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UNCERTAINTIES PAGE

Does taking probiotics routinely with antibiotics prevent antibiotic associated diarrhoea?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com

Diarrhoea develops in association with antibiotic treatment in 1% to 44%[1 2] of cases, and ranges from mild episodes that resolve when antibiotics are stopped to serious complications such as toxic megacolon, bowel perforation, and death. Risk is increased with extremes of age, co-morbidity, oral broad spectrum antibiotics (particularly clindamycin, β-lactams, and third generation cephalosporins), prolonged antibiotic duration, previous antibiotic associated diarrhoea, and hospitalisation. Probiotics—live microorganisms that, when administered in adequate amounts, confer a health benefit on the host—are present in products available in shops as foodstuffs, and in formulations used for specific therapeutic purposes. Probiotics are thought to combat antibiotic associated diarrhoea through restoring resistance to colonisation by pathogenic bacteria after the normal colonic microflora have been damaged by antibiotics, by breaking down non-absorbable compounds into absorbable products, by interfering with pathogenic toxins, and by enhancing immunity. Effects of probiotics vary by strain owing to differing resistance to gastric acid and bile, ability to colonise mucosa, and susceptibility to antibiotics.[3]

Probiotics carry theoretical risks, including infection beyond the gut and transfer of antibiotic resistant genes. However, so far, there have been no reports of bacteraemia or fungaemia attributable to the probiotics in trials included in published systematic reviews.[4-10]

Lactobacillus bacteraemia is rare and has a low mortality rate.[11] Cancer, diabetes, broad spectrum antibiotic therapy, organ transplantation, and abscess may be risk factors for lactobacillus bacteraemia. Twelve cases of lactobacillus bacteraemia have been reported in patients taking a probiotic and 24 cases of fungaemia associated with the probiotic *Saccharomyces boulardii*. However, many lactobacillus strains are human commensals and a review identified only five well documented published cases where the consumed probiotic strain was the same as a clinical isolate.[11] Mild to moderate gastrointestinal side effects and rash are generally no more common than in patients on placebo probiotic.[6]

Probiotics may therefore be an attractive option for preventing antibiotic associated diarrhoea because they are cheap (the cost of preventing one case in selected hospital patients may be as low as £50; €60, $79)[12] and safe.

What is the evidence of uncertainty?

We conducted a review of meta-analyses, updated with subsequent randomised controlled trials. We searched PubMed, EMBASE, the *Cochrane Library*, and *Clinical Evidence* in October 2011 for meta-analyses published in the past five years in English and trials published after their search dates on probiotics to prevent antibiotic associated diarrhoea using the search terms "probiotic" and "antibiotic associated diarrhoea [or diarrhea]". We excluded prevention studies, small pilot studies, studies that were not placebo controlled, studies published only in abstract form, studies focusing on antibiotic associated diarrhoea caused by a single organism (such as *Clostridium difficile*), and systematic reviews without meta-analysis.

The commonest outcome measure was diarrhoea, defined as three loose stools in a 24 hour or 48 hour period.⇓ The type of probiotic tested, study populations, and effect sizes varied widely between studies, with both statistically significant[2] and non-significant[13 14] findings for the primary outcome and widely differing rates of antibiotic associated diarrhoea. Many of the trials identified in the systematic reviews were of poor quality.[6 9 18] Reasons included poor allocation concealment, inadequate power, possible publication bias, variation in outcome measures, lack of intention to treat analyses, variation in follow-up duration, lack of cost-benefit data, variation in illness severity, and the small proportion of eligible patients

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enrolled. We found no head to head comparisons of probiotic strains.

Is ongoing research likely to provide relevant evidence?

We searched the Current Controlled Trials database (www.controlled-trials.com) for ongoing randomised controlled trials using the previously described search terms. Six placebo controlled trials are in progress examining the effect of probiotics in preventing antibiotic associated diarrhoea in hospitalised patients. Three (ISRCTN57305201, ISRCTN10768531, and isrctn19604441) are investigating the effect of a mixed probiotic, VSL#3, containing eight species of bacteria licensed for use in irritable bowel syndrome, with one recruiting exclusively from intensive care units (ISRCTN10768531). One trial (NCT01087892) is investigating the effect of Actimel, which contains three species (*Lactobacillus casei* DN 114 001, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*) and one (ISRCTN70017204) is investigating the effect of a probiotic that contains two strains of *Lactobacillus acidophilus* (National Collection of Industrial, Food and Marine Bacteria (NCIMB) 30157 and 30156), *Bifidobacterium bifidum* (NCIMB 30153) and *Bifidobacterium lactis* (NCIMB 30172). One (ISRCTN86623192) is investigating the effect of *S boulardii.* These studies will provide information on probiotics to prevent antibiotic associated diarrhoea in a wider range of hospitalised patients and may be large enough to provide information on which subgroups of patients are at greatest risk and are most likely to benefit.

No randomised controlled trials have specifically assessed the use of probiotics with antibiotics in care homes. Robust data are lacking on levels of antibiotic use and on frequency and severity of associated diarrhoea this setting. Our Probiotics for Antibiotic Associated Diarrhoea (PAAD) Study (ISRCTN79548440) is in an observational phase to determine whether a trial of probiotics to prevent antibiotic associated diarrhoea is justified and feasible in care homes.

There is an absence or insufficiency of high quality evidence to support routine use of probiotics to prevent antibiotic associated diarrhoea in all people, regardless of age, comorbidity, and care setting. For example, few trials have been done in primary care,[9] and we found none from intermediate and social care settings. We found no pragmatic, open implementation studies.

What should we do in the light of uncertainty?

Good evidence exists to support using probiotics with *S boulardii* and *Lactococcus rhamnosus* GG (ATCC 53103)[5 6 7] to prevent antibiotic associated diarrhoea, with emerging evidence for certain mixed strains that include *L casei* or *L acidophilus*.[10] Probiotics also seem to be more effective at higher doses.[2 6 8] However, because insufficient evidence exists to support routinely using probiotics for this purpose, and because of the low incidence and generally mild severity of antibiotic associated diarrhoea in otherwise healthy people, we recommend against routine use of probiotics in all people taking antibiotics to prevent antibiotic associated diarrhoea. Not all probiotics evaluated as part of clinical trials are commercially available in the United Kingdom. Nevertheless, probiotics are cheap and safe, so routine use with antibiotics is justified in frail patients in hospital and possibly in children. Those who have previously had antibiotic associated diarrhoea should be offered probiotics when they are treated with antibiotics, regardless of setting, but probiotics should be avoided in people who are seriously immunocompromised. As probiotics seem more effective at higher doses,[2 6 8] doses of at least 50 billion colony forming units should be used; probiotics should be taken for the duration of antibiotic treatment and continued for a week thereafter.

Evidence about the effectiveness of many strains is absent or insufficient. Head to head studies of probiotic strains are needed, as well as more studies to identify groups of patients at greatest risk and most likely to benefit, especially in the community and in intermediate care.

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Table

Table 1| Systematic reviews of randomised placebo controlled trials (RCTs) and subsequent individual trials of probiotics to prevent antibiotic associated diarrhoea

Reference (search date)	Number of studies and/or total number of participants, care setting	Intervention: organism in probiotic and daily dose (colony forming units)	Outcome (risk ratio) for antibiotic associated diarrhoea
Systematic reviews			
McFarland 2010[5] (1976-2009)	10 RCTs, 1858 adults, 4 trials in hospitalised patients, 1 outpatient, 3 in patients receiving antibiotic treatment for *H pylori* infection	*S boulardii*, ranging from 4×10^9 to 2×10^{10}	0.47 (95% CI 0.35 to 0.63)
Avadhani 2010[10] (unclear)	8 RCTs, 1220 adults, inpatients	3 trials of *S boulardii*, 1 of *L rhamnosus*, 4 of mixed strains that included *L casei*, *L acidophilus*, *L bulgaricus*, *S thermophilus*, *B bifidum*, and *L rhamnosus*, range of doses	0.56 (95% CI 0.44 to 0.71)
McFarland 2006[6] (1977-2005)	25 RCTs, 2810 children and adults, inpatients and outpatients including *H pylori* treatment	6 trials *S boulardii*, 6 trials *L rhamnosus*, 6 other single strains, and 7 mixed strains, ranging from 1×10^7 to 1×10^{11} (mean dose 3×10^9)	Combined 0.43 (95% CI 0.31 to 0.58); *S boulardii* 0.37 (95% CI 0.26 to 0.52); *L rhamnosus* 0.31 (95% CI 0.13 to 0.72)
Kale-Pradham 2010[7] (inception -May 2008)	10 RCTs, 1862 children and adults, inpatients and outpatients	Single agent lactobacillus, ranging from 2×109 to 4×10^{10}	Combined 0.35 (95% CI 0.19 to 0.67); adults 0.24 (95% CI 0.08 to 0.75); children 0.44 (95% CI 0.18 to 1.08)
Sazawal 2006[9] (inception -February 2006)	19 RCTs, children and adults, inpatients and outpatients	Single (5 *L rhamnosus*) and mixed, ranging from 1×7^{10} to 1×10^{10}	0.48 (95% C1 0.35 to 0.65)
Szajewska 2006[4] (1966-December 2005)	6 RCTs, 766 children, inpatients and outpatients	2 RCTs lactobacillus GG, one *S boulardii*, 3 mixed, dose range unclear	0.44 (95% CI 0.25 to 0.77)
Johnston 2007[8] (inception to August 2006)	9 RCTs, 1946 children, inpatients and outpatients	6 single, 3 mixed containing (alone or in combination) *Lactobacillus spp, Bifidobacterium spp, Streptococcus spp, S boulardii*, ranging from 8.25×10^6 to 4×10^{10}	Per-protocol analysis 0.49 (95% CI 0.32 to 0.74); intention to treat analysis 0.90 (95% CI 0.50 to 1.63); 5 studies of higher dose (5 to 40 × 10^9 day) 0.35 (95% CI 0.25 to 47); 3 studies of low dose (<5×10^9 day) 0.89 (95% CI 0.53, 1.48)
Randomised controlled trials published after search dates of systematic reviews			
Gao 2010[2]	255 adults, inpatients, 744 of 1120 (66.5%) eligible participants were not recruited	Combination of *L acidophilus* and *L casei* in low (5×10^9) or high (10×10^9) dose	High dose 0.34 (95% CI 0.20 to 0.60) Low dose 0.64 (95% CI 0.42 to 0.97); 15.5% low dose, 28.2% high dose intervention, and 44.1% placebo treated patients developed diarrhoea
Lonnermark 2010[13]	239 adults, inpatients and outpatients in a university hospital infectious diseases clinic	*L plantarum,* 1×10^{10}	1.25 (95% CI 0.40 to 3.92); 7.5% intervention and 6.0% treated placebo patients developed diarrhoea
Song 2010[14]	214 adults, inpatients, 10 tertiary hospitals treated for a range of respiratory tract infections (mostly pneumonia)	*L rhamnosus* and *L acidophilus*, 2×10^9	0.54 (95% CI 0.17 to 1.74); 3.9% intervention and 7.2% placebo treated patients developed diarrhoea
Psaradellis 2010[15]	437 adults, treated for a minimum of 12 hours in a hospital ward or emergency room in 8 centres	*L acidophilus* and *L casei*, 5×10^{10}	0.74 (95% CI 0.53 to 1.02); 21.8% intervention and 29.4% placebo treated patients developed diarrhoea
Merenstein 2009[16]	125 children with upper respiratory tract infections aged 1-5, in primary care	Kefir fermented milk from grains containing *Lactococcus lactis, Lactococcus plantarum, Lactococcus rhamnosus, Lactococcus casei, Lactococcus lactis* subspecies *diacetylactis, Leuconostoc cremoris*, *Bifidobacterium longum*, *Bifidobacterium breve, Lactobacillus acidophilus,* and *Saccharomyces florentinus;* doses of organisms not given	0.82 (95% CI, 0.54 to 1.43); 18.0% intervention and 21.9% placebo treated children developed diarrhoea
Szymanski 2008[17]	78 children aged 5 months to 16 years with respiratory tract infections, inpatients and outpatients	*B longum, L rhamnosus*, and *L plantarum,* twice daily at 10^8	0.50 (95% CI 0.06 to 3.50); 2.5% intervention and 5.3% placebo treated children developed diarrhoea