Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis

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GRIN PM, KOWALEWSKA PM, ALHAZZANI W, FOX-ROBICHAUD AE. *Lactobacillus* for preventing recurrent urinary tract infections in women: meta-analysis. *Can J Urol* 2013;20(1):6607-6614.

Introduction: *Urinary tract infections (UTIs) are the most common infections affecting women, and often recur. Lactobacillus probiotics could potentially replace low dose, long term antibiotics as a safer prophylactic for recurrent UTI (rUTI). This systematic review and meta-analysis was performed to compile the results of existing randomized clinical trials (RCTs) to determine the efficacy of probiotic Lactobacillus species in preventing rUTI.*

Materials and methods: *MEDLINE and EMBASE were searched from inception to July 2012 for RCTs using a Lactobacillus prophylactic against rUTI in premenopausal adult women. A random-effects model meta-analysis was performed using a pooled risk ratio, comparing incidence of rUTI in patients receiving Lactobacillus to control.*

Results: *Data from 294 patients across five studies were included. There was no statistically significant difference in the risk for rUTI in patients receiving Lactobacillus versus controls, as indicated by the pooled risk ratio of 0.85 (95% confidence interval of 0.58-1.25, p = 0.41). A sensitivity analysis was performed, excluding studies using ineffective strains and studies testing for safety. Data from 127 patients in two studies were included. A statistically significant decrease in rUTI was found in patients given Lactobacillus, denoted by the pooled risk ratio of 0.51 (95% confidence interval 0.26-0.99, p = 0.05) with no statistical heterogeneity (I^2 = 0%).*

Conclusion: *Probiotic strains of Lactobacillus are safe and effective in preventing rUTI in adult women. However, more RCTs are required before a definitive recommendation can be made since the patient population contributing data to this meta-analysis was small.*

Key Words: urinary tract infection, cystitis, probiotics, *Lactobacillus*, meta-analysis, systematic review

Introduction

Urinary tract infection (UTI) is an acute, bacterial infection that occurs when pathogens colonize the vagina and ascend into the urinary system.[1] It is the most common infection in premenopausal adult women, incurring significant morbidity along with billions of dollars in health care costs annually.[2] Moreover, approximately 20-30 percent of women develop recurrent urinary tract infections (rUTIs),[3,4] which require multiple courses of antibiotic treatment.[5] Currently, the clinically prescribed prophylaxis for women experiencing frequent recurring infections is a long term, low dose regimen of antimicrobials such as trimethoprim-sulfamethoxazole or fluoroquinolones.[6] Although this method of prophylaxis has been shown to reduce the incidence of UTI, the benefit ends when the antimicrobial regimen is discontinued. There are also several side effects associated with these antibiotics, which predominantly include vaginal

Accepted for publication September 2012

Acknowledgements
We would like to thank Dr. Gregor Reid from the University of Western Ontario for sending us the full-text articles of his studies, which were not available online.

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itching, skin rash and/or nausea.[7] Furthermore, antibiotic resistance among uropathogens has been shown to increase in response to long term use.[8,9] Thus, there is need for alternative prophylactic measures.

Probiotics, defined by the World Health Organization and Food and Agriculture Organization of the United Nations as "live microorganisms which when administered in adequate amounts confer a health benefit on the host",[10] may be an acceptable alternative to antimicrobials. Specifically, *Lactobacillus* probiotics have been examined for years as a possible prophylaxis for rUTI. In fact, several indigenous species of lactobacilli are found in the vaginal flora of healthy women and these lactobacilli are thought to play a protective role against pathogenic colonization.[11] Probiotic *Lactobacillus* strains may prevent rUTI through a number of conferred benefits:[11] 1) by restoring balance to the vaginal flora after antimicrobial treatment for an initial UTI, 2) by helping to maintain a normal vaginal pH of < 4.5 through lactic acid production, and 3) by producing the microbicidal compound H_2O_2. However, there is no clear evidence in support of a specific strain or dosage as the most beneficial, and there is no definitive evidence that these probiotics are able to prevent rUTI.

Very few clinical trials have tested *Lactobacillus* for prevention of rUTI, and these studies are small in size, making it impractical to draw conclusions about effectiveness from any single trial. Only one previous systematic review[12] analyzed *Lactobacillus* for prevention of rUTI, and new evidence appeared in the literature[13] since the inconclusive findings of this review were published. Furthermore, no meta-analysis has been performed on the use of probiotics to prevent rUTI. Therefore, we performed a systematic review and meta-analysis of randomized clinical trials (RCTs) to determine whether probiotic strains of *Lactobacillus* are safe and effective in preventing rUTIs.

Materials and methods

We performed this systematic review and meta-analysis using Cochrane Collaboration methodology to evaluate the effectiveness of *Lactobacillus* probiotics in preventing rUTI.

Search strategy

The primary electronic search was performed using PubMed and Ovid for the databases MEDLINE and EMBASE, respectively. PubMed was searched from inception to July 9, 2012 using combinations of the following terms: *Lactobacillus*, probiotic, lactic acid bacteria, or lactobacilli; and urinary infection, urinary tract infection, recurrent urinary tract infection, cystitis, UTI, or rUTI. Ovid included articles from 1974 to July 9, 2012 with combinations of the following search terms: cystitis, urinary tract infection, or recurrent urinary tract infection; and probiotic agent, *Lactobacillus*, or lactic acid bacterium. No restrictions were placed on the electronic searches. A secondary search was performed using the reference lists of relevant articles found electronically, and the reference list of one previous systematic review,[12] that examined *Lactobacillus* as a prophylactic agent in several different urogenital infections.

Inclusion criteria

We searched for parallel group RCTs comparing *Lactobacillus* with placebo or other prophylactic regimens for rUTI. Studies were eligible if they included a population of premenopausal adult women with a history of prior UTI (defined as one or more UTIs within the last 12 months before entering a study).

Study selection

Two of the reviewers screened the titles and abstracts of articles retrieved through the electronic search, and found full text articles for relevant studies. The kappa statistic was used to quantify the degree of agreement between the reviewers' independent searches. The same reviewers also manually scanned the reference lists of relevant studies for the secondary search. Study authors were contacted if their full study was not available through other sources. All four reviewers assessed all relevant studies against the inclusion criteria.

Risk of bias and data appraisal

All of the articles were evaluated according to the Cochrane Collaboration's tool for assessing risk of bias[14] to determine internal validity, with conflicting judgments resolved. Each trial was judged for risk of bias associated with the method of sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), addressing incomplete outcome data (attrition bias), and outcome reporting. Information regarding population characteristics, strain of *Lactobacillus*, dose and length of treatment, duration of follow up, and outcomes was extracted and summarized in a study characteristics table. The primary outcome for this meta-analysis was the incidence of at least one rUTI. The secondary outcome was adverse events, which we analyzed qualitatively.

Data analysis

For each individual study, risk ratios (RRs) with 95%

confidence intervals (CIs) were calculated using per protocol analysis, where the event was one or more rUTI experienced by a patient during the complete study period. The random-effects model for meta-analysis was used to combine the dichotomous outcomes of studies into a pooled RR. Statistical heterogeneity among the studies was assessed using the I^2 statistic, where I^2 values of 25%, 50% and 75% indicate low, moderate, and high heterogeneity, respectively.[15] The number needed to treat (NNT) was calculated using an assumed control event rate of 30% for rUTI. Forrest plots were generated using Cochrane Collaboration's RevMan version 5.1. Two pooled analyses were performed with this software. The first consisted of all studies meeting the inclusion criteria for the search. The second was an *a priori* sensitivity analysis, which included studies that tested specifically for the efficacy of probiotic *Lactobacillus* in preventing rUTI.

Results

Search results

The electronic search retrieved 744 articles (including duplicates across databases). After screening titles and abstracts, a total of seven full-text articles[13,16-21] were evaluated. Two of these articles[20,21] were excluded because they did not meet the *a priori* inclusion criteria. One additional study[22] was found by searching the reference lists of the seven articles mentioned above. This study was included in the systematic review, but excluded from meta-analysis because the study compared two treatment groups of *Lactobacillus* and *Lactobacillus* Growth Factor. As a result, five studies[13,16-19] randomizing 294 patients to *Lactobacillus* treatment or control groups were included in the meta-analysis. The kappa statistic for agreement among reviewers in their independent searches was equal to 1. The results of the search are shown in Figure 1.

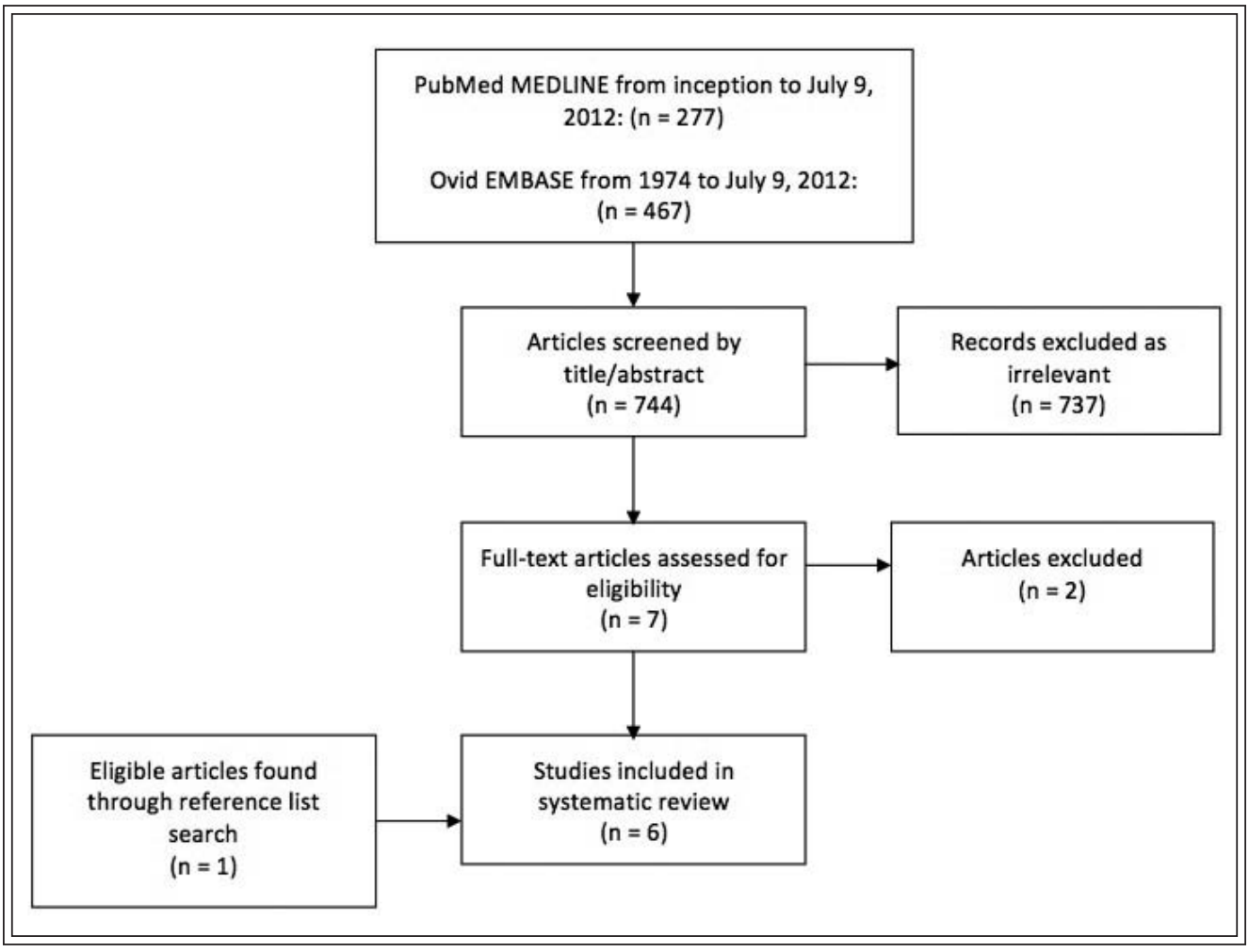


Figure 1. Flow chart depicting literature search

TABLE 1. **Characteristics of included studies**

Study Reference	Type of study (control type)	Blinding	All patients (n)	Patients included (pooled analyses)	Patient description
Reid et al[19]	Randomized, placebo controlled trial	Double blind	41	34	Pre-menopausal adult women with an acute, uncomplicated lower UTI
Baerheim et al[18]	Randomized, placebo controlled trial	Double blind	48	47	Women ages 18-50 with ≥ 3 UTIs in prior 12 months and no UTI at study entry
Reid et al[22]	Randomized trial (two intervention comparison without placebo)	Double blind	55	n/a, not pooled with other studies	Pre-menopausal adult women with ≥ 4 UTIs in prior 12 months, and no UTI at study entry
Kontiokari et al[17]	Randomized trial, three arms (*Lactobacillus*, cranberry, open control)	None	150	90	Adult women with current UTI caused by *Escherichia coli*
Czaja et al[16]	Randomized, placebo controlled trial	Double blind	30	30	Pre-menopausal adult women with ≥ 3 UTIs in prior 12 months or ≥ 2 UTIs in prior 6 months
Stapleton et al[13]	Randomized, placebo controlled trial	Double blind	100	96	Pre-menopausal adult women with an acute, uncomplicated lower UTI and ≥ 1 UTI treated within prior 12 months

Study characteristics and risk of bias assessment

The characteristics of the included studies are shown in Tables 1 and 2. The risk of bias assessment for eligible studies is shown in Table 3. Two of the studies[17,22] showed high risk of bias after evaluation using the Cochrane Collaboration's risk of bias tool. The study by Kontiokari et al was not blinded, and therefore exhibits a high risk of performance and detection bias. The 1995 study by Reid et al was classified as being at high risk of attrition bias due to the very high dropout rate of 22%.

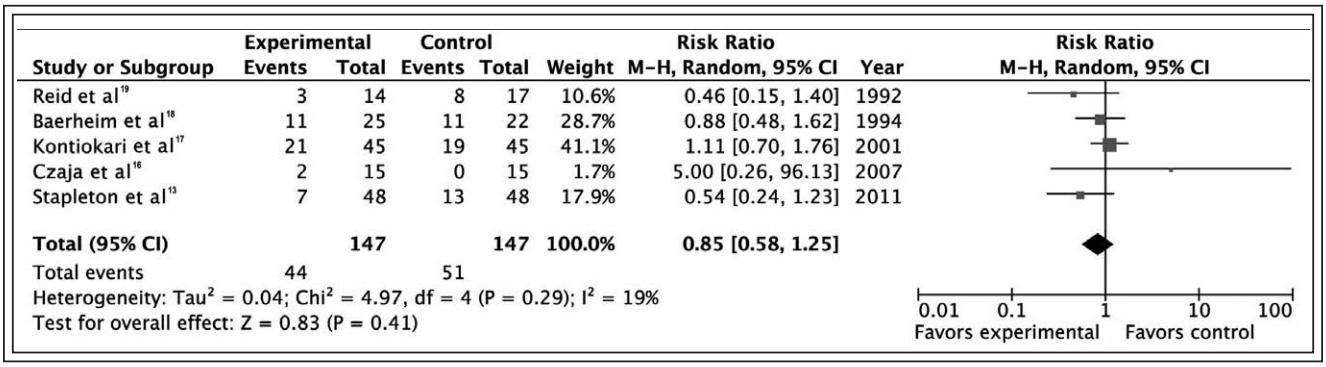


Figure 2. Forest plot of studies meeting the search criteria. Events = patients acquiring one or more recurrent UTIs; CI = Confidence Interval; Random = Random-Effects Model; M-H = Mantel-Haenszel; DF = degrees of freedom; I^2 = heterogeneity.

TABLE 2. **Characteristics of included studies (continued)**

Study Reference	*Lactobacillus* administration method	Dose and strain	Length of treatment	Duration of follow up	RR (95% CI), p value
Reid et al[19]	UTI treated with antimicrobials for first 3 days, followed by *Lactobacillus* vaginal suppositories	> 1.6 x 10^9 CFU/suppository *Lactobacillus rhamnosus* GR-1 and *Lactobacillus* fermentum B-54	Twice weekly for 2 weeks, then at the end of each week for the next 2 months	6 months	0.45 (0.15-1.40) p = 0.2682
Baerheim et al[18]	Vaginal suppositories	> 7.5 x 10^8 CFU/suppository *Lactobacillus casei v rhamnosus* LCR35	Twice weekly for 26 weeks	6 months	0.88 (0.48-1.62) p = 0.9057
Reid et al[22]	Vaginal suppositories	> 1 x 10^9 CFU/suppository *L. rhamnosus* GR-1 and *L. fermentum* B-54	Weekly for 12 months	12 months	n/a, no control
Kontiokari et al[17]	UTI treated with antimicrobials until eradicated, followed by an oral drink of *Lactobacillus*	> 4 x 10^{10} CFU/100 mL drink *L. rhamnosus* GG	5 days per week for 12 months	12 months	1.11 (0.70-1.76) p = 0.8320
Czaja et al[16]	Vaginal suppositories	5 x 10^8 CFU/suppository	Daily for 5 days	4 weeks	5.00 (0.26-96.13) p = 0.4642
Stapleton et al[13]	UTI treated with antimicrobials, followed by vaginal suppositories starting 7-10 days later	10^8 CFUs/mL in suppository *Lactobacillus crispatus* CTV-05	Daily for 5 days, then once weekly for 10 weeks	10 weeks	0.54 (0.24-1.23) p = 0.2089

Quantitative data synthesis

The pooled analysis for studies meeting the search criteria included 294 patients from five RCTs,[13,16-19] Figure 2. The use of *Lactobacillus* was associated with a trend toward reduction of risk of rUTI (RR 0.85; 95% CI 0.58-1.25, p = 0.41; I^2 = 19%), but these results were not statistically significant.

A sensitivity analysis, which included patients from two RCTs, showed that the use of *Lactobacillus* was associated with a significant reduction in the risk of

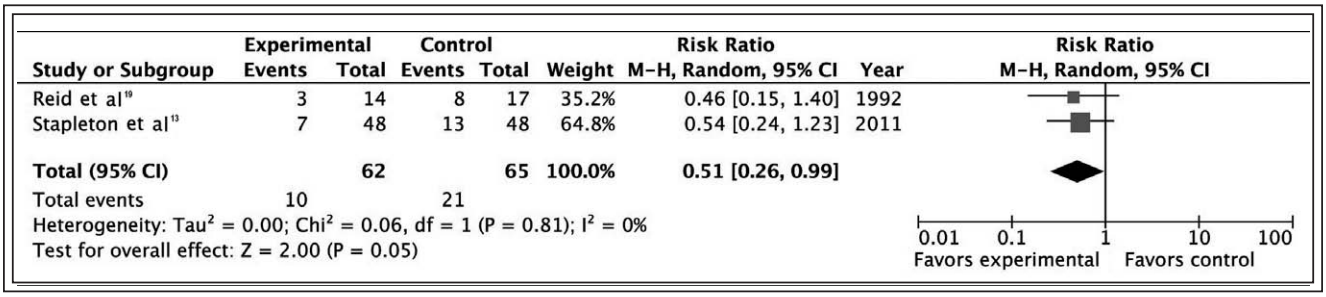
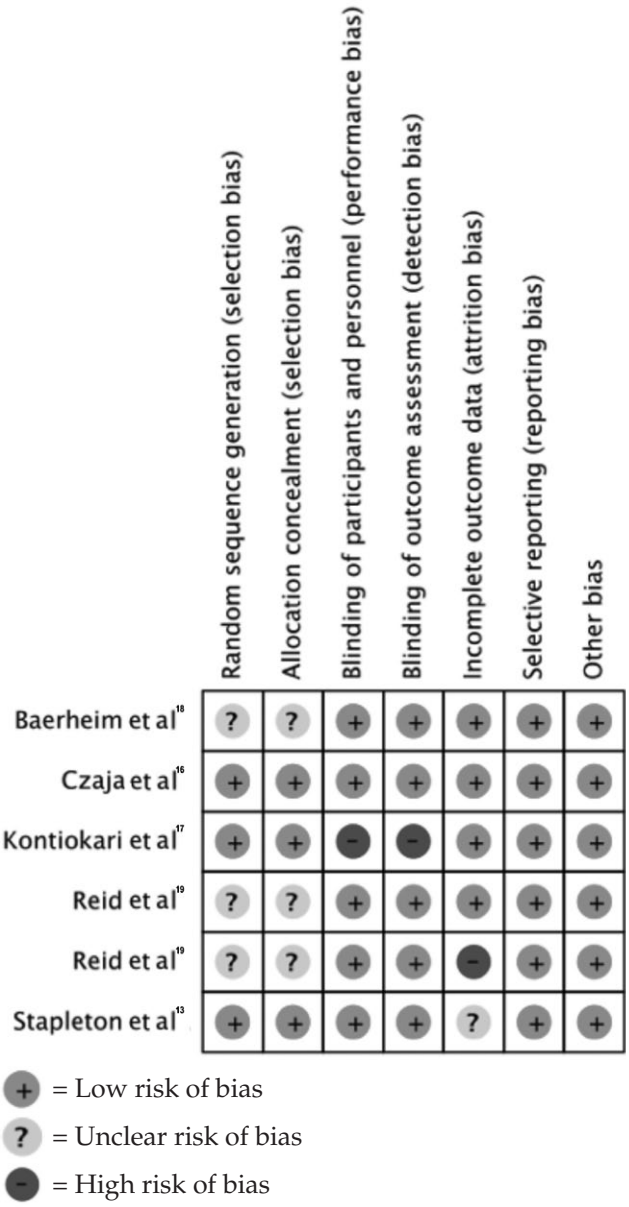


Figure 3. Forest plot of studies testing for efficacy of *Lactobacillus* probiotics. Events = patients acquiring one or more recurrent UTIs; CI = Confidence Interval; Random = Random-Effects Model; M-H = Mantel-Haenszel; DF = degrees of freedom; I^2 = heterogeneity.

TABLE 3. **Risk of bias assessments**



rUTI (RR 0.51; 95% CI 0.26-0.99, p = 0.05, I^2 = 0%) when compared with control, Figure 3. This translates to a NNT of 7 to prevent one UTI, for an assumed control rate of 30%. The study by Czaja et al[16] was excluded from this analysis since it was a safety trial, which did not test for the efficacy of *Lactobacillus* intervention. The study by Baerheim et al was also excluded as there was no vaginal colonization established in this study, where *Lactobacillus casei var. rhamnosus* LCR35 was examined.[18] Furthermore, this strain has questionable probiotic properties in the urogenital environment: only one in vitro study[23] evaluated the potential of this strain as a urogenital probiotic, and there have been no clinical trials testing its efficacy. The study by Kontiokari et al[17] was excluded because the administration of *Lactobacillus rhamnosus GG* orally has since been proven ineffective in establishing vaginal colonization.[24,25]

Secondary outcomes

The two studies by Reid et al reported no adverse events.[19,22] Adverse events in the 2011 study by Stapleton et al were reported by 56% of patients in the *Lactobacillus* treatment group and by 50% of patients in the placebo group, the most common of which were vaginal discharge, itching or moderate abdominal discomfort.[13] Baerheim et al reported that four patients (16%) in the *Lactobacillus* treatment group and one patient (5%) in the placebo group complained about discharge on the day following suppository insertion, with no other side effects reported.[18] In the phase I trial by Czaja et al, patients reported experiencing mainly abnormal vaginal discharge, external genital irritation, and vaginal candidiasis.[16] Finally, Kontiokari et al reported no adverse events.[17]

Discussion

The current systematic review was performed with meta-analysis to determine if *Lactobacillus* probiotics are effective in preventing rUTI. Our meta-analysis consisted of data from 294 patients across five studies. The results of this analysis show no statistically significant evidence that *Lactobacillus* probiotics prevent rUTI. Our sensitivity analysis included data from 127 patients across two studies that used probiotic strains of *Lactobacillus* shown to colonize the vaginal epithelium. The evidence from this analysis suggests that probiotic *Lactobacillus* strains prevent rUTI. The removal of studies with strains that do not achieve vaginal colonization is an important consideration. When quantifying the effect of *Lactobacillus* probiotics, these studies may have falsely skewed the pooled estimate towards lack of effect by simply using an ineffective strain that by definition is not a probiotic.

This review focused on a population of premenopausal women to increase the specificity of the results and because few, if any, RCTs have tested *Lactobacillus* probiotics for rUTI in postmenopausal women, pregnant women or the pediatric population. Also, common risk factors for UTI in premenopausal women are different from those in other groups. These include recent sexual intercourse, use of a diaphragm with spermicide or spermicidal condoms, a history of UTI, and recent antimicrobial use.[26-29] A multivariate analysis by Scholes et al found high frequency of sexual intercourse to be

the greatest risk factor for UTI, although the reason for this remains unclear.[26] The remaining risk factors all appear to either cause or result from a depletion of lactobacilli in the vaginal microbiota, which allows uropathogens to colonize the vagina and later ascend into the urinary tract.[30] The use of *Lactobacillus* suppositories could reduce the risk caused by these factors by simply restoring balance to the vaginal microbiota, and thus restoring protection against uropathogens at the point of entry. Additionally, it is known that all lactobacilli produce lactic acid, which helps maintain a healthy low vaginal pH of approximately 4.5 that in turn inhibits pathogen survival.[11] Also, certain probiotic strains of *Lactobacillus* provide additional benefits. Specifically, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus crispatus* CTV-05 produce H_2O_2, a strong antimicrobial that induces membrane stress on uropathogenic bacteria.[11,31] Such stress has been shown to prevent growth of *Escherichia coli* and its adhesion to the vaginal epithelium.[11] Along with *L. rhamnosus* GR-1 and *L. crispatus* CTV-05, *Lactobacillus fermentum* B-54 was also shown in clinical trials to be highly capable of colonization and survival within the vaginal environment.[13,19,22]

Although promising, the current literature is inconclusive regarding the use of probiotics for preventing rUTIs since no large clinical trials have been performed. Several recent reviews suggested that *Lactobacillus* probiotics are safe and effective in preventing rUTIs, but cannot be recommended clinically due to absence of evidence from large clinical trials.[32-34] The studies we reviewed confirm that *Lactobacillus* suppositories could be used safely; some patients experienced only mild side effects. Moreover, these side effects can be attributed to the suppository vehicle of administration rather than *Lactobacillus* itself, since both control and experimental groups experienced a similar rate of side effects. The only study to administer *Lactobacillus* orally found that patients experienced no side effects, further supporting our observation that the suppository method of administration is responsible for adverse events. Additionally, *L. rhamnosus* GR-1 has been shown to colonize the vagina after oral administration of $> 10^9$ CFU twice daily for 14 days in a different study.[21] Therefore, oral administration may be a feasible solution to the occurrence of side effects and could result in better patient compliance.

There are several strengths and limitations associated with our analysis. The rigorous standards we set in our search criteria yielded studies involving, specifically, a high-risk population of premenopausal women. Some background research on specific strains allowed us to perform a sensitivity analysis that only included probiotic strains proven to confer benefits in the urogenital environment. Through this analysis, homogeneity in the probiotic administration method was also achieved since the single study testing oral *Lactobacillus* used an ineffective strain, and was consequently removed. Additionally, the two studies included in the sensitivity analysis did not exhibit high risk of bias in their methodology. Although decreased incidence of rUTI in patients given *Lactobacillus* was found through this analysis, there are some limitations that must be considered. This analysis included two studies with only 127 patients combined. Also, there is considerable heterogeneity in study duration. The study lengths ranged from 4 weeks to 12 months, with those included in the sensitivity analysis being 10 weeks and 12 months long.

Conclusion

Further research is required to determine whether probiotic strains of *Lactobacillus* prevent rUTI in premenopausal women. Our analysis suggests that suppositories containing *L. crispatus* CTV-05 or a combination of *L. rhamnosus* GR-1 and *L. fermentum* B-54 are most effective. Therefore future RCTs should study these strains, over a 6 to 12 month period, to build upon the existing evidence for efficacy of these probiotics in prevention of rUTI. We also found that no serious adverse events have been caused by *Lactobacillus* in studies involving healthy premenopausal women, which supports the case for carrying out additional clinical trials. Moreover, studies need to address whether oral administration of the *Lactobacillus* strains mentioned above are also effective and whether this mode of administration eliminates side effects while increasing patient compliance. Until further research is completed, these probiotic strains of *Lactobacillus* delivered in suppositories may be considered, but not definitively recommended, as a safe alternative to antimicrobials for UTI prophylaxis in high risk women when antimicrobial resistance is an issue. □

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