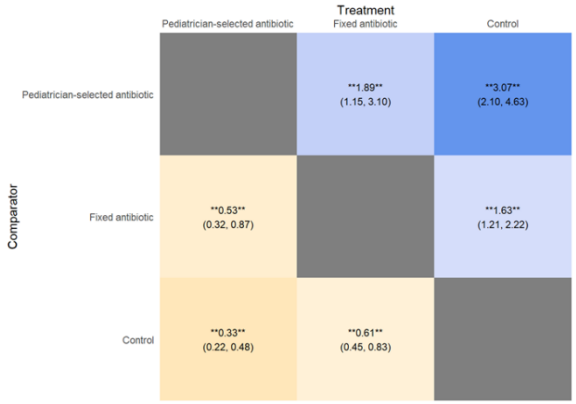


Supplemental Figures 16. Grouped NMA for recurrence of UTI at 6 months and 12 months

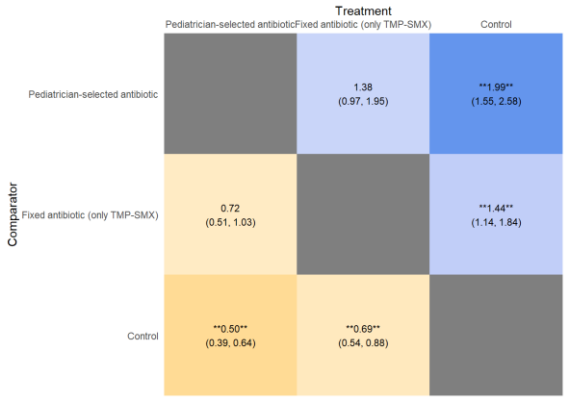




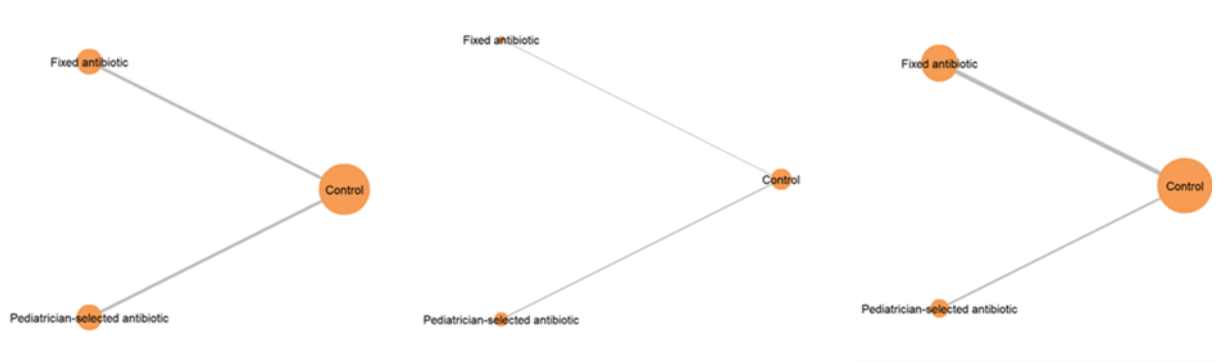
Supplemental Figures 17. League table for grouped NMA of UTI recurrence at 6 months



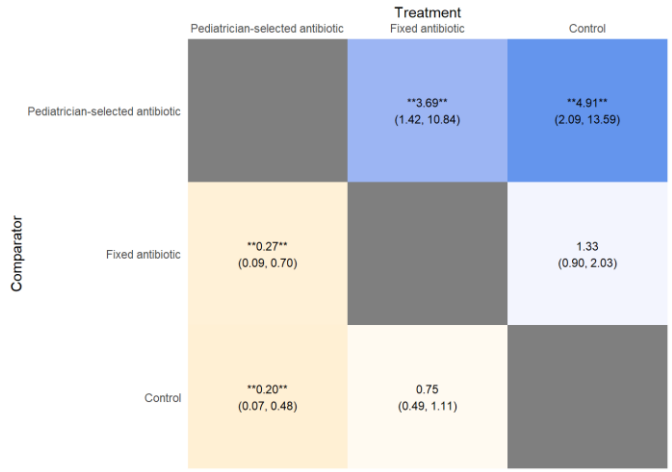
Supplemental Figures 18. League table for grouped NMA of UTI recurrence at 12 months



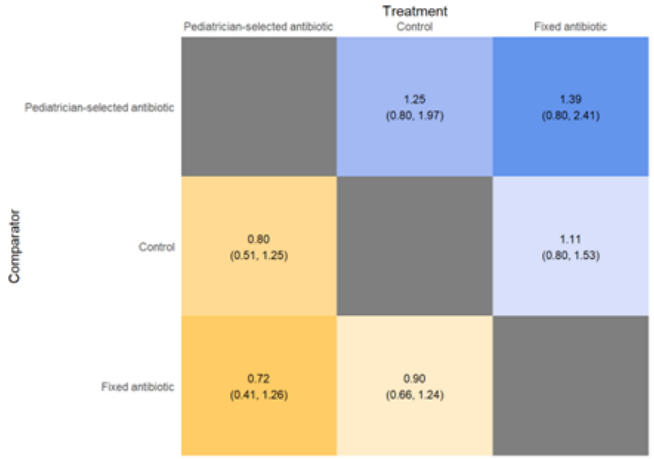
Supplemental Figures 19. Network plot for NMA for new kidney scar, asymptomatic bacteriuria and antimicrobial resistance



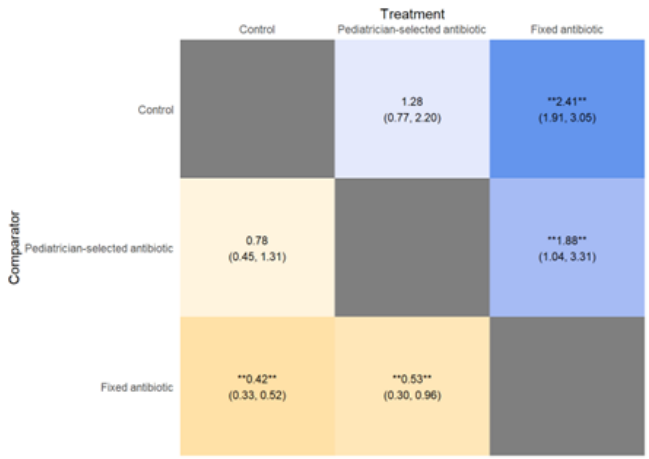
Supplemental Figures 20. League table for grouped NMA of asymptomatic bacteriuria



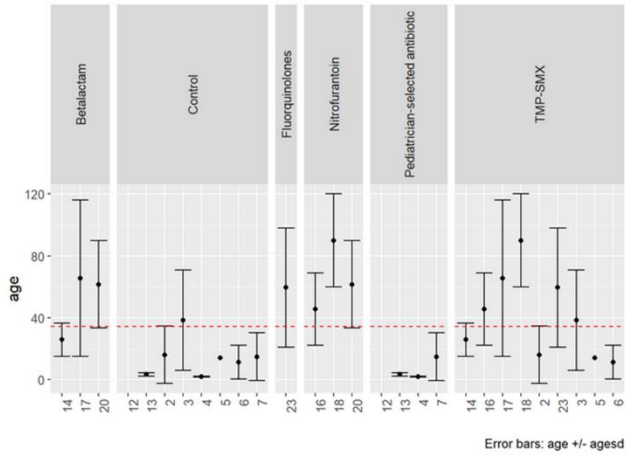
Supplemental Figures 21. League table for grouped NMA of new kidney scar



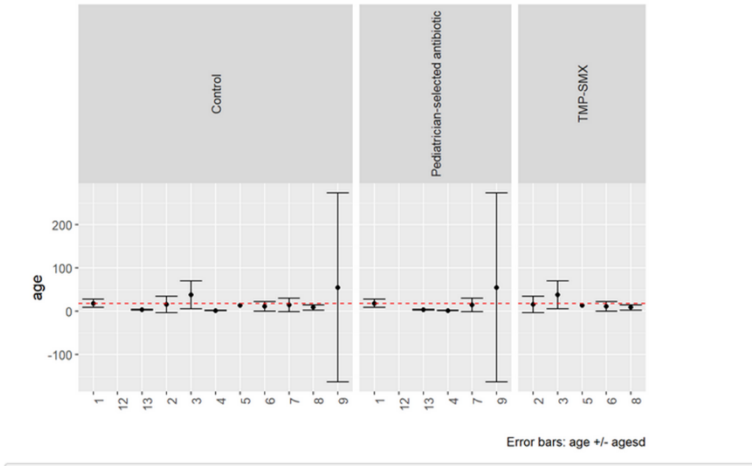
Supplemental Figures 22. League table for grouped NMA of antimicrobial resistance



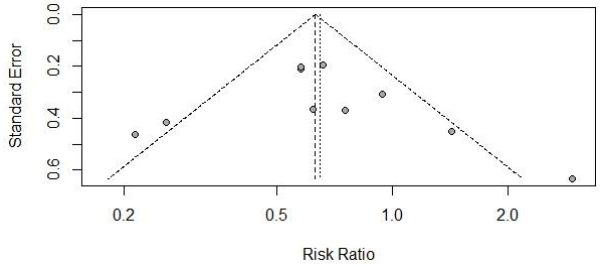
Supplemental Figures 23. Mean and standard error plot of recurrence at 6 months NMA



Supplemental Figures 24. Mean and standard error plot of recurrence at 12 months NMA



Supplemental Figures 25. Funnel plots for incidence of UTI at 12 months.



Supplemental information 3. Egger's test results for UTI recurrence at 12 months

```
Linear regression test of funnel plot asymmetry

Test result: t = 0.45, df = 8, p-value = 0.6621
Bias estimate: 0.6481 (SE = 1.4283)

Details:
- multiplicative residual heterogeneity variance (tau^2 = 2.6261)
- predictor: standard error
- weight:    inverse variance
- reference: Egger et al. (1997), BMJ
```