

# Primary care

## Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial

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### Abstract

**Objective** To test whether oral or vaginal lactobacillus can prevent vulvovaginitis after antibiotic treatment.

**Design** Randomised, placebo controlled, double blind, factorial 2×2 trial.

**Setting** Fifty general practices and 16 pharmacies in Melbourne, Australia.

**Participants** Non-pregnant women aged 18-50 years who required a short course of oral antibiotics for a non-gynaecological infection: 278 were enrolled in the study, and results were available for 235.

**Interventions** Lactobacillus preparations taken orally or vaginally, or both, from enrolment until four days after completion of their antibiotic course.

**Main outcome measures** Participants' reports of symptoms of post-antibiotic vulvovaginitis, with microbiological evidence of candidiasis provided by a self obtained vaginal swab.

**Results** Overall, 55/235 (23% (95% confidence interval 18% to 29%)) women developed post-antibiotic vulvovaginitis. Compared with placebo, the odds ratio for developing post-antibiotic vulvovaginitis with oral lactobacillus was 1.06 (95% confidence interval 0.58 to 1.94) and with vaginal lactobacillus 1.38 (0.75 to 2.54). Compliance with antibiotics and interventions was high. The trial was terminated after the second interim analysis because of lack of effect of the interventions. Given the data at this time, the chances of detecting a significant reduction in vulvovaginitis with oral or vaginal lactobacillus treatment were less than 0.032 and 0.0006 respectively if the trial proceeded to full enrolment.

**Conclusions** The use of oral or vaginal forms of lactobacillus to prevent post-antibiotic vulvovaginitis is not supported by these results. Further research on this subject is unlikely to be fruitful, unless new understandings about the pathogenesis of post-antibiotic vulvovaginitis indicate a possible role for lactobacillus.

### Introduction

The use of many complementary and alternative medicines remains controversial. In Australia and the United States, the estimated annual expenditure associated with use of such treatments is \$A2.3bn

(£0.9bn) and \$27.1bn (£15bn) respectively, which is more than that spent on prescription drugs.<sup>1,2</sup>

Probiotics, microorganisms that have antagonist activity against pathogens in vivo, have long been promoted as health enhancing in general and specifically as useful for vaginal problems.<sup>3</sup> Probiotics are commonly used<sup>4-6</sup> and recommended<sup>7</sup> for vulvovaginitis that develops after antibiotic treatment—a condition of concern to many women<sup>4</sup> and usually caused by *Candida albicans*.<sup>8</sup> Lactobacilli are a genus of bacteria, many species of which have been evaluated for their probiotic potential, and may be found in yoghurt. Our previous study found that 40% of a sample of 751 women with a history of vulvovaginitis had used yoghurt or lactobacillus orally or vaginally to prevent post-antibiotic vulvovaginitis,<sup>4</sup> but no published trials have tested the effectiveness of this treatment.

The aim of our present study was to test whether oral or vaginal lactobacillus can prevent post-antibiotic vulvovaginitis.

### Participants and methods

#### Participants

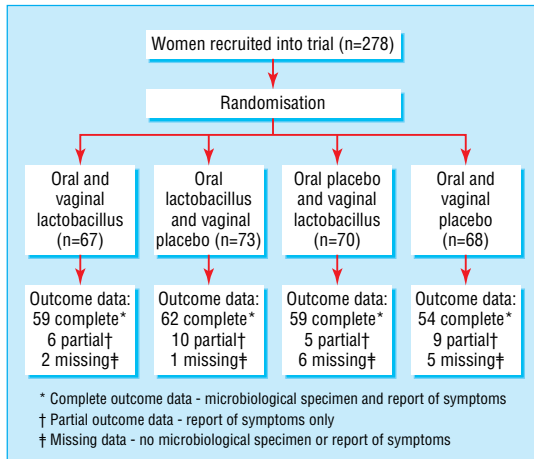
Recruitment took place in Melbourne, Australia, from November 2001 until July 2003, through 50 general practices and 16 pharmacies.<sup>9</sup> Eligible women were aged 18-50 years with non-gynaecological infections who started short term treatment with oral antibiotics within 48 hours of enrolment. Women were ineligible if they had vaginal symptoms, had used vaginal antifungal agents within the past fortnight or other antibiotics within the past month, or were pregnant or immunocompromised. We obtained informed written consent from all participants.

#### Design

We used a 2×2 factorial design to test (a) an oral powder, either Lactobac (containing *Lactobacillus rhamnosus* and *Bifidobacterium longum*) or placebo (maltodextrin powder) and (b) a vaginal pessary, either Femilac (containing *L rhamnosus*, *L delbrueckii*, *L acidophilus*, and *Streptococcus thermophilus*) or placebo (maltodextrin). Active treatments and placebos were



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Participant flow through study

identical in appearance. Participants took half a teaspoon of powder twice daily 20 minutes before meals and one pessary at night for 10 days (during the six day antibiotic course and for four days after).

*Assignment and masking*

Using computer generated random numbers, we assigned women to receive one of four combinations of oral and vaginal treatment (see figure) in block randomised groups of eight. To ensure allocation concealment, an independent research fellow oversaw the labelling and packaging of trial treatments and held the randomisation schedule. Participants, recruiters, and microbiology staff were blinded to group assignment.

*Outcome measures*

On recruitment to the study, participants underwent a baseline survey and provided a self collected vaginal swab. The survey and swab were repeated four days after completion of the interventions, generally 14 days after recruitment or at the time of developing symptoms of vulvovaginitis. Swabs were initially examined microscopically—by making a Gram stained smear—and then cultured for two days before visual examination for colonies of candida species.

The primary outcome was symptomatic vulvovaginal candidiasis, defined as symptoms (vaginal itch or irritation with or without discharge) plus candida isolated from the follow up vaginal swab.

**Statistical analysis**

On the basis of the 23% incidence of post-antibiotic vulvovaginitis that we found in our earlier survey,<sup>4</sup> we calculated that, to detect a clinically meaningful halving of infections to 11.5% for active treatment, we needed outcome data for 372 women for 80% power and significance level of 5% for a two sided test.

Our analysis was on the basis of intention to treat, with two pre-specified comparisons—(a) oral lactobacillus versus placebo and (b) vaginal lactobacillus versus placebo. The Data Monitoring Committee reviewed our interim analyses after recruitment of 126 and 252 women. It used O'Brien and Fleming's procedure and stopping rules,<sup>10</sup> with a nominal P value of 0.0005 at the first analysis and 0.014 at the second.

We used logistic regression to examine the effects of the two interventions. As this was a factorial design, we adjusted the effect of each intervention for the other in the model. The factorial design also allowed us to test for interaction between the two treatment factors, but the study was not specifically powered to detect such an effect.

**Results**

Viability of the lactobacilli and correct labelling of the interventions were confirmed in three independent tests. After the second interim analysis showed no evidence of effect with active treatment, the Data Monitoring Committee recommended terminating the trial early. At this stage, the committee had 62% of the expected data, and stochastic curtailment methods showed that if the trial proceeded to full enrolment the chances of detecting a significant reduction in vulvovaginitis with oral or vaginal lactobacillus treatment were less than 0.032 and 0.0006 respectively.

A total of 278 women were randomised (26 while awaiting the second interim analysis results). Because of the recruitment method used, it was not practical to document the entire eligible population. However, an audit of 132 eligible women by 13 recruiters showed that 25% agreed to randomisation and that non-participants were similar to participants in key characteristics (age, use of oestrogen based drugs, and antibiotic prescribed) (results not shown).

Complete data for the main outcomes were available for 235 women. Table 1 shows participants' key baseline characteristics, which were reasonably balanced between the treatment groups.

**Effects of the interventions**

Overall, 55/235 of the participants (23% (95% confidence interval 18% to 29%)) developed post-antibiotic vulvovaginitis. Table 2 shows the results for the factorial groups. The odds ratios for developing vulvovaginitis while taking oral lactobacillus was 1.06 (95% confidence interval 0.58 to 1.94) and while taking vaginal lactobacillus was 1.38 (0.75 to 2.54).

There was no evidence of an interaction between oral and vaginal treatments (results not shown). Only

**Table 1** Baseline characteristics of 278 women in trial of oral and vaginal lactobacillus for preventing post-antibiotic vulvovaginitis by treatment group. Values are numbers (percentages\*) unless stated otherwise

Characteristics	Oral lactobacillus		Oral placebo	
	Vaginal lactobacillus (n=67)	Vaginal placebo (n=73)	Vaginal lactobacillus (n=70)	Vaginal placebo (n=68)
<b>Demographic</b>				
Mean (SD) age (years)	35.8 (7.7)	35.8 (8.4)	32.7 (9.1)	33.5 (8.3)
Single women	20 (30)	12 (17)	24 (35)	18 (27)
Completed tertiary education	36 (54)	41 (57)	41 (59)	39 (58)
Ever drinks alcohol	58 (87)	63 (88)	52 (75)	55 (82)
Income >\$A1000/week	27 (41)	44 (65)	31 (48)	33 (51)
<b>Risk factors</b>				
Using oestrogen based drugs	21 (31)	17 (23)	21 (30)	22 (33)
Regular menstrual cycle	50 (75)	45 (63)	47 (68)	50 (75)
Prone to post-antibiotic vulvovaginitis (self assessed)†	15 (22)	17 (25)	18 (27)	22 (34)
Baseline vaginal swab positive for candida species	16 (24)	17 (23)	17 (24)	9 (13)
Taking narrow spectrum antibiotics	20 (30)	15 (21)	15 (21)	20 (29)

\*Discrepancies in the percentages because of missing responses.

†Responded "Often" or "Always" to question: "How often do you get thrush when taking antibiotics?"

**Table 2** Number of cases of post-antibiotic vulvovaginitis in women taking oral and vaginal lactobacillus, by treatment group

	Oral lactobacillus		Oral placebo	
	Vaginal lactobacillus (n=67)	Vaginal placebo (n=73)	Vaginal lactobacillus (n=70)	Vaginal placebo (n=68)
No of women with outcome data	59	63	59	54
No of women with vulvovaginitis	14	15	17	9
Percentage (95% CI) of women with vulvovaginitis	24 (14 to 37)	24 (14 to 36)	29 (18 to 42)	17 (8 to 29)

three of the 29 asymptomatic women with a positive follow up swab for candida reported symptoms of vaginitis after the end of the trial.

## Discussion

This study found that oral and vaginal probiotic treatments with a main constituent of *Lactobacillus rhamnosus* were ineffective in preventing post-antibiotic vulvovaginal candidiasis.

### Strengths of study

These results should be generalisable to non-pregnant premenopausal women, as recruitment was through a wide, community based network with broad inclusion criteria. Randomisation, blinding, and allocation concealment were effective, and compliance with antibiotic and intervention treatments was high. We obtained at least some outcome data from 95% of participants. Self collection of vaginal specimens by patients for diagnosis of infections is a convenient, validated method for many potential pathogens.<sup>11</sup>

The decision to end the trial prematurely was clear after consideration of the conditional power calculations at the second interim analysis. It was considered unethical to continue recruitment to a trial with no potential benefit.<sup>12</sup>

### Limitations of study

A limitation of this trial was inadequate documentation of the entire eligible population, although audit results confirmed that participants were similar to non-participants. We might have missed some late cases of vulvovaginitis because of follow up at 14 days, but all women with a vaginal swab at follow up that was positive for candida were again questioned about symptoms of vulvovaginitis. Reliance on self obtained vaginal swabs may have led to our underestimating the number of cases, but this should have affected the active treatment and placebo arms equally.

Our results derive from one formulation and dose of lactobacillus. Arguably, it is not appropriate to generalise to other probiotics advocated to prevent vulvovaginitis. However, there is no scientifically plausible explanation to suggest how lactobacilli could be effective. The exact role of these predominant vaginal bacteria in vaginal health is not yet certain.<sup>13, 14</sup> Unlike in bacterial vaginosis, which is associated with increased vaginal pH and where hydrogen peroxide producing lactobacilli play a role in treatment,<sup>15</sup> in acute vulvovaginal candidiasis the vaginal pH remains normal<sup>16</sup> and lactobacilli are as likely to be the dominant bacteria in asymptomatic women.<sup>17</sup> Up to 20% of asymptomatic women have candida present, and the exact mechanism by which antibiotics increase the risk of developing symptomatic candidiasis is

## What is already known on this topic

Post-antibiotic vulvovaginitis is a common problem for women and may affect their concordance with prescribed antibiotics

Products containing lactobacillus species are widely used in the belief that they will prevent post-antibiotic vulvovaginitis, but there is no evidence to support this belief

## What this study adds

This randomised controlled trial shows that neither oral nor vaginal forms of lactobacillus taken during and for four days after antibiotics were effective in preventing post-antibiotic vulvovaginitis

Unless a biologically plausible theory develops to explain a role for lactobacillus, further research in this subject is unlikely to be fruitful

unknown.<sup>16</sup> This uncertainty reflects lack of understanding of the complex role of immunity in vaginal candidiasis, which seems to function at local levels rather than systemically.<sup>18</sup>

## Conclusions

Even if a viable hypothesis existed to explain a role for lactobacilli, to be effective, oral lactobacilli would need to survive gastric acidity and ingested antibiotics and then colonise the lower bowel and vagina. Lactobacillus pessaries are also subject to the effects of antibiotics. Unless a biologically plausible theory develops, further research in this subject is unlikely to be fruitful.

The use of lactobacillus in post-antibiotic vulvovaginitis is an example of a treatment that has widespread use despite lack of a biologically plausible basis or evidence of effectiveness. Our results should prompt health professionals to inform women that lactobacillus is unlikely to prevent post-antibiotic vulvovaginitis and that they should consider using proved antifungal treatment if symptoms develop.

We thank all the women, general practitioners, and pharmacists who participated in this study. Nutrition Care and Institut Rosell kindly donated the treatments and placebos used. Health Care Network developed a software prompt for use in trial recruitment. Mayne Health and Gribbles Pathology provided free transportation of some microbiological specimens. We thank Professor Judith Lumley for chairing the Data Monitoring Committee and Ms Cate Nagle for managing the randomisation schedule.

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Ethical approval: The Royal Australian College of General Practitioners and the Royal Women's Hospital, Melbourne, granted ethical approval.

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## Identification of potential candidates for varicella vaccination by history: questionnaire and seroprevalence study

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Guidance from the Joint Committee on Vaccination and Immunisation regarding varicella vaccination of workers in healthcare settings is imminent.<sup>1</sup> The new recommendations will advise that all those with a negative or uncertain history of chickenpox or shingles at pre-employment assessment should be tested for varicella zoster virus IgG. Vaccination with the newly licensed varicella vaccine will be advised for those with a seronegative result.

A history of chickenpox has a high positive predictive value for immunity among healthcare workers in Europe, where the seroprevalence is as high as 98.5%.<sup>2</sup> The validity of a history of chickenpox is unknown in those from tropical countries, however, where the mean age of infection is in early adulthood.<sup>3</sup> Guy's and St Thomas' Hospital NHS Trust in inner London has some 8000 staff and 4700 healthcare students of increasingly heterogeneous origins.<sup>4,5</sup> We conducted a questionnaire and seroprevalence study at the hospital to ascertain the relations between history of chickenpox, countries of birth and residence, and serological status.

### Participants, methods, and results

From September 2001 to July 2002 a nurse administered questionnaire was completed for 747 staff and students consecutively attending pre-employment screening. Country of birth or of first residence was noted, together with age range during subsequent residence in other countries. Recruits were asked about prior chickenpox or shingles, with details recorded. Serology was requested in line with usual practice. Immune status was determined by using the Diamedix enzyme immunoassay kit for varicella zoster virus IgG (Miami, FL, USA).

Of 629 (84%) recruits tested, six yielded equivocal results and were excluded from further analysis. Those who denied or were unsure of past infection were considered as one group. We assigned participants to "temperate" or "tropical" subgroups according to country of birth or first residence. We compared differences in seroprevalence and proportions of groups with a positive history by using the  $\chi^2$  test; we also analysed other variables (unadjusted and adjusted) using logistic regression.

The table shows the results. Additional information about prior chickenpox (nature and site of rash, residual scar) did not increase the positive predictive value. Shingles had a positive predictive value of 100%, however, with all 22 participants testing IgG positive. Twenty nine participants in the temperate group had not lived solely in temperate zones during their first 12 years and had a reduced risk of testing seropositive (odds ratio 0.35 compared with those born and brought up in a temperate climate)—similar to that of those born and brought up in a tropical climate (odds ratio 0.36).

Participants from Sub-Saharan Africa and the Caribbean were disproportionately represented among the 52 seronegative participants (29% (15) and 17% (9) respectively, compared with just 18% (113) and 5% (31) respectively among all new recruits). Among participants with a history of prior infection, the false positive rate was 9.3% in the tropical group versus 3.7% in the temperate group ( $P = 0.019$ ) (table).

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