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Schwenger EM, Tejani AM, Loewen PS

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Probiotics for preventing urinary tract infections in adults and children.
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[Intervention Review]

Probiotics for preventing urinary tract infections in adults and children

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ABSTRACT

Background

Urinary tract infection (UTI) is a common bacterial infection that can lead to significant morbidity including stricture, abscess formation, fistula, bacteraemia, sepsis, pyelonephritis and kidney dysfunction. Mortality rates are reported to be as high as 1% in men and 3% in women due to development of pyelonephritis. Because probiotic therapy is readily available without a prescription, a review of their efficacy in the prevention of UTI may aid consumers in making informed decisions about potential prophylactic therapy. Institutions and caregivers also need evidence-based synopses of current evidence to make informed patient care decisions.

Objectives

Compared to placebo or no therapy, did probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality, when used to prevent UTI in susceptible patient populations?

Compared to other prophylactic interventions, including drug and non-drug measures (e.g. continuous antibiotic prophylaxis, topical oestrogen, cranberry juice), did probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality when used to prevent UTIs in susceptible patient populations?

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 21 September 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) of susceptible patients (e.g. past history of UTI) or healthy people in which any strain, formulation, dose or frequency of probiotic was compared to placebo or active comparators were included.

Data collection and analysis

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at comparing probiotics to no therapy, placebo, or other prophylactic interventions were included. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes.

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Main results

We included nine studies that involved 735 people in this review. Four studies compared probiotic with placebo, two compared probiotic with no treatment, two compared probiotics with antibiotics in patients with UTI, and one study compared probiotic with placebo in healthy women. All studies aimed to measure differences in rates of recurrent UTI.

Our risk of bias assessment found that most studies had small sample sizes and reported insufficient methodological detail to enable robust assessment. Overall, there was a high risk of bias in the included studies which lead to inability to draw firm conclusions and suggesting that any reported treatment effects may be misleading or represent overestimates.

We found no significant reduction in the risk of recurrent symptomatic bacterial UTI between patients treated with probiotics and placebo (6 studies, 352 participants: RR 0.82, 95% CI 0.60 to 1.12; I^2 = 23%) with wide confidence intervals, and statistical heterogeneity was low. No significant reduction in the risk of recurrent symptomatic bacterial UTI was found between probiotic and antibiotic treated patients (1 study, 223 participants: RR 1.12, 95% CI 0.95 to 1.33).

The most commonly reported adverse effects were diarrhoea, nausea, vomiting, constipation and vaginal symptoms. None of the included studies reported numbers of participants with at least one asymptomatic bacterial UTI, all-cause mortality or those with at least one confirmed case of bacteraemia or fungaemia. Two studies reported study withdrawal due to adverse events and the number of participants who experienced at least one adverse event. One study reported withdrawal occurred in six probiotic participants (5.2%), 15 antibiotic participants (12.2%), while the second study noted one placebo group participant discontinued treatment due to an adverse event.

Authors' conclusions

No significant benefit was demonstrated for probiotics compared with placebo or no treatment, but a benefit cannot be ruled out as the data were few, and derived from small studies with poor methodological reporting.

There was limited information on harm and mortality with probiotics and no evidence on the impact of probiotics on serious adverse events. Current evidence cannot rule out a reduction or increase in recurrent UTI in women with recurrent UTI who use prophylactic probiotics. There was insufficient evidence from one RCT to comment on the effect of probiotics versus antibiotics.

PLAIN LANGUAGE SUMMARY

Probiotics for preventing urinary tract infections in adults and children

Background

Urinary tract infections (UTIs) occur in kidneys, ureters, urethra or bladder. UTIs are one of the most common bacterial infections and can lead to other health problems.

Probiotics (live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host) are thought to work by preventing other infectious bacteria from climbing up the urinary tract and causing infection. We were interested in studying any form of probiotics (bacteria used to change balance of bacteria) compared with no treatment, antibiotics, hormone therapy, cranberry juice or other interventions in people at risk of UTI. To assess if probiotics were effective, we planned to measure how many people had recurrent UTIs.

Study characteristics

We conducted a literature search up to September 2015 and nine studies were eligible for inclusion according to our selection criteria. The nine studies reported data on 735 participants and investigated probiotics for preventing UTI: seven studies involved women or girls with recurrent UTIs, one looked at children with abnormal urinary tracts, and one investigated UTI in healthy women.

Key results

Generally, studies were poor quality with high risk of bias. Aside from the different populations, there were also many different species of probiotics used, different dosage forms such as vaginal and oral, and probiotics were given for varying lengths of time. All of these factors may have affected our results.

Most studies did not collect information on adverse effects so we were unable to estimate any harms associated with probiotic therapies. We found no significant reduction in the risk of recurrent symptomatic bacterial UTI between patients treated with probiotics and placebo and no significant reduction in the risk of recurrent symptomatic bacterial UTI was found between probiotic and patients treated with antibiotics.

Quality of the evidence

The currently available evidence shows no reduction in UTI using probiotics.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Probiotics compared with placebo or antibiotics for urinary tract infections (UTI)

Patient or population: adults and children at risk of UTI

Settings: outpatient

Intervention: probiotics

Comparison: placebo or antibiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Probiotics				
Symptomatic bacterial UTI in adults and children in patients with and without recurrent UTI **Probiotics versus placebo** (follow-up)	**395 per 1000**	**296 per 1000** (197 to 446)	**RR** 0.75 (0.50, 1.13)	352 (6)	⊕⊕⊖⊖ **low**	Risk of bias was assessed at unclear or high in most domains and suggest that results are imprecise or overestimate probiotic effects versus placebo
Symptomatic bacterial UTI in adults and children with recurrent UTI **Probiotics versus placebo** (follow-up)	**421 per 1000**	**315 per 1000** (227 to 425)	**RR** 0.74 (0.54, 1.01)	275 (4)	⊕⊕⊖⊖ **low**	Risk of bias was assessed at unclear or high in most domains and suggest that results are imprecise or overestimate probiotic effects versus placebo
Symptomatic bacterial UTI in women with recent UTI **Probiotics versus antibiotics** (follow-up)	**666 per 1000**	**745 per 1000** (632 to 885)	**RR** 1.12 (0.95, 1.33)	223 (1)	⊕⊕⊖⊖ **low**	Risk of bias was assessed at unclear or high in most domains and suggest that results are imprecise or overestimate probiotic effects versus antibiotics. Imprecision also due to small sample from only one RCT

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Symptomatic bacterial UTI in children with VUR **Probiotics versus placebo** (follow-up)	**270 per 1000**	**145 per 1000** (64 to 332)	**RR** 0.54 (0.24, 1.23)	96 (1)	⊕⊕⊖⊖ **low**	Risk of bias was assessed at unclear or high in most domains of and suggest that results are imprecise or overestimate probiotic effects versus placebo. Imprecision also due to small sample from only one RCT

*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

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.

UTi - urinary tract infection

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BACKGROUND

Description of the condition

Urinary tract infections (UTIs) are defined as infections of kidneys, ureters, urethra, or bladder due to bacterial colonisation. UTIs are one of the most common bacterial infections and can lead to significant morbidity including strictures, abscess formation, fistulas, bacteraemia, sepsis, pyelonephritis, and kidney dysfunction. Mortality rates are reported to be as high as 1% in men and 3% in women due to development of pyelonephritis. One in two women experience UTI at some point in their lifetime. UTI incidence in men is related to age (1.1% to 1.6% in the first 10 years of life, 5 to 8 infections/year/10,000 men up to age 50 years, and higher after age 50 due to prostate enlargement and subsequent complications) (Foxman 2003, Howes 2009; Howes 2010). Elderly people are more susceptible to asymptomatic UTI; prevalence is 30% in women and 10% in men per year in women and men (Richards 2004).

Several interventions have been studied for preventing UTI. Mixed results have been seen for intravaginal hormonal therapy for women and management of incontinence (Perrotta 2008; Ouslander 1995; Schnelle 1995). Improved urinary catheter technology and catheter management strategies have demonstrated efficacy in reducing UTI incidence (CDC 2000; Christensen 2001; Maki 2001; Richards 2001; Saint 2000). A systematic review of randomised controlled trials (RCTs) concluded that there is some evidence that cranberry juice reduces the incidence of UTIs in women (Jepson 2012). Prophylactic antibiotics have been shown to reduce the incidence of UTIs in non-pregnant women with recurrent UTIs (Albert 2004) and may reduce asymptomatic UTIs in children (Williams 2011).

Description of the intervention

Probiotics are defined as "a preparation of, or a product containing viable, defined micro-organisms in sufficient numbers, which alter the microflora (by implantation or colonisation) in a compartment of the host and by that exert beneficial health effects in this host" (Schrezenmeir 2001). There are a number of species and strains of probiotics available that are used in many formulations administered via several different routes.

How the intervention might work

Probiotic organisms (e.g. lactobacillus) are thought to establish a barrier against infectious pathogens ascending the urinary tract, colonising, and subsequently causing infection. The protective effects thought to be exerted by probiotics are thought to include reducing pathogen adherence, growth and colonisation, and modulating host defences (Bruce 1988; Hawthorn 1990; Heineman 2000; Osset 2001; Velraeds 1998).

Why it is important to do this review

A 2006 systematic review concluded that carefully selected strains of probiotics when tested in case-control studies and RCTs had mixed effects in terms of UTI prophylaxis (Falagas 2006). The authors concluded that there was some in vitro and in vivo evidence that probiotics restore normal vaginal flora and prevent recurrent UTI in women (Falagas 2006).

Probiotic therapy is readily available without prescription. A review of their efficacy in preventing UTIs may aid consumers and healthcare providers to make informed decisions about potential prophylactic therapy.

OBJECTIVES

Our review aimed to assess:

1. Compared to placebo or no therapy, do probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality, when used to prevent UTIs in susceptible patient populations?
2. Compared to other prophylactic interventions, including drug and non-drug measures (e.g. continuous antibiotic prophylaxis, topical oestrogen, cranberry juice), do probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality when used to prevent UTIs in susceptible patient populations?

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at comparing probiotics to no therapy, placebo, or other prophylactic interventions were included.

Types of participants

- Men, women, and children with histories of recurrent bacterial UTI (two episodes within the last two months)
- Men and women over the age of 60 years
- Pregnant women
- Men, women and children with an indwelling catheter or requiring intermittent catheterisation
- Men, women and children with an abnormal urinary tract (for example vesicoureteric reflux, urinary obstruction, dysfunctional voiding)
- Men and women resident in residential and long-term care facilities
- Men and women with asymptomatic bacteriuria.

Studies exclusively involving critically ill or immunosuppressed patients were excluded. Applicable patient data were extracted from studies with mixed populations.

Types of interventions

- All available probiotics in any formulation including tablets, capsules, food products (i.e. shakes, yogurt) for preventing UTIs in adults and children.
- Any study in which probiotics were used for the treatment (versus prevention) of suspected or proven bacterial UTI was excluded.
- Studies investigating prophylaxis with probiotics in combination with antibiotics were not included. These topics were beyond the scope of this review.

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Types of outcome measures

Primary outcomes

Numbers of patients with at least one symptomatic bacterial UTI in each group (as confirmed by a catheter specimen of urine, midstream urine specimen if possible, or a clean catch specimen and defined as > 10^5 CFU/mL, or as defined by authors).

Secondary outcomes

- Numbers with at least one asymptomatic bacterial UTI (confirmed by a catheter specimen of urine, midstream urine specimen if possible, or a clean catch specimen)
- Withdrawal due to adverse events
- Total adverse events
- All-cause mortality
- Numbers with at least one non-fatal serious adverse events
- Numbers with at least one confirmed case of bacteraemia or fungaemia.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register to 21 September 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. Titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however studies and reviews that potentially included relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and where necessary, the full text of these studies to determine which satisfied inclusion criteria. There were no language restrictions.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were to be translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancies among published versions was planned to be highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Dichotomous outcomes results were expressed as risk ratio (RR) with 95% confidence intervals (CI). All prespecified outcomes were dichotomous; therefore no analysis of continuous outcome data was necessary.

Unit of analysis issues

Data from all patients individually randomised to each intervention were included in the analyses. Care was taken to identify situations in which data had been censored or excluded or if data presented were the total number of events or the total number of patients with a first event. Authors were contacted for clarification if necessary. The rates of each outcome in the probiotic groups group were compared to the rate of that outcome in control groups to calculate risk differences. If the rates for an outcome were not provided, a narrative summary of data was presented. UTI rates were extracted for numbers of patients experiencing at least one UTI, not the number of UTIs in a treatment group.

Dealing with missing data

In general if there were missing data, the authors of the study were contacted for clarification to determine if details were available. If

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not, or if authors did not respond to requests, the worst outcome was imputed for all missing data points in the experimental treatment group (i.e. worst case scenario). A sensitivity analysis was performed to see if the effect size for any particular outcome was sensitive to conducting the worst case scenario with imputed data versus ignoring the missing data (i.e. using only the available data).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

A funnel plot was not created because of the few included studies; the resulting analysis would likely be underpowered to detect possible publication bias (Higgins 2011).

Data synthesis

Data were pooled using relative risks with the random-effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted for studies comparing probiotics with placebo or active comparators. In addition, a post-hoc subgroup analysis was conducted for different patient characteristics: adult women; children, and children with vesicoureteral reflux.

Sensitivity analysis

Sensitivity analysis was performed to test for robustness of the results. Analysis of the following categories was undertaken separately.

1. Studies without proper randomisation or concealment of allocation compared to those without these characteristics.
2. Studies performed without intention-to-treat (ITT) analysis compared to those with an ITT analysis.
3. Unblinded studies versus blinded studies.
4. Studies using different probiotic formulations.
5. The effects of probiotics when there is missing data for patients receiving probiotics, these patients are assumed to have had the worst possible outcome.

RESULTS

Description of studies

Results of the search

We identified 389 records. Following assessment of titles and abstracts, 28 full-text records were screened. Of these, nine studies (14 records) were included and eight studies (10 records) were excluded. Two ongoing studies were identified (NCT00781625; ProSCIUTTU Study 2014), one study is awaiting translation (Skerk 2010), and one study was identified prior to publication (Reid 1995). These four studies and will be assessed in a future update of this review (Figure 1).

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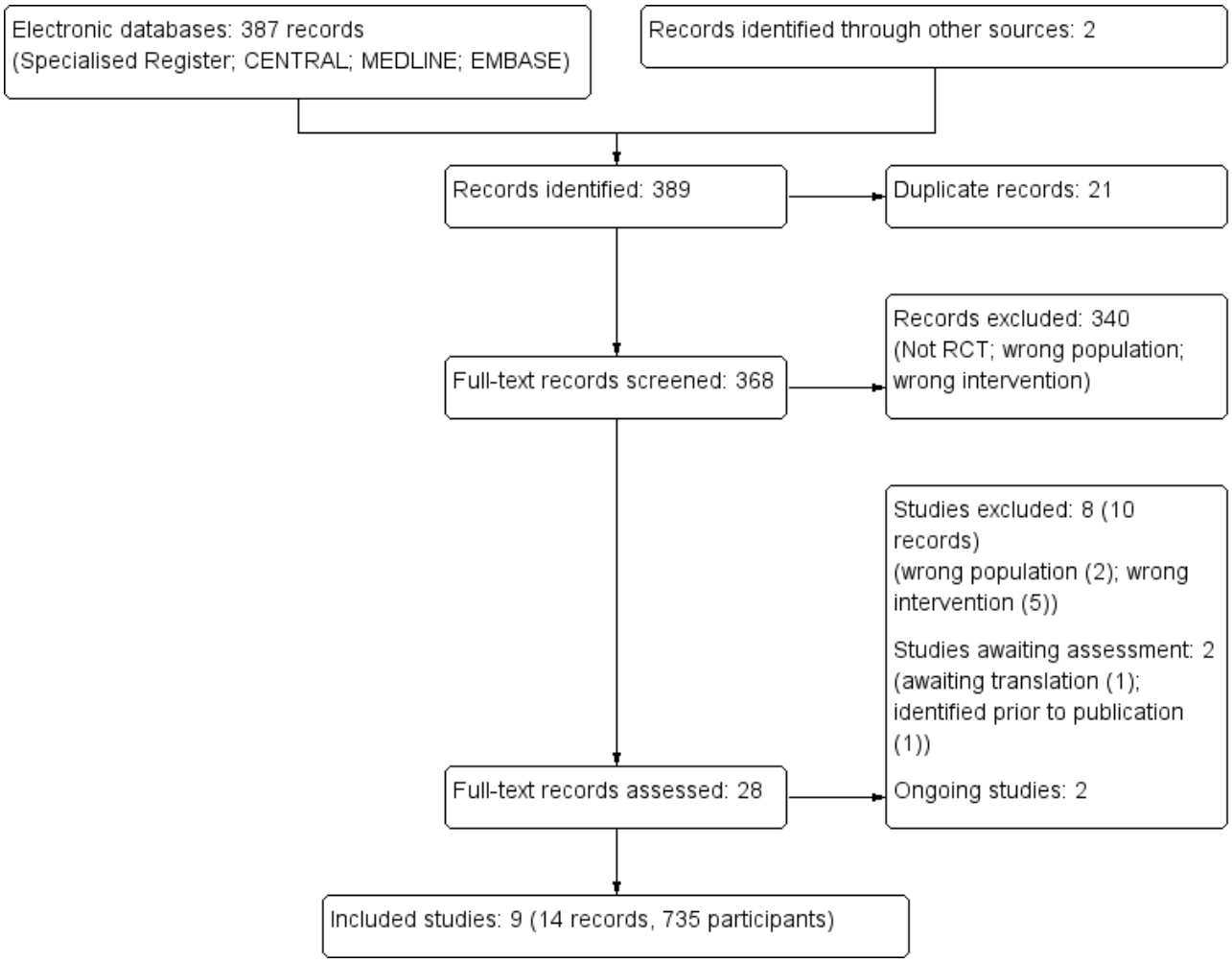
Figure 1. Study flow diagram



Included studies

We included nine studies in this review (Baerheim 1994; Czaja 2007; Ferrara 2009; Kontiokari 2001; Lee 2007a; NAPRUTI Study II 2006; Reid 1992; Reid 2003; Stapleton 2011).

Six studies compared probiotics with placebo (Baerheim 1994; Czaja 2007; Reid 1992; Stapleton 2011) or no comparator (Ferrara 2009; Kontiokari 2001); two studies compared probiotics with antibiotic prophylaxis in patients with UTI (one in adults (NAPRUTI Study II 2006) and one in children with VUR (Lee 2007a)); and one study compared probiotics with placebo in healthy women (Reid 2003).

Design

The included studies were parallel RCTs with a mix of active comparators, placebo or no comparators. Efficacy of the probiotics in placebo-controlled studies (Baerheim 1994; Czaja 2007; Ferrara 2009; Kontiokari 2001; Reid 1992; Stapleton 2011) could not be compared to studies that used effective prophylactic measures such as antibiotics (NAPRUTI Study II 2006). Placebo-controlled studies were therefore analysed separately from active comparator studies. The 'no comparator' arms of the Kontiokari 2001 and Ferrara 2009 studies were used to include them with the four studies comparing probiotics with placebo.

Based on Jepson 2012, it appears that cranberry juice cannot be recommended for the prevention of UTI due to small effect sizes and studies with significant biases that limit the reliability of the data. There is also no identified evidence that lingonberry juice alone or in combination with cranberry juice has proven efficacy or safety versus placebo for the prevention of UTI. It is for this reason that probiotics were not compared versus cranberry juice (Ferrara 2009) or cranberry-lingonberry juice (Kontiokari 2001).

Sample sizes

The smallest study included 30 participants (Czaja 2007) and the largest 252 participants (NAPRUTI Study II 2006). Most studies (60%) included 100 participants or fewer (Baerheim 1994; Czaja 2007; Ferrara 2009; Reid 1992; Reid 2003; Stapleton 2011).

Setting

All nine studies took place in outpatient settings.

Participants

Patient populations differed in terms of time since the last acute UTI and previous use of prophylactic antibiotics. Only Reid 2003 included exclusively healthy women. Three studies required participants with acute UTI at inclusion to be treated before

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commencing the study (Ferrara 2009; Kontiokari 2001; Stapleton 2011), Reid 2003 randomised women to acute antibiotic therapy before randomising them to prophylaxis; and three studies listed acute UTI or recent antibiotic use as exclusion criteria (Baerheim 1994; Czaja 2007; NAPRUTI Study II 2006). The study in children with VUR included children with persistent primary VUR following 12 months of antibiotic prophylaxis (Lee 2007a).

Interventions

The species and mode of administration of the probiotic intervention varied widely among studies, as did duration of therapy (eight weeks to 12 months). Details of formulations and species of probiotics in the studies are presented in Characteristics of included studies.

Outcomes

Only Reid 2003 did not report our primary outcome of UTI, although definitions varied by study (Characteristics of included studies). Few studies reported on our prespecified secondary outcomes. Four studies reported on adverse events (Czaja 2007; Reid 1992; Reid 2003; Stapleton 2011), and only two considered serious adverse events (Czaja 2007; NAPRUTI Study II 2006).

Excluded studies

Seven studies were excluded (Characteristics of excluded studies). Dani 2002 was conducted in a neonatal population; Colodner 2003 did not include an arm where participants did not receive a probiotic; Molander 1990 did not include investigation of a probiotic; and NCT00900653 studied a combination of probiotic and hormonal therapies. Manley 2007 and Pushkarev 2005 studied treatment rather than prophylaxis; Ranganathan 2009 enrolled people with chronic kidney disease (CKD) to determine if probiotics exerted renoprotective effects and reduced uraemia symptoms.

Risk of bias in included studies

NAPRUTI Study II 2006 was large and methods and events were adequately reported; however, most studies had small sample sizes and reported insufficient methodological detail to enable robust assessment (Figure 2; Figure 3).

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

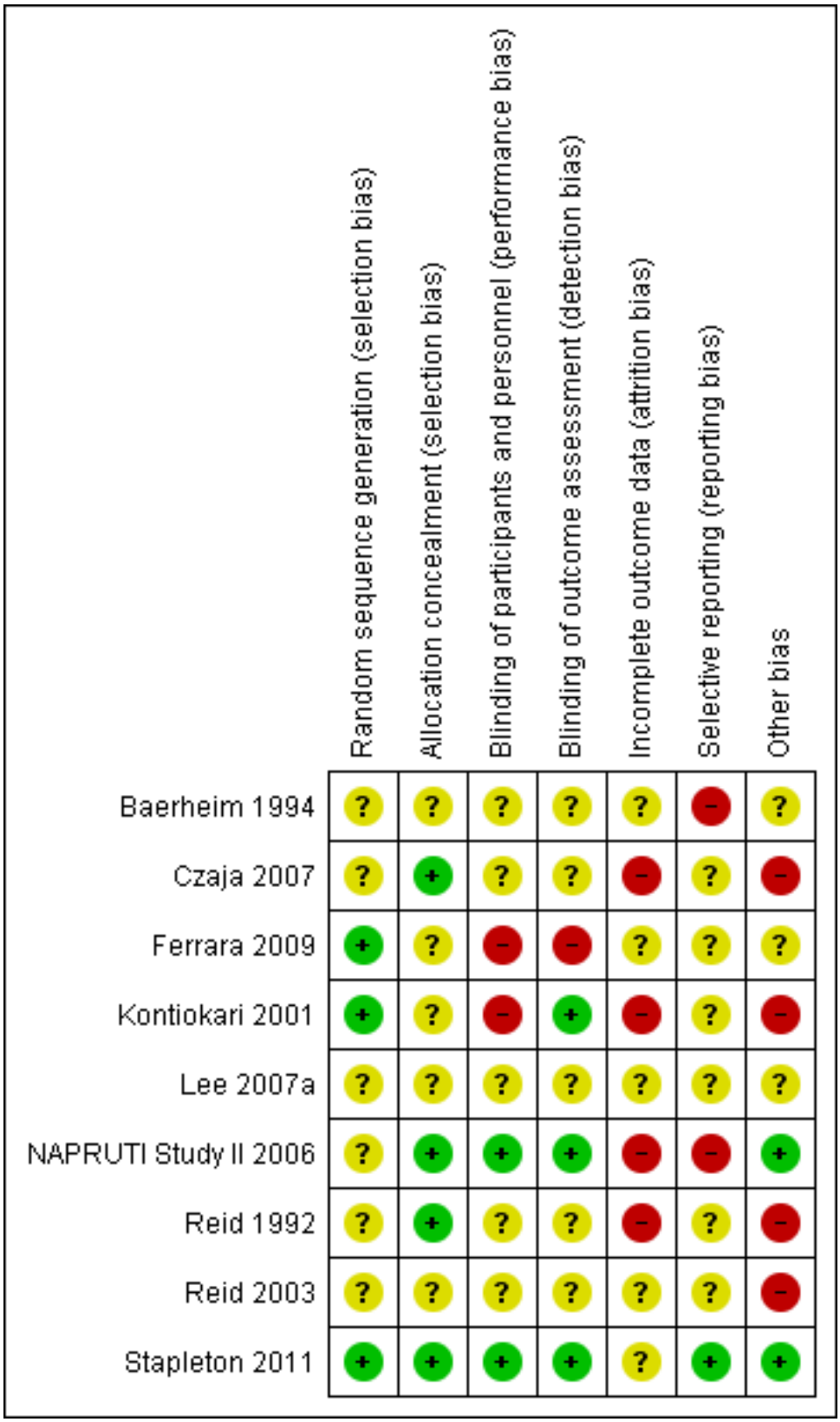

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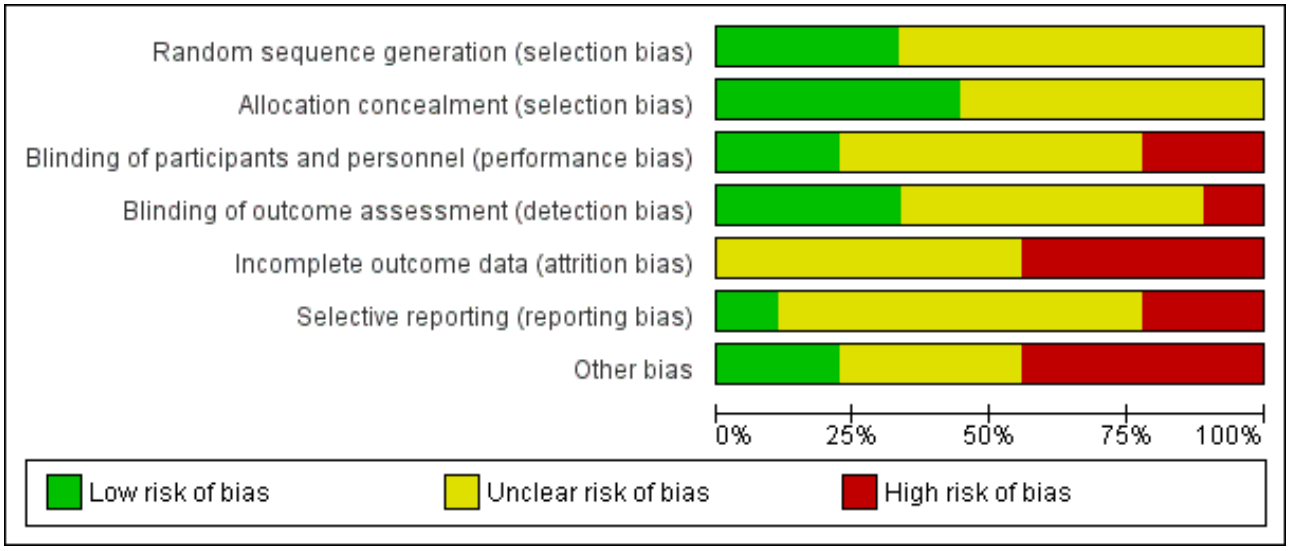
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Overall, there was a high risk of bias among the included studies. This meant that we were unable to draw firm conclusions or determine if any reported treatment effects may be misleading or represent overestimates.

Allocation

Three studies (Ferrara 2009; Kontiokari 2001; Stapleton 2011) reported on adequate methods of sequence generation and the other six studies (Baerheim 1994; Czaja 2007; Lee 2007a; NAPRUTI Study II 2006; Reid 1992; Reid 2003) did not describe sequence generation methods.

Four studies reported adequate allocation concealment (Czaja 2007; NAPRUTI Study II 2006; Reid 1992; Stapleton 2011). Allocation concealment was unclear for the remaining five studies.

Blinding

Two included studies were adequately described as double blind (NAPRUTI Study II 2006; Stapleton 2011), two were open label (Ferrara 2009; Kontiokari 2001) and there were insufficient data to assess blinding for the remaining studies; blinding was either not reported or lacked sufficient detail to determine who was blinded.

Incomplete outcome data

Satisfactory explanation was provided for changes in the number of participants for only one of the studies assessed (Czaja 2007). Reid 2003 had a significant proportion of their small study population excluded from analysis; attrition was significant and not explained satisfactorily in three studies (Kontiokari 2001; NAPRUTI Study II 2006, Stapleton 2011). Remaining studies lacked sufficient information to determine if attrition was likely to result in significant bias. Due to this incomplete follow-up, worst case scenarios were undertaken for both the probiotics in comparison to placebo analysis and the probiotics in comparison to antibiotics analysis.

Selective reporting

Many of the included studies either did not report secondary outcomes, or lacked sufficient detail in reporting secondary outcomes; many of our prespecified secondary outcomes were not addressed, including all-cause mortality and number with at least one confirmed case of bacteraemia or fungaemia.

We searched for published protocols for the included studies. Protocols were found for NAPRUTI Study II 2006 and Stapleton 2011. The outcomes reported in Stapleton 2011 aligned completely with the published protocol. The published report of the NAPRUTI Study II 2006 included several outcomes that were not prespecified in the protocol: mean number of antibiotic prescriptions for UTI treatment; and a subgroup analysis of mean number of clinical recurrences in women with complicated versus uncomplicated UTI.

Other potential sources of bias

Several studies were funded by manufacturing companies (Czaja 2007; Reid 1992), and one had an issue with supply that resulted in treatment duration inequality between the study arms (Kontiokari 2001). UTI definitions were fairly consistent among studies, although microbiological criteria ranged from at least 10^3 CFU/mL to 10^5 CFU/mL and clinical criteria were more stringent in some studies compared with others.

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcome

The primary outcome was to assess numbers of participants with at least one symptomatic bacterial UTI in each group (as confirmed by a catheter specimen of urine, midstream urine specimen if possible, or a clean catch specimen, and defined as > 10^5 CFU/mL or as defined by triallists).

Analyses were conducted according to probiotics in women and probiotics in children with VUR. Placebo-controlled studies were

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subdivided into studies that enrolled women and children who had recently been treated with antibiotics for UTI (Ferrara 2009; Kontiokari 2001; Reid 1992; Stapleton 2011) and studies enrolling participants who had previous UTIs (Baerheim 1994; Czaja 2007). We decided to first determine if probiotics exerted a positive effect versus placebo before analysing studies versus active comparators.

A meta-analysis of six studies that involved 352 randomised women and children demonstrated no significant reduction in the risk of recurrent symptomatic bacterial UTI between probiotics and placebo (Analysis 1.1 (6 studies, 352 participants): RR 0.82, 95% CI 0.60 to 1.12; I^2 = 23%), heterogeneity was low. The confidence interval for all studies suggests a range that includes a 15.8 % absolute decrease to a 4.7% absolute increase in the risk of recurrent bacterial UTI with probiotics versus placebo given that the placebo rate of recurrence was 39.5% over 8 to 52 weeks.

NAPRUTI Study II 2006 reported no significant difference in the rate of recurrent symptomatic bacterial UTI in women between probiotics and antibiotics (Analysis 2.1 (1 study, 223 women): RR 1.12, 95% CI 0.95 to 1.33).

Lee 2007a included children with VUR. There was no significant difference in the rate of recurrent symptomatic bacterial UTI between probiotics and antibiotics (Analysis 3.1 (1 study, 96 children): RR 0.54, 95% CI 0.24 to 1.23).

We analysed six month recurrent UTI data from Kontiokari 2001. However, the authors also reported recurrent UTI at 12 months; a sensitivity analysis demonstrated that the results of the meta-analysis did not change meaningfully if 12 month data were used. Three studies did not report on this outcome and this may have improved the precision of the effect size if the data were available. Stapleton 2011 reported 17 and 13 recurrent symptomatic bacterial UTIs for probiotics and placebo respectively. However, correspondence with the lead author indicated that two women in each arm of the study had symptomatic UTI but these were not confirmed with positive cultures; therefore, these events were excluded. We included these unconfirmed UTI in our analysis. In a sensitivity analysis, the results of the meta-analysis did not change meaningfully if only culture-confirmed UTI data were used.

Secondary outcomes

None of the included studies reported numbers of participants with at least one asymptomatic bacterial UTI, all-cause mortality or those with at least one confirmed case of bacteraemia or fungaemia. The only secondary outcomes of interest reported by the included studies were withdrawal due to adverse events, total adverse events and numbers of participants with at least one non-fatal serious adverse event.

Withdrawal due to adverse events was reported by NAPRUTI Study II 2006 and Stapleton 2011. NAPRUTI Study II 2006 reported that withdrawals due to adverse events occurred in six probiotic participants (5.2%) versus 15 antibiotic participants (12.2%). Stapleton 2011 noted that one placebo group participant discontinued treatment due to an adverse event.

Ferrara 2009, Kontiokari 2001, and Reid 1992 did not report adverse events. NAPRUTI Study II 2006 and Stapleton 2011 reported participants who experienced at least one adverse event but data were not meta-analysed because participants in the NAPRUTI Study II 2006 control group received an antibiotic, and Stapleton 2011 provided a placebo to control group participants. NAPRUTI Study II 2006 reported that 66 probiotic (57.4%) and 72 antibiotic participants (58.5%) respectively experienced at least one adverse event (the most commonly reported adverse effects in both groups were diarrhoea, nausea, vomiting, constipation and vaginal symptoms). Reid 2003 identified adverse events through a questionnaire that was sent to patients. They reported that no probiotic patients reported an adverse event however it is unclear how many comparator group patients experienced at least one adverse event; they only reported that 2 comparator patients reported yeast infections.

Stapleton 2011 reported that 28 probiotic (56%) and 25 placebo participants (50%) experienced at least one adverse event (the most common were vaginal discharge, itching and moderate abdominal discomfort).

Baerheim 1994 stated that treatment was well tolerated in both groups; four participants from the probiotic arm and one from placebo complained of discharge, with no other adverse effects noted.

Czaja 2007 documented a range of self-reported adverse effects including abnormal vaginal discharge, external genital irritation, vaginal candidiasis, vaginal odour, abdominal pain and dysuria. Abnormal vaginal discharge occurred in about half of all participants, but the overall frequency of adverse effects was low.

NAPRUTI Study II 2006 and Czaja 2007 reported serious adverse events. In NAPRUTI Study II 2006, no significant difference in serious adverse events was noted; 17 probiotic (14.8%) and 14 antibiotic participants (11.4%) experienced at least one serious adverse event.

Subgroup analyses

In a post-hoc subgroup analysis, there was no significant difference in recurrence of UTI between the subgroups of women without a UTI prior to enrolment compared (Analysis 1.1.1 (2 studies, 77 participants): RR 1.12, 95% CI 0.65 to 1.93; I^2 = 0%) with those with UTI being treated with antimicrobials at enrolment (Analysis 1.1.2 (4 studies, 275 participants): RR 0.74, 95% CI 0.52 to 1.05; I^2 = 16%). The overall pooled estimate for all studies in both subgroups was not significantly different from the pooled estimate of each subgroup (Test for subgroup differences: Chi^2 = 1.57, df = 1 (P = 0.21), I^2 = 36.5%).

Sensitivity analyses

Sensitivity analyses were planned to determine if treatment effects on recurrent symptomatic bacterial UTI rates differed in studies based on a number of variables. Removal of studies that were open label or that had unclear allocation concealment did not change the effect of probiotics on recurrent symptomatic bacterial UTI however only few studies had unclear allocation concealment (Baerheim 1994; Ferrara 2009; Kontiokari 2001) or were open label (Ferrara 2009; Kontiokari 2001) and it was felt that sensitivity analyses would not be informative and maybe misleading.

Sensitivity analysis was also conducted for symptomatic bacterial UTI involving Czaja 2007, NAPRUTI Study II 2006 and Stapleton 2011 as these three studies suggested that not all randomised patients were included in the UTI analysis; hence we wanted to see the impact of imputing data for a worst case scenario. In this analysis

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all missing patients in one group were assumed to have had UTI, and those missing from the other group were assumed to not have had UTI. For the comparison of probiotics versus placebo, the effect did not change using a worst case scenario for probiotics (Analysis 1.2: RR 0.94, 95% CI 0.63 to 1.39; I^2 = 49%). For the comparison of probiotics versus antibiotics, a worst case scenario for antibiotics of the NAPRUTI Study II 2006 now demonstrated that fewer probiotic patients experienced a recurrent symptomatic bacterial UTI versus antibiotics (25 antibiotic patients, Analysis 2.3; RR 0.83, 95% CI 0.74 to 0.94). When the worst case scenario analysis for probiotics was conducted, more probiotic patients had recurrent symptomatic bacterial UTI (5 probiotic patients, Analysis 2.2; RR 1.19, 95% CI 1.01 to 1.40).

DISCUSSION

Summary of main results

This review included nine studies involving a total of 735 participants. No significant difference in risk of recurrent UTI was seen for probiotics in comparison to placebo or antibiotic prophylaxis in either women or children. There was no significant difference found between probiotics and either placebo or antibiotic prophylaxis for harms.

The studies included in this review were generally small and of poor quality with inconsistent and limited reporting of harm, and as such the data are insufficient to exclude either a benefit or harm from probiotics versus either placebo or antibiotic prophylaxis.

Only NAPRUTI Study II 2006 compared probiotics and antibiotics; no significant difference in the rate of recurrent symptomatic bacterial UTI or harm was found between groups.

Adverse events, when reported, were poorly described with insufficient data to perform statistical evaluation. Overall the frequency of reported side effects was low and mild in nature (e.g. vaginal discomfort).

We suggest caution when interpreting the lack of a subgroup difference in Analysis 1.1, as there were too few studies to be able to confidently conclude the presence or absence of subgroup differences.

There was insufficient evidence to comment on the differences in effects of probiotics in children and women as only one study included only children (Ferrara 2009) and a subgroup analysis may be misleading.

Overall completeness and applicability of evidence

We included nine studies in this review ranging from 30 to 252 participants totalling a relatively small overall sample of 735 participants. No statistically significant difference was seen in recurrent symptomatic bacterial UTI. Given the low overall quality and quantity of data available a decrease or increase in recurrent symptomatic UTI cannot be ruled out.

There was some reporting bias in that several studies did not report on symptomatic bacterial UTI, and very limited information on harm. For example, Reid 2003 did not report symptomatic bacterial UTI recurrence; these data would have been valuable because the meta-analysis of studies that did report this outcome did not rule out a clinically important increased or decreased risk. These studies also included different patient populations resulting in the analysis of separate small groups of studies instead of the evidence base as a whole.

There was insufficient evidence to determine if probiotics provide a therapeutic advantage over placebo for susceptible patient populations (e.g. previous history of UTI, women, school-aged girls, men with enlarged prostates, and the elderly). Included studies randomised primarily women and young girls with no studies enrolling men with enlarged prostates or the elderly.

Quality of the evidence

Our assessments suggested an unclear or high risk of bias (Figure 2; Figure 3, Summary of findings for the main comparison). As such, evidence has been downgraded to low for all outcomes listed in the Summary of findings for the main comparison. This suggested that treatment effects were likely overestimated and that better methodological control is required in future research. Future studies should model methods from Stapleton 2011. Adequate allocation concealment was described in four of the eight included studies; only two studies were double blinded. Attrition bias was of concern in all but one included study.

The available evidence varied in terms of probiotic used, route of delivery and duration of therapy. These differences make drawing specific conclusions difficult and likely contribute to the heterogeneity seen in the pooled estimates. Most included studies did not systematically collect adverse event information, thus we could not draw conclusions regarding the potential harms associated with these therapies.

Potential biases in the review process

Our literature search included several international databases and search criteria were intentionally broad to identify as many potentially relevant articles as possible. We did not exclude studies published in languages other than English. We contacted study authors for missing information.

Agreements and disagreements with other studies or reviews

Grin 2013 is the most recent systematic review on this topic. Grin 2013 included five RCTs, against nine included in this review. Our assessment is that Grin 2013 limited their search to include only studies that included premenopausal women with history of UTI. Our inclusion criteria did not limit to a particular population nor did it exclude studies in healthy people (e.g. Reid 2003 enrolled healthy women and met our inclusion criteria). Grin 2013 concluded that it was possible that certain strains lactobacillus-containing suppositories could prevent recurrent UTI in premenopausal women. Grin 2013 suggested that more RCTs were required to be certain of the effect on recurrent UTI. In addition, Grin 2013 suggested that current RCTs did not enable definitive conclusions to be made about the safety of probiotics.

In general, our conclusions are similar to Grin 2013 in that more RCTs are required to determine the net health impact of probiotics, although our conclusions apply to a broader patient population.

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AUTHORS' CONCLUSIONS

Implications for practice

There was insufficient evidence to determine whether or not probiotics reduce the risk of further UTIs in susceptible patient populations (e.g. previous history of UTI, women, school-aged girls, men with enlarged prostates, and the elderly) compared with either placebo or antibiotic prophylaxis. This conclusion is limited by the generally high risk of bias in the small number of studies available, with limited reporting on harm, mortality and serious adverse events.

Implications for research

Larger well-designed RCTs are necessary and should include recurrent symptomatic UTI as primary outcome. The potential for probiotics to reduce recurrent UTI in women and children with recently-treated UTI compared to those without a recently-treated UTI should be explored. Optimal probiotic agents, dosing and duration of therapy also remain to be determined. Studies should be placebo-controlled or contain both a placebo and active antibiotic control group. Emphasis should be placed on the measurement of harm as well as development of recurrent UTI during follow-up. We feel that until there is sufficient evidence that probiotics provide a therapeutic advantage over placebo, future studies should not focus on active comparators alone.

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baerheim 1994

Methods	• Study design: parallel RCT • Study duration: subjects were recruited from February 1990 and followed up for 6 months (final follow-up date unknown)
Participants	• Setting: outpatient • Country: Norway • Female with 3 or more episodes of distal urinary symptoms during the previous 12 months, with at least 1 episode having been medically verified as a lower UTI. Subjects should have been free of infection at inclusion, and no antibiotic treatment should have been taken during the previous 3 weeks • Number: treatment group (25); control group (22) • Mean age, 95% CI (years): treatment group (36.9, 33.6 to 40.2); control group (35.1, 30.7 to 39.5) • Exclusion criteria: pregnancy at inclusion or during study period, use of a diaphragm, any complicating illness (e.g. diabetes, cancer, urinary tract obstruction)

Interventions	Treatment group
	• Vaginal suppositories containing *L. casei v rhamnosus* (Gynophilus (R))
	  ◦ At least 7.5 x 10^8 live *L. Casei v rhamnosus* per suppository, twice weekly for 26 weeks
	Control group
	• Placebo vaginal suppositories
	  ◦ Solid semisynthetic glycerides (97.3%) and colloidal silica (2.7%) twice weekly for 26 week

Outcomes	• Occurrence of distal urinary symptoms
	  ◦ defined as dysuria, urinary frequency, and/or suprapubic discomfort
	• Acute lower UTI
	  ◦ defined as the presence of all of the following: acute lower urinary symptoms, leucocyturia (≥ 5 leucocytes/HPF), bacteriuria (≥ 10^4 CFU/mL) of uropathogens, or any amount of *Staphylococcus saprophyticus*

Notes	• Organon A/S, Oslo, Norway provided drug and funding support
	• PI contacted 7 May 2012 to clarify several questions, and responded 10 May 2012:
	  ◦ The random number sequence was generated by the pharmaceutical company producing the vaginal suppositories. Allocation concealment was ensured through packages sent to physicians by patient serial number. One patient withdrew from the study early, from the placebo arm, prior to experiencing an event, with no data collected
	  ◦ We also requested clarification regarding information sent from physicians who were seen by patients presenting with lower UTI symptoms to investigators. These physicians were provided with dip-slides and a registration form which was pre-addressed to the investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Baerheim 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Double-blind..." Page 240 - Materials and methods. Not described further
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "One was later excluded on her own request before she started to use the vaginal suppositories." Page 240 - Results 1/48 lost prior to initiation of therapy. Authors did not report to which arm the patient had been randomised
Selective reporting (reporting bias)	High risk	Main outcome reported with non-significant difference between groups. Two outcomes described in the methods (compliance and causative pathogen) were not reported and no explanation was given. No protocol published or in a clinical trial registry
Other bias	Unclear risk	Organon A/S, Oslo, Norway provided drug and funding support Limited reporting of harm. Control group had a significant increase in *Lactobacilli*, intervention group did not - explained as regression to mean. Page 240 - Results

Czaja 2007

Methods	• Study design: parallel RCT • Study duration: recruitment date unknown, patients were followed for 6 months (final follow-up date unknown)
Participants	• Setting: outpatient • Country: USA • Female with three or more uncomplicated UTIs diagnosed in the past year, or 2 uncomplicated UTIs diagnosed in the past 6 months; regular menstrual cycles, or amenorrhoea for at least 6 months secondary to use of a hormonal contraceptive; a normal Pap smear documented in the last year or at the baseline clinic visit; abstinence from sexual activity or participation in a mutually monogamous sexual relationship; use of birth control; agreement not to use other intravaginal products; agreement not to use tampons or have intercourse between the baseline and first follow-up visit, and capability to understand English and provide informed consent • Number: treatment (15); control (15) • Median age, range (years): treatment group (23, 18 to 35); control group (21, 19 to 32) • Exclusion criteria: history of urologic abnormality, recent urologic surgery or urinary catheterization; history of complicated pyelonephritis, or renal calculi, hysterectomy; recent STI or bacterial vaginosis; risk factors for STI and HIV; history of recurrent genital herpes; menses anticipated within 10 days; pregnancy; lactation; recent antibiotic or antifungal use; diabetes or other immunocompromised state; drug or alcohol abuse; use of (NuvaRing); prior use of the study drug; allergy to study drug components; abnormal initial pelvic examination
Interventions	Treatment Group • *L. crispatus* CTV-05 vaginal suppository ◦ Dose of 5 x 10^8 CFU to be inserted daily for 5 days Control Group

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Czaja 2007 *(Continued)*

	• Placebo suppositories ○ Preservation matrix and maltodextrins to be inserted daily for 5 days

Outcomes	• Cystitis
	  ○ not defined
	• Adverse drug reactions
	  ○ collected on a prepared diary card during the first week of the study
	• Serious adverse drug reactions
	  ○ not defined

Notes	• Osel, Inc. (Palo Alto, CA, USA) supplied *L. crispatus* CTV-05 vaginal suppositories and placebo • The study was funded by DK PO1 053369 (WES) and R01DK070906 (AES) • Attempted to contact the authors 7 May 2012 but the email delivery failed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Pre-packaged by manufacturer according to randomisation schedule and supplied to the study site sequentially labelled with subject number
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "In a double-blind fashion..." "*L. crispatus* CTV-05 and placebo suppositories were similar in appearance..." Page 2 - Study design. Authors did not specify who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "In a double-blind fashion..." Page 2 - Study design. Authors did not specify who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Low risk at four weeks - 30/30 women completed the baseline, 1- and 4-week visits. High risk at six months - 9/15 intervention and 10/15 control patients completed the 6-month phone call - figure 1, page 3 Two intervention patients completed treatment over 6 days instead of 5 and one control patient used 6 suppositories over 6 days - page 2 results
Selective reporting (reporting bias)	Unclear risk	All outcomes appear to be reported, adverse drug reactions reporting may have been subjective. There was no published protocol or clinical trial registry protocol available
Other bias	High risk	Product supplied by the manufacturer

Ferrara 2009

Methods	• Study design: parallel RCT • Study duration: recruitment began in June 2005 and patients were followed for 6 months (final follow up date unknown)
Participants	• Setting: ambulatory clinic • Country: Italy

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Ferrara 2009 *(Continued)*

	• Female with more than 1 UTI due to *E. coli* (> 10^5 CFU/mL in clean voided midstream urine) in the last year before the beginning of the study, without antimicrobial prophylaxis • Number: treatment group (27); control group 1 (28); control group 2 (29) • Mean age, range: 7.5, 3 to 14 years • Exclusion criteria: structural obstructions and/or deformities of the urinary tract or impaired kidney function

Interventions	Treatment group
	• *Lactobacillus GG* drink
	  ◦ 4 x 10^7 CFU of *Lactobacillus GG*/100 mL 5 days/month for 6 months
	Control group 1
	• Cranberry concentrate juice
	  ◦ 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate in 50 mL water without sugar additives daily for 6 months
	Control group 2
	• No intervention

Outcomes	• Recurrence of UTI ◦ defined as urine culture with growth > 10^5 CFU/mL upon presentation with the following UTI symptoms (frequency, urgency, dysuria, haematuria, nocturia, fever or back or hip pain)

Notes	• Source of funding not reported
	• Authors contacted 7 May 2012. We did not receive a response:
	  ◦ Which allocation concealment techniques were used if any?
	  ◦ We have assumed that the trial is open-label, is that correct?
	  ◦ Of those who dropped out, if they had an event prior to dropping out, were they still counted in the analysis?
	  ◦ The manuscript mentions that some participants were treated with antibiotic prophylaxis/therapy – did this include only treatment for acute UTI or did it also include prophylaxis of future UTIs with antibiotics?

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised into three groups using random number tables"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four children dropped out of the study (5%) for poor compliance to the protocol (one from cranberry juice arm, one from *Lactobacillus GG* arm and two

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Ferrara 2009 *(Continued)*

		from control arm). Unclear how data was collected or accounted for in these patients.
Selective reporting (reporting bias)	Unclear risk	No reporting on any of the secondary outcomes of this review. No protocol was published or in a clinical trial registry
Other bias	Unclear risk	Patients had previously treated UTIs Funding unclear Described 5/27 probiotic intervention patients and 7/29 control patients requiring "antimicrobial prophylaxis" Page 371 - Results. Not further described

Kontiokari 2001

Methods	• Study design: parallel RCT • Study duration: Recruitment began in 1993 with 12 months of follow-up (final follow up date unknown
Participants	• Setting: outpatient • Country: Finland • Women with a UTI caused by *E. coli* (> 10^5 CFU/mL in a clean voided midstream urine) • Number: treatment group (49); control group 1 (50); control group 2 (50) • Mean age ± SD (years): treatment group (32 ± 9.8); control group 1 (30 ± 11.8); control group 2 (29 ± 10.5) • Exclusion criteria: current use of antimicrobial prophylaxis

Interventions	Treatment group
	• *Lactobacillus GG* drink
	  ◦ 4 x 10^{10} CFU/mL *Lactobacillus GG*/100 mL given 5 days/week for 1 year
	Control group 1
	• Cranberry-lingonberry juice
	  ◦ 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate in 50 mL water without sugar additives daily for 6 months
	Control group 2
	• No intervention

Outcomes	• First recurrence of symptomatic UTI ◦ defined as urine culture with growth > 10^5 CFU/mL upon presentation with the following UTI symptoms (frequency, urgency, dysuria, haematuria, nocturia, fever or back or hip pain)

Notes	• Funded by Emil Aaltonen, Juho Vaini and Alma and KA Snellman Foundations
	• The authors were contacted 7 May 2012 and responses received on 8 May 2012:
	  ◦ Which allocation concealment techniques were used?
	  ■ The codes were kept in brown nontransparent envelopes which were opened only after a patient had decided to take part into the trial
	  ■ The encrypting of codes was broken only after all data were fed into the computers. The staff members recruiting the patients were not participating in the process of randomisation or sealing the envelopes. Neither was the staff analysing the data participating in the process of recruitment

Risk of bias

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Kontiokari 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomly allocated into three groups by using tables of random numbers and a block technique..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement Quote: "...a block technique using a block size of 6." Page 1 - Study population and design
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...laboratory staff were unaware as to which of the treatment groups participants belonged." Page 2 - Study population and design
Incomplete outcome data (attrition bias) All outcomes	High risk	4/50 cranberry patients, 4/50 lactobacillus patients and 5/50 control patients dropped out of the study Page 2 – Results “One subject in the lactobacillus group who was taking postcoital antimicrobials was excluded from the analysis” Page 2 “Only cultures with > 10^5 CFU/mL were accepted and recorded as events. A urine sample with no bacterial growth was required between two episodes before they were regarded as separate events. Women who had three or more episodes in six months were offered antimicrobial prophylaxis” Page 2 – Each woman contributed days at risk until she dropped out, became pregnant, or started antibiotic prophylaxis Page 3 – "We also did an analysis based on the assumption that women who dropped out of the intervention groups subsequently had a UTI whereas those left in the control group did not, but the differences in the occurrence of the first urinary tract infection remained significant (P = 0.046 at 12 months). We also did an analysis based on the assumptions that women who dropped out of the intervention groups subsequently had a UTI whereas those who left the control group did not, but the differences in the occurrence of the first UTI remained significant (P = 0.046 at 12 months)"
Selective reporting (reporting bias)	Unclear risk	Outcome appears to be completely reported including some additional outcomes that had not been pre-specified. No published protocol or clinical registry protocol available.
Other bias	High risk	"The dosing frequencies and the duration of the prophylaxis were based on the availability of the products from our suppliers.” Page 1 Lactobacillus given for one year but juice given for six months Page 1

Lee 2007a

Methods	• Study design: parallel RCT

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Lee 2007a *(Continued)*

	• Study duration: recruitment began in 2002 with 1e year of follow-up (final follow up date unknown)
Participants	• Setting: outpatient • Country: South Korea • Persistent primary VUR after antibiotic prophylaxis for one year • Number: treatment group (60); control group (60) • Mean age ± SD (years): treatment group (19 ± 12.1); control group (21 ± 11.4) • Sex (M/F): treatment group (44/16); control group (45/15) • Exclusion criteria: secondary VUR

Interventions	Treatment group
	• *Lactobacillus acidophilus*
	  ○ 1 X 10^8 CFU/g (ATCC 4356) twice daily for 1 year
	Control group
	• TMP/SMX
	  ○ 2/10 mg/kg given once daily before sleep for 1 year

Outcomes	• Recurrent UTI ○ defined as significant bacteriuria (> 10^3 CFU/mL in suprapubic aspiration or > 10^5 in catheterised or clean voided midstream samples) in symptomatic children (fever, dysuria, pus in diaper)

Notes	• Source of funding not reported
	• The authors were contacted 7 May 2012 with the following questions> No response was received:
	  ○ How was the random number sequence generated?
	  ○ Which allocation concealment techniques were used if any?
	  ○ Which individuals were blinded in the trial? Participants and physicians?
	  ○ Were the outcome assessors also blinded?
	  ○ Would it be possible to know how many of the participants attended outpatient clinics other than the study sites?

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...prospectively randomised..." "...stratified randomisation..." Page 1316 - Patients and methods Not described further
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/60 in the probiotic group and 1/60 in the antibiotic group were noncompliant (< 80%) Pg1316 - Patients and methods

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Lee 2007a *(Continued)*

		May have gone to outpatient clinics, therefore may have missed some cases of UTI – Page 1317 No loss to follow up described
Selective reporting (reporting bias)	Unclear risk	Outcome appears to be completely reported. Causative organism was not pre-specified but was reported. No published or clinical trial registry protocol available
Other bias	Unclear risk	No placebo comparator Unclear funding source

NAPRUTI Study II 2006

Methods	• Study design: parallel non-inferiority RCT • Study duration: recruitment began in 2005 and patients were followed for 12 months (final follow up date unknown)
Participants	• Setting: outpatient • Country: The Netherlands • Postmenopausal women with a history of at least 3 self-reported symptomatic UTIs in the last year • Number: treatment group (125); control group (127) • Mean age ± SD (years): treatment group (63.2 ± 8.6); control group (65.4 ± 8.3) • Exclusion criteria: UTI symptoms at inclusion; antibiotic use in the past 2 weeks; relevant interactions of TMP/SMX with concurrent medications or contraindications; kidney failure and kidney transplant

Interventions	Treatment group
	
	• *L. rhamnosus* GR-1 and *L. reuteri* RC-14
	  ◦ One capsule containing at least 10^9 CFU twice daily and 1 placebo at night for 12 months
	
	Control Group
	
	• TMP/SMX
	  ◦ 480 mg tablet at night and 1 placebo capsule twice daily for 12 months

Outcomes	• Number of symptomatic UTIs
	  ◦ defined as a UTI based on a woman's report of symptoms, usually dysuria, frequency, and/or urgency
	• Proportion of patients with at least one clinical recurrence
	  ◦ defined as above
	• *E. coli* resistance to TMP/SMX
	  ◦ isolated from faeces and urine of asymptomatic women at 1 and 12 months
	• Number of microbiologically confirmed symptomatic UTIs
	  ◦ defined as a UTI based on the combination of clinical symptoms and bacteriuria (at least 10^3 CFU/mL bacteria in midstream urine)
	• Proportion of patients with at least one microbiologic recurrence
	  ◦ defined as above
	• Proportion of patients experiencing SAEs

Notes	• Placebo capsules (not the active substances) were donated by Chr Hansen A/S, Denmark • Funding was provided by grant 62000017 from the Netherlands Organization for Health Research and Development

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NAPRUTI Study II 2006 *(Continued)*

- Authors were contacted 19 April 2013 with the following questions. Response received 16 May 2013:
  - When asked for the number of people having at least 1 recurrence of UTI in each treatment group
    - From baseline, 108 and 115 women started prophylaxis on TMP/SMX and lactobacilli, respectively. In these groups, 72 and 86 women experienced at least 1 UTI, respectively. Note however that the data were censored, since women could drop out of the study before the end of the 12 month prophylaxis period. Therefore, we used the Kaplan-Meier estimator to correct for this censoring. Note also that the raw numbers are therefore less usable e.g. for performing a meta-analysis, since those are not corrected for the censoring
  - Drop out before the end of the 12 month prophylaxis period occurred in 22 patients in the TMP/SMX and 35 patient in the *Lactobacilli* group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The coordinating centre prepared drug randomisation lists for each study site in advance." Page 705 - Intervention No further description
Allocation concealment (selection bias)	Low risk	"Concealed randomisation was ensured using computer-aided block randomisation (block size remained masked), with prestratification by centre and presence (yes/no) of complicating host factors"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, double dummy. Asked patients to guess which arm they had been in after the study ended
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Analysis on main outcome measures was performed before breaking the treatment code." Page 706 - Statistical Analysis
Incomplete outcome data (attrition bias) All outcomes	High risk	"...performed an intention-to-treat analysis among participants who took at least one dose of study medication." Page 706 - Statistical Analysis 12 TMP/SMX patients and 2 *Lactobacilli* patients were not included in the analysis as they withdrew consent prior to receiving the assigned medication Two additional TMP/SMX patients were lost to follow up as were six *Lactobacilli* patients. Complete follow up data for six months: TMP/SMX 100/115, *Lactobacilli* 98/123 Complete follow up data for 12 months: TMP/SMX 90/115, *Lactobacilli* 84/123 Complete follow up data for 15 months: TMP/SMX 88/115, *Lactobacilli* 79/123
Selective reporting (reporting bias)	High risk	The registered protocol states Primary outcomes 1. The numbers of recurrences of symptomatic UTI 2. Time to first occurrence of antibiotic resistance in urine or faeces Secondary outcomes 1. Incidence of other infections 2. Incidence of asymptomatic bacteriuria events 3. Quality of life 4. Costs per prevented UTI

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NAPRUTI Study II 2006 *(Continued)*

		However, the published report states the following outcomes were measured (and these were not mentioned in the protocol): Mean number of antibiotic prescriptions for treatment of UTIs and subgroup analysis of mean number of clinical recurrences in women with complicated versus uncomplicated UTIs
Other bias	Low risk	The study appears to be free of other sources of bias

Reid 1992

Methods	• Study design: parallel RCT • Study duration: recruitment date not reported, patients were followed for 6 months (final follow up date unknown)
Participants	• Setting: outpatient • Country: Canada • Premenopausal women with signs and symptoms of an acute lower UTI with dysuria, frequency, urgency, or nocturia, but no flank pain or fever and positive screening results for bacteriuria using a leukocyte esterase strip • Number: treatment group (19); control group (21) • Mean age ± SD: 23 ± 4.4 years • Exclusion criteria: pregnancy; diabetes; known allergy to fluoroquinolones or TMP/SMX; history of urinary cancer or other urinary tract abnormalities; use of medications other than the study medications

Interventions	Treatment group
	• *Lactobacillus casei* var *rhamnosus* GR-1 and *Lactobacillus fermentum* B-54 vaginal suppository
	  ◦ 1.6 x 10^9 organisms/capsule, intravaginally, twice a week for 2 weeks then at the end of each of the next 2 months
	Control group
	• Sterilised skim milk placebo vaginal suppository
	  ◦ intravaginally, twice a week for 2 weeks then at the end of each of the next 2 months

Outcomes	• UTI recurrence
	  ◦ defined as both asymptomatic and symptomatic bacteriuria with urine cultures performed routinely during follow up visits
	• Adverse effects
	  ◦ determined by questioning the patients about signs of rash, vomiting, diarrhoea, nausea, irritation, or discharge

Notes	• Funding was provided by grants from Merck-Frosst, Canada and University Research Incentive Fund of Ontario, Canada
	• The authors were contacted 7 May 2012 with the following questions:
	  ◦ Did the patients enrolled in this trial have a history of recurrent UTI?
	  ◦ How was the random number sequence generated?
	  ◦ Which of the groups involved in the trial were blinded?
	  ◦ No response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...each patient randomly received one capsule..." Page 12 - Study design

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Reid 1992 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation was blinded randomly by hospital pharmacists
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	"Six patients decided not to take suppositories..." Page 13 - Results "...31 of the original 41 patients complied well..." Page 13 - Results "...nine did not return for long-term follow up so could not be included in recurrent UTI analysis" Table Page 13
Selective reporting (reporting bias)	Unclear risk	All outcomes appear to be reported in full. No published protocol cited or available.
Other bias	High risk	Sponsored by Merck Frosst Used skim milk placebo – unknown effect on promotion or inhibition of UTI or lactobacillus growth/colonisation

Reid 2003

Methods	• Study design: parallel RCT • Study duration: recruitment date not reported, patients were followed up for 90 days (final follow up date unknown)
Participants	• Setting: outpatient • Country: Canada • Women with no history of urogenital infection in the previous 12 months, no urogenital abnormalities and not on any medications, reporting to physicians in full health • Number: treatment group (32); control group (32) • Mean age, range: 35, 19 to 46 years • Exclusion criteria: not reported

Interventions	Treatment group
	• *L. rhamnosus* GR-1 and *L. fermentum* RC-14
	  ◦ Freeze-dried > 10^9/strain/vial in gelatin capsules orally once daily for 60 days
	Control group
	• Calcium carbonate placebo
	  ◦ Orally once daily for 60 days

Outcomes	• Adverse events ◦ Gathered on completion of the study through a questionnaire
Notes	• Funding provided by Proctor and Gamble, NSERC and Kidney Foundation of Canada • No reporting of symptomatic bacterial UTI

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Reid 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly allotted to receive either a freeze dried capsule containing the *L. rhamnosus* GR-1 and *L. fermentum* RC-14 or calcium carbonate placebo by mouth once daily for 60 days"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The subjects and investigators were blinded to the therapy." No mention of double-dummy methods or details of how people were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	No protocol registered or published
Other bias	High risk	Funded by Procter and Gamble

Stapleton 2011

Methods	• Study design: parallel RCT • Study duration: recruitment began in February 2006 and patients were followed up for 10 weeks (final follow up date unknown)
Participants	• Setting: outpatient • Country: USA • Premenopausal women aged 18 to 40 years with current, symptomatic uncomplicated cystitis (dysuria, frequency or urgency and pyuria, and positive urine culture ≥ 10^2 CFU/mL of one or more uropathogen or ≥10^5 CFU/mL *Lactobacillus* as a single organism); participants also had at least one prior symptomatic UTI treated within the past 12 months • Number: treatment group (50); control group (50) • Median age, range (years): treatment group (21, 18 to 31); control group (21, 18 to 36) • Exclusion criteria: current complicated cystitis or pyelonephritis; history of urologic abnormality or renal calculi and various other concomitant conditions

Interventions	Treatment group
	• Lactin-V gelatin capsules with no applicator
	  ○ 108 CFU/mL vaginally, once daily for 5 days
	Control group
	• Placebo vaginal suppositories
	  ○ Vaginally, once daily for 5 days

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Stapleton 2011 *(Continued)*

Outcomes	• Adverse events
	  ◦ obtained through a structured interview at 1 week and 10 weeks
	• Recurrent cystitis
	  ◦ defined as development of acute cystitis symptoms and urine culture

Notes	• Funding provided by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Research in Women's Health, National Institutes of Health
	• Can you explain why 2 people from each group were not included in this analysis? And do you know if they were ever assessed for symptomatic UTI?
	  ◦ These women had symptomatic episodes for which they were treated empirically, without a urine culture result. They were excluded due to the lack of culture confirmation for a treated symptomatic episode during their follow-up.
	• In the flow sheet, a few more people didn't complete the 10 weeks (43 versus 50 and 44 versus 50...what happened to them and why were they not included? Was any information on their outcomes collected?
	  ◦ They did not attend the last scheduled follow-up visits. Some had recurrences before they were LTFU. Those that did not have recurrences recorded were assumed to have been negative for a recurrence in the main ITT analysis, since our clinic is their main health care provider. Per protocol analyses was also performed and yielded similar results.
	• How many people in each group had specimens that they saved because the clinic was closed and were any unusable?
	  ◦ With the exception of UTIs during evenings or weekends, most specimens were collected during clinic hours. For UTI episodes occurring outside of clinic hours, patients had a Vacutainer set for collecting and storing urine for culture. The 4 UTI episodes in item 2 above were events where the UTI occurred when the clinic was closed and the urine was either not collected or was unusable.
	• Note: Telephone conversation with Pacita Roberts and Ann Stapleton 10 January 2013
	  ◦ There were no cases of bacteraemia, fungaemia or any deaths or SAEs during the trial
	  ◦ 50 patients per group were used as the denominators for the adverse effect data
	  ◦ All those participating in outcome assessment, data analysis, patient care, and the patients themselves, were blinded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study participants were randomly assigned to Lactin-V or placebo by use of a computer-generated randomised number system in blocked assignments to achieve equal sample sizes in both groups"
Allocation concealment (selection bias)	Low risk	"The assigned intervention substance (Lactin-V or placebo) was packaged in identically appearing packets according to assignment and sequential study number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Confirmed with author (telephone, 10 January 2013) that everyone associated with patient care, data analysis, study interventions or outcome assessment was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Confirmed with author (telephone, 10 January 2013) that everyone associated with patient care, data analysis, study interventions or outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two people in each group were not included in the final analysis for UTI. Reason submitted by study team (email communication 10 January 2013): "These women had symptomatic episodes for which they were treated empirically, without a urine culture result. They were excluded due to the lack of culture confirmation for a treated symptomatic episode during their follow-up."

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Stapleton 2011 *(Continued)*

		In the flow sheet, a few more people did not complete the 10 weeks follow-up (43 versus 50 probiotic patients and 44 versus 50 control patients) "They did not attend the last scheduled follow-up visits. Some had recurrences before they were LTFU. Those who did not have recurrences recorded were assumed to have been negative for a recurrence in the main ITT analysis, since our clinic is their main health care provider. Per protocol analyses was also performed and yielded similar results"
Selective reporting (reporting bias)	Low risk	Registered protocol aligns with published report
Other bias	Low risk	Grant funded

CFU - colony forming units; CI - confidence intervals; HIV - human immunodeficiency virus; HPF - high power field; ITT - intention-to-treat; LTFU - loss to follow-up; PI - primary investigator; RCT - randomised controlled trial; SAE - serious adverse event; SD - standard deviation; STI - sexually transmitted infection; TMP/SMX - trimethoprim/sulphamethoxazole; UTI - urinary tract infection; VUR - vesicoureteric reflux

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Colodner 2003	Same product used as intervention in both study arms
Dani 2002	Neonatal population
Manley 2007	Probiotic was used for treatment, not prophylaxis
Mohseni 2013	Not probiotic monotherapy (combined with antibiotics)
Molander 1990	Intervention used was a hormone product, not a probiotic
NCT00900653	Intervention was a combination of low dose oestriol and *Lactobacilli*
Pushkarev 2005	Probiotic was used for treatment, not prophylaxis
Ranganathan 2009	Enrolled patients had CKD. Probiotics were tested for renoprotective effects and to relieve symptoms of uraemia. Patients were not selected for their susceptibility for UTI

CKD - chronic kidney disease; UTI - urinary tract infection

Characteristics of studies awaiting assessment *[ordered by study ID]*

Reid 1995

Methods	
Participants	
Interventions	
Outcomes	
Notes	Full-text article currently not available

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Skerk 2010

Methods	RCT
Participants	N = 117. Probiotic = 56; control = 61 Inclusion criteria: lower UTI (dysuria, polyuria, urgency) symptoms, identical microbiological findings or cervical swab and urinary culture, leucocyturia, ultrasound ruling out urinary tract abnormalities Exclusion criteria were not reported
Interventions	All participants received antimicrobial therapy for seven days then Acidophilus probiotic orally for three months and vaginally for seven days simultaneously or no treatment
Outcomes	Recurrent cystitis
Notes	Abstract only available in English and the manuscript is yet to be translated (Croatian)

UTI - urinary tract infection

Characteristics of ongoing studies *[ordered by study ID]*

NCT00781625

Trial name or title	Probiotics/Lactobacillus as a Prophylactic Aid in Recurrent Bacterial Cystitis in Women. A randomised, Prospective, Double-Blinded, Placebo Controlled, Multi-Center Study
Methods	Double-blind, randomised, parallel efficacy study
Participants	Women aged 18 to 70 years with more than three UTIs in the previous year, without urinary tract abnormalities. For complete Inclusion and exclusion criteria see http://www.clinicaltrials.gov/ct2/show/NCT00781625
Interventions	Oral UREX-cap-5 Vaginal UREX-cap-5 Oral placebo Y cap G-3 Vaginal placebo Y cap G-3
Outcomes	Primary outcomes • Reduction in number of episodes of lower UTI over six months • Improvement of QoL over six months Secondary outcomes • Improvement of immune function over six months • Effects are non-dependent of nutritional status over six months • Effects are non-dependent of known factors contributing to UTIs over six months • Decrease inflammation in the urinary bladder epithelium over six months • Normalises vaginal microflora over six months
Starting date	October 2008

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NCT00781625 *(Continued)*

Contact information	Caroline Ursin Skagemo, MD Gunn Iren Meling, PhD, MD
Notes	Email from author 26 March 2013. No data to report

ProSCIUTTU Study 2014

Trial name or title	A multicenter randomised double-blind, double-dummy placebo-controlled study to assess the efficacy, safety and cost-utility of Probiotic prophylaxis of spinal cord injury Urinary Tract Infection. A Therapeutic Trial (ProSCIUTTU)
Methods	Double-blind, multicenter, double-dummy, randomised, placebo-controlled study
Participants	Men or women with spinal cord injury suffering from recurrent UTI resulting from multi-resistant organisms. Men or women with stable multiple sclerosis or cerebral vascular disease, with documented neurogenic bladder on video urodynamic assessment, who also suffer from recurrent UTI resulting from multi-resistant organisms. For complete inclusion and exclusion criteria see http://www.anzctr.org.au/ACTRN12610000512022.aspx
Interventions	Oral probiotic, two lactobacillus/Bifidobacterium capsules daily for six months Oral placebo, two capsules daily for six months
Outcomes	Primary • Time to first symptomatic UTI and total number of UTIs over the six month period Secondary • Change of multi-resistant organism colonisation status in the nares, rectum, groin or urine • Quality of life measure with economic evaluation using the SF36, SF36 walk-wheel and SF6D questionnaire • St Marks Incontinence, Cleveland Constipation, Basic and Extended International Bowel Surveys
Starting date	August 2010
Contact information	Dr Bon San Bonne Lee Spinal Injuries Unit, Prince of Wales Hospital, Randwick, Australia
Notes	Email sent 26 March 2013 requesting study publication or an update

UTI - urinary tract infection

DATA AND ANALYSES

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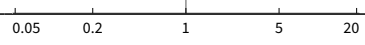
Comparison 1. Probiotics versus placebo in adults and children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic bacterial UTI	6	352	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.12]
1.1 Versus placebo	2	77	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.65, 1.93]
1.2 Versus placebo with recurrent UTI	4	275	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.52, 1.05]
2 Worst case scenario - symptomatic bacterial UTI	6	352	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.63, 1.39]
2.1 Versus placebo	2	77	Risk Ratio (M-H, Random, 95% CI)	3.71 [0.12, 112.47]
2.2 Versus placebo with recurrent UTI	4	275	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.60, 1.19]

Analysis 1.1. Comparison 1 Probiotics versus placebo in adults and children, Outcome 1 Symptomatic bacterial UTI.

Study or subgroup	Probiotics n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Versus placebo					
Baerheim 1994	14/25	11/22		24.23%	1.12[0.65,1.93]
Czaja 2007	0/15	0/15			Not estimable
Subtotal (95% CI)	**40**	**37**		**24.23%**	**1.12[0.65,1.93]**
Total events: 14 (Probiotics), 11 (Comparator)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.41(P=0.68)					
1.1.2 Versus placebo with recurrent UTI					
Ferrara 2009	11/26	18/27		25.67%	0.63[0.38,1.07]
Kontiokari 2001	19/45	18/46		27.52%	1.08[0.66,1.77]
Reid 1992	3/14	8/17		7.19%	0.46[0.15,1.4]
Stapleton 2011	9/50	15/50		15.39%	0.6[0.29,1.24]
Subtotal (95% CI)	**135**	**140**		**75.77%**	**0.74[0.52,1.05]**
Total events: 42 (Probiotics), 59 (Comparator)					
Heterogeneity: Tau^2=0.02; Chi^2=3.58, df=3(P=0.31); I^2=16.31%					
Test for overall effect: Z=1.69(P=0.09)					
Total (95% CI)	**175**	**177**		**100%**	**0.82[0.6,1.12]**
Total events: 56 (Probiotics), 70 (Comparator)					
Heterogeneity: Tau^2=0.03; Chi^2=5.17, df=4(P=0.27); I^2=22.65%					
Test for overall effect: Z=1.27(P=0.2)					
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.21), I^2=36.51%					



Favours probiotics — Favours comparator

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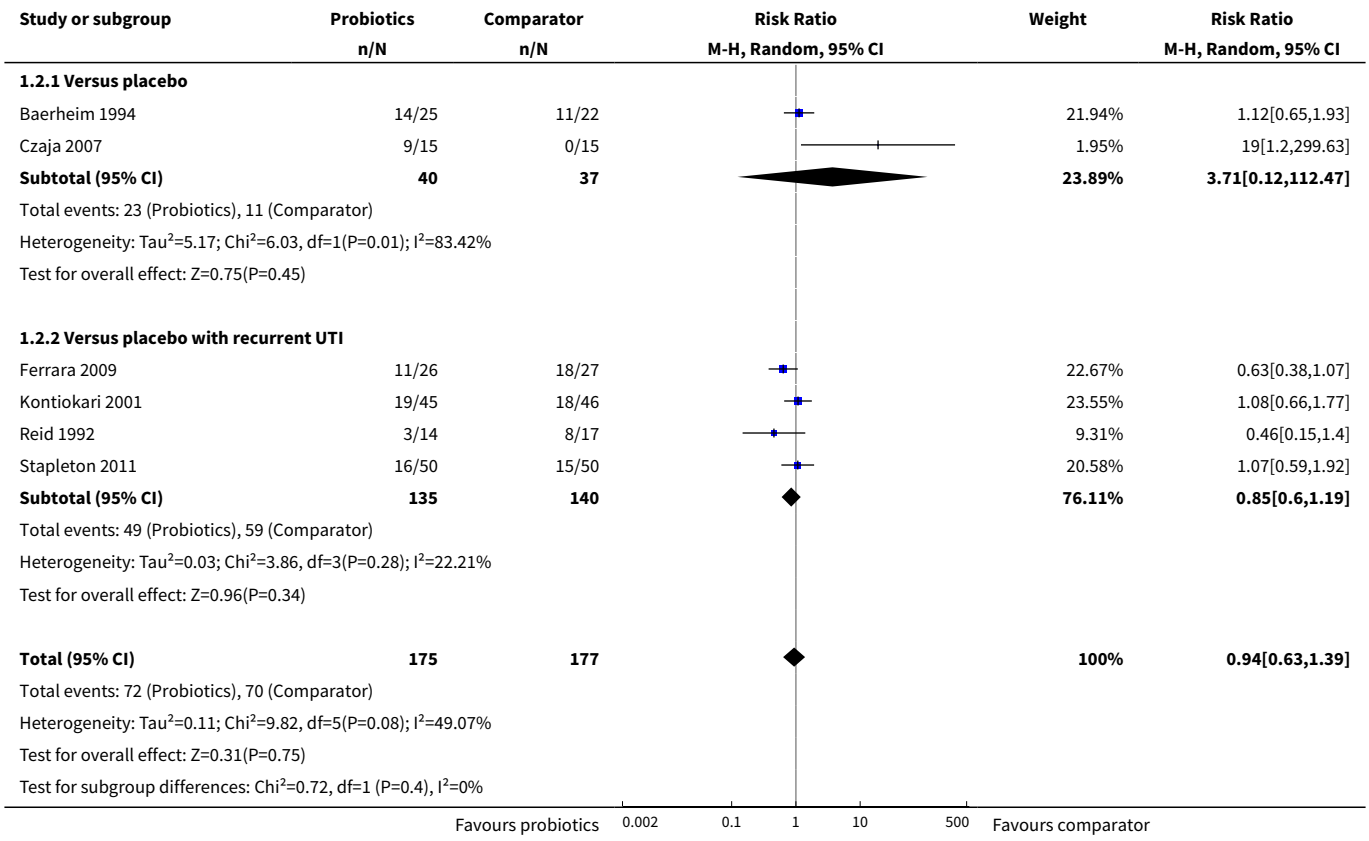
Analysis 1.2. Comparison 1 Probiotics versus placebo in adults and children, Outcome 2 Worst case scenario - symptomatic bacterial UTI.



Comparison 2. Probiotics versus antibiotics in women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic bacterial UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Versus antibiotics with recent UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Worst case scenario probiotics - symptomatic bacterial UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Versus antibiotics with recent UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Worst case scenario antibiotics - symptomatic bacterial UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Versus antibiotics with recent UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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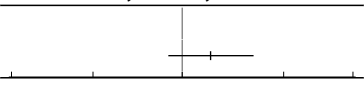
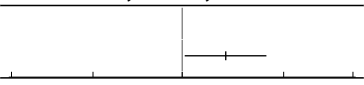
Analysis 2.1. Comparison 2 Probiotics versus antibiotics in women, Outcome 1 Symptomatic bacterial UTI.

Study or subgroup	Probiotics n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.1.1 Versus antibiotics with recent UTI				
NAPRUTI Study II 2006	86/115	72/108		1.12[0.95,1.33]



Analysis 2.2. Comparison 2 Probiotics versus antibiotics in women, Outcome 2 Worst case scenario probiotics - symptomatic bacterial UTI.

Study or subgroup	Probiotics n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.2.1 Versus antibiotics with recent UTI				
NAPRUTI Study II 2006	91/115	72/108		1.19[1.01,1.4]



Analysis 2.3. Comparison 2 Probiotics versus antibiotics in women, Outcome 3 Worst case scenario antibiotics - symptomatic bacterial UTI.

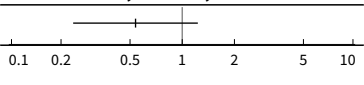
Study or subgroup	Probiotics n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.3.1 Versus antibiotics with recent UTI				
NAPRUTI Study II 2006	86/115	97/108		0.83[0.74,0.94]

Comparison 3. Probiotics versus control in children with vesicoureteric reflux

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic bacterial UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Probiotics versus control in children with vesicoureteric reflux, Outcome 1 Symptomatic bacterial UTI.

Study or subgroup	Probiotic n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lee 2007a	7/48	13/48		0.54[0.24,1.23]



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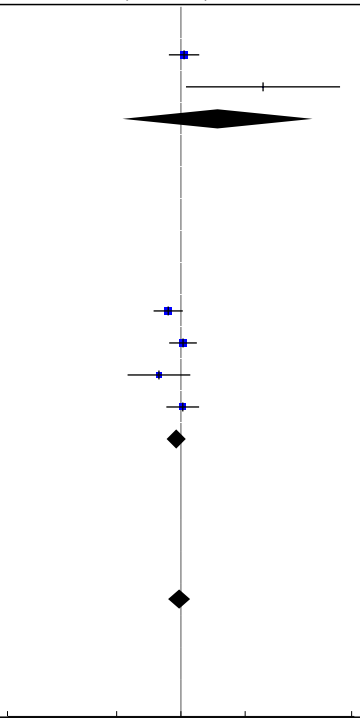
Comparison 4. Worst case scenario imputation - symptomatic bacterial UTI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Placebo comparison	6	352	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.63, 1.39]
1.1 Versus placebo	2	77	Risk Ratio (M-H, Random, 95% CI)	3.71 [0.12, 112.47]
1.2 Versus placebo with recurrent UTI	4	275	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.60, 1.19]
2 Antibiotic comparison - worst case probiotics	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Versus antibiotics with recent UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Antibiotic comparison - worst case antibiotics	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Versus antibiotics with recent UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Worst case scenario imputation - symptomatic bacterial UTI, Outcome 1 Placebo comparison.

Study or subgroup	Probiotic n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Versus placebo					
Baerheim 1994	14/25	11/22		21.94%	1.12[0.65,1.93]
Czaja 2007	9/15	0/15		1.95%	19[1.2,299.63]
Subtotal (95% CI)	**40**	**37**		**23.89%**	**3.71[0.12,112.47]**
Total events: 23 (Probiotic), 11 (Comparator)					
Heterogeneity: Tau^2=5.17; Chi^2=6.03, df=1(P=0.01); I^2=83.42%					
Test for overall effect: Z=0.75(P=0.45)					
4.1.2 Versus placebo with recurrent UTI					
Ferrara 2009	11/26	18/27		22.67%	0.63[0.38,1.07]
Kontiokari 2001	19/45	18/46		23.55%	1.08[0.66,1.77]
Reid 1992	3/14	8/17		9.31%	0.46[0.15,1.4]
Stapleton 2011	16/50	15/50		20.58%	1.07[0.59,1.92]
Subtotal (95% CI)	**135**	**140**		**76.11%**	**0.85[0.6,1.19]**
Total events: 49 (Probiotic), 59 (Comparator)					
Heterogeneity: Tau^2=0.03; Chi^2=3.86, df=3(P=0.28); I^2=22.21%					
Test for overall effect: Z=0.96(P=0.34)					
Total (95% CI)	**175**	**177**		**100%**	**0.94[0.63,1.39]**
Total events: 72 (Probiotic), 70 (Comparator)					
Heterogeneity: Tau^2=0.11; Chi^2=9.82, df=5(P=0.08); I^2=49.07%					
Test for overall effect: Z=0.31(P=0.75)					



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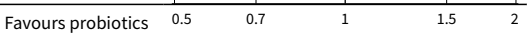
Study or subgroup	Probiotic n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.72, df=1 (P=0.4), I²=0%					

Analysis 4.2. Comparison 4 Worst case scenario imputation - symptomatic bacterial UTI, Outcome 2 Antibiotic comparison - worst case probiotics.

Study or subgroup	Probiotics n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 Versus antibiotics with recent UTI				
NAPRUTI Study II 2006	91/115	72/108		1.19[1.01,1.4]



Analysis 4.3. Comparison 4 Worst case scenario imputation - symptomatic bacterial UTI, Outcome 3 Antibiotic comparison - worst case antibiotics.

Study or subgroup	Probiotics n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.3.1 Versus antibiotics with recent UTI				
NAPRUTI Study II 2006	86/115	97/108		0.83[0.74,0.94]

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Probiotics, this term only 2. probiotic*:ti,ab,kw in Clinical Trials 3. MeSH descriptor Lactobacillus explode all trees 4. Lactobacill*:ti,ab,kw in Clinical Trials 5. Yakult:ti,ab,kw in Clinical Trials 6. Actimel:ti,ab,kw in Clinical Trials 7. ProViva:ti,ab,kw in Clinical Trials 8. Cultura:ti,ab,kw in Clinical Trials 9. Verum:it,ab,kw in Clinical Trials 10.MeSH descriptor Bifidobacterium, this term only 11.Bifidobacter*:ti,ab,kw in Clinical Trials 12.Activia:ti,ab,kw in Clinical Trials 13.MeSH descriptor Enterococcus explode all trees 14.Enterococc*:ti,ab,kw in Clinical Trials 15.MeSH descriptor Streptococcus thermophilus explode all trees 16.Streptococcus thermophilus:ti,ab,kw in Clinical Trials

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(Continued)

	17.MeSH descriptor Saccharomyces explode all trees 18.Saccharomyces:ti,ab,kw in Clinical Trials 19.DiarSafe:ti,ab,kw in Clinical Trials 20.(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) 21.MeSH descriptor Urinary Tract Infections explode all trees 22.MeSH descriptor Cystitis explode all trees 23.MeSH descriptor Pyelonephritis, this term only 24.(uti or utis):ti,ab,kw in Clinical Trials 25.bacteriuria*:ti,ab,kw in Clinical Trials 26.(pyuria or pyuric or pyurias):ti,ab,kw in Clinical Trials 27.cystitis:it,ab,kw in Clinical Trials 28.bladder* NEAR/5 (ulcer* or ulcus):ti,ab,kw in Clinical Trials 29.((bladder or genitourin* or renal or ureter* or ureth* or urin* or urolog* or urogen*) NEAR/5 (infect* or bacteria* or microbiol*)):ti,ab,kw in Clinical Trials 30.pyelonephr*:ti,ab,kw in Clinical Trials 31.pyelocystit*:ti,ab,kw in Clinical Trials 32.(#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31) 33.(#20 AND #32)
MEDLINE	1. Probiotics/ 2. probiotic$.tw. 3. Lactobacill$.tw. 4. exp Lactobacillus/ 5. Yakult.tw. 6. Actimel.tw. 7. ProViva.tw. 8. Cultura.tw. 9. Verum.tw. 10.Bifidobacter$.tw. 11.Bifidobacterium/ 12.Activia.tw. 13.Enterococc$.tw. 14.exp Enterococcus/ 15.Streptococcus thermophilus.tw. 16.Streptococcus thermophilus/ 17.exp Saccharomyces/ 18.Saccharomyces.tw. 19.DiarSafe.tw. 20.or/1-19 21.exp Urinary Tract Infections/ 22.exp Cystitis/ 23.exp Pyelonephritis/ 24.(uti or utis).tw. 25.urinary tract infection$.tw 26.cystitis.tw. 27.pyelonephritis.tw. 28.bacteriuria.tw. 29.(pyuria or pyuric or pyurias).tw. 30.or/21-29 31.and/20,30

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(Continued)

EMBASE	1. Probiotic Agent/ 2. probiotic$.tw. 3. exp lactobacillus/ 4. Lactobacill$.tw. 5. Yakult.tw. 6. Actimel.tw. 7. ProViva.tw. 8. Cultura.tw. 9. Verum.tw. 10.exp bifidobacterium/ 11.Bifidobacter$.tw. 12.Activia.tw. 13.exp enterococcus/ 14.Enterococc$.tw. 15.Streptococcus Thermophilus/ 16.Streptococcus thermophilus.tw. 17.exp saccharomyces/ 18.Saccharomyces.tw. 19.DiarSafe.tw. 20.or/1-19 21.Urinary Tract Infection/ 22.exp Cystitis/ 23.Pyelonephritis/ 24.(uti or utis).tw. 25.urinary tract infection$.tw 26.bacteriuria$.tw. 27.(pyuria or pyuric or pyurias).tw. 28.cystitis.tw. 29.pyelonephr$.tw. 30.or/21-29 31.and/20,30

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequential-

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(Continued)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	ly numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse

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(Continued)

	effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: ES, AT, PL
- Study selection: ES, AT
- Extract data from studies: ES, AT
- Enter data into RevMan: ES, AT
- Carry out the analysis: ES, AT, PL
- Interpret the analysis: AT, PL
- Draft the final review: ES, AT, PL
- Disagreement resolution: PL
- Update the review: ES, AT, PL

DECLARATIONS OF INTEREST

- Erin M Schwenger: None known
- Aaron M Tejani: None known
- Peter S Loewen: None known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol specified that men, women and children who were at risk of recurrent UTI would be included in the review. We intended this to exclude children aged under one year old, and did so during the selection of studies, although this was not made clear in the protocol.

In addition, we had planned to conduct subgroup analysis of studies comparing probiotics with placebo or active comparators. However, there was only one study with an active comparator (antibiotics) known to have efficacy versus placebo (NAPRUTI Study II 2006). We chose to analyse this separately rather than as a subgroup. Ferrara 2009 and Kontiokari 2001 used comparators with no known efficacy or safety advantage versus placebo and we did not feel it would be appropriate to compare these with probiotics. No subgroup analyses were conducted for these two studies.

We conducted post-hoc subgroup analyses for studies that enrolled participants who had recent UTI compared with studies that enrolled patients who had not had a recent UTI (Analysis 1.1).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Bacterial Infections [*prevention & control]; Probiotics [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Urinary Tract Infections [*prevention & control]

MeSH check words

Adult; Child; Female; Humans; Male

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