

# Probiotics: are they worth taking?

Pamela Mason looks at the evidence for the benefits of ingesting “friendly bacteria”

Probiotics are live cultures of micro-organisms, usually bacteria, that, when ingested, survive passage through the upper gastrointestinal tract and have beneficial effects on the host (see below). The most common bacteria used in probiotics include *Lactobacillus* species, bifidobacteria, some streptococci and other gram-positive cocci. These micro-organisms should resist gastric acid, bile salts and pancreatic enzymes, and adhere to and readily colonise the bowel where they displace potentially dangerous bacteria and create an environment that is unfavourable for the multiplication of such pathogens.

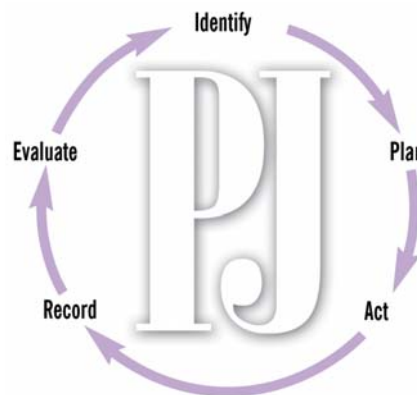
In the UK, probiotics are available in foods or food supplements, sometimes sold combined with prebiotics (see Panel 1), vitamins and minerals and digestive enzymes. However, in Italy, one probiotic product, a suspension of *Bacillus subtilis* spores manufactured by sanofi-aventis, has been available over the counter since 1999 for the treatment and prevention of gastrointestinal disorders. Increasingly popular, probiotics in the UK are consumed as fermented dairy products, such as yogurts and drinks, fruit juices, and dry preparations (ie, tablets, capsules and powders).

Uses suggested for probiotics include:

- To reduce the incidence and severity of diarrhoea
- To reduce the risk of allergic conditions
- To improve immune function
- To manage inflammatory bowel conditions, such as Crohn’s disease, ulcerative colitis and irritable bowel syndrome
- To prevent *Helicobacter pylori* gastritis
- To reduce symptoms of lactose intolerance
- To reduce vaginal infections
- To decrease blood cholesterol
- To protect against bowel cancer



Claims on probiotic products include helping to support the body’s natural defences



## Identify knowledge gaps

1. Can you list three suggested uses for probiotics and the evidence for these suggestions?
2. What are the quality issues for probiotics?
3. What is a prebiotic?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society’s areas of competence for pharmacists are listed in “Plan and record”, (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to “appropriate management of common symptoms” (see appendix 4 of “Plan and record”).

Over 400 species of bacteria can be found in the human gut. The most common are bac-teroides (30 per cent of all gut bacteria), clostridium, fusobacterium, eubacterium, ru-minococcus, peptococcus, peptostreptococcus and bifidobacterium. *Escherichia* and lacto-bacillus are present to a lesser extent. The gut microflora aids digestion and some organisms produce vitamins and minerals.

The normal gut microflora also provides protection against pathogenic organisms and it is thought that probiotics alter the balance of the gut microflora to maximise this effect. This idea is lent credence by the observation that breast-fed babies (who have fewer gastroin-terstitial and respiratory infections than bottle-fed babies) pass stools in which 99 per cent of the bacteria are bifidobacteria. Breast milk is rich in prebiotics and this may be why growth of bifidobacteria is encouraged. In compari-son, the gut microflora in bottle-fed babies is much more diverse, with higher levels of bac-teroides, clostridia and *Escherichia Coli*.

The presence of “good bacteria” in the gut could reduce the risk of infection through several mechanisms:

- They might compete with pathogens for nutrients and adhesion sites in the gut and so reduce the chances of pathogens colonising the gut

## Panel 1: Prebiotics

Prebiotics are non-digestible food substances that promote the growth of beneficial bacteria in the gastrointestinal tract. Chemically, prebiotics are oligosaccharides and examples include inulin-type fructans, fructooligosaccharides and oligofructoses, which are present in many fruits and vegetables.

Prebiotics resist digestion in the upper part of the gastrointestinal tract and are fermented by endogenous anaerobic micro-organisms in the colon to produce lactic acid and short chain carboxylic acids (eg, acetic, butyric and propionic acid). This fermentation provides metabolic substrates to the cells of the colon, stimulating growth of the bifidobacteria population.

Prebiotics also promote the absorption of calcium and magnesium, and possibly other minerals and trace elements within the colon. Evidence is also emerging that they may reduce serum lipids, particularly triglycerides. They are also being investigated for a possible protective effect in bowel cancer, constipation, inflammatory bowel conditions, allergic dermatitis and lactose intolerance.

- They secrete antimicrobial substances and produce an acidic environment that inhibits the growth and survival of pathogens
- They may break down toxins responsible for adverse effects produced by pathogens
- They may influence an immune response, which could enhance ability to fight infection.

Factors that might affect the composition of gut flora include antibiotic therapy, gastrointestinal disease, poor diet, age and stress.

Probiotics are intended to be taken daily. Doses are generally expressed in millions or billions of bacteria. Examples of doses used in studies are shown in Panel 2. For how long a probiotic should be taken is unclear. For “traveller’s diarrhoea” (diarrhoea associated with a change in climate, social conditions or sanitary standards), some products should be started two weeks before departure and continued for one week after return, but in trials, probiotics have been taken for between two weeks and 12 months.

### Diarrhoea

Probiotics have been claimed to help prevent and treat diarrhoeal disease, including antibiotic-associated diarrhoea, traveller’s diarrhoea and infectious diarrhoea in adults and children. Many studies have been conducted and several systematic reviews and meta-analyses are now available. One meta-analysis (n=4,844) indicated that probiotics reduced the risk of antibiotic-associated and traveller’s diarrhoea.<sup>1</sup> Another large meta-analysis (n=3,164) showed that probiotics could reduce the risk of antibiotic-associated diarrhoea, including that caused by *Clostridium difficile*.<sup>2</sup> Lactobacilli and *Saccharomyces boulardii* have been identified as having particular benefit in this regard.

Overall, meta-analyses appear to indicate that probiotics can reduce the risk of acute infectious diarrhoea in children and adults. There is also some evidence that probiotics can reduce the duration of diarrhoea if an attack occurs — an effect that is most marked for diarrhoea associated with human rotavirus, a common cause of infant diarrhoea.

### Allergic disease

Several randomised controlled trials (RCTs) have investigated the potential for probiotics to help prevent or treat allergic disease, such as eczema. Three recent RCTs looked at the effect of using probiotics for three months on atopic dermatitis. One trial showed no significant effect,<sup>3</sup> but the other two showed an improvement in the condition. In one trial, the improvement was only seen in food-sensitised children<sup>4</sup> and in the other trial, a synbiotic (a combination of a probiotic and a prebiotic) was used.<sup>5</sup> A larger trial on 1,223 pregnant women and their babies (four probiotic strains were used by the mothers two to four weeks before delivery and given to babies for six months) showed no effect on any allergic disease by the age of two years, but a decrease

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in atopic dermatitis.<sup>6</sup> Although evidence from these clinical trials is not definitive, probiotics may be particularly effective for atopy in infancy or when given to mothers with a high risk of producing an atopic infant during pregnancy. Earlier trials indicate that probiotic use leads to a reduction in inflammatory mediators.

It is thought that optimising gut flora might reduce the risk of allergic disease by preventing increases in gut permeability associated with infection (and so improving the barrier to antigen penetration) or stimulating anti-allergic immunological responses.

### Immunity

Studies have shown that probiotics influence immune parameters. However, the clinical significance of these results is unknown because most of these studies did not have a clinical end-point.

Three recent RCTs have investigated the effect of probiotic bacteria on the common cold. Taking probiotic strains for at least three months significantly shortened common cold episodes and reduced the severity of symptoms<sup>7</sup> and, in conjunction with vitamins and minerals, reduced the incidence and severity of symptoms in otherwise healthy adults.<sup>8</sup> The third trial showed that the intake of a probiotic had no effect on the incidence of common colds, but shortened duration of episodes and severity of symptoms.<sup>9</sup>

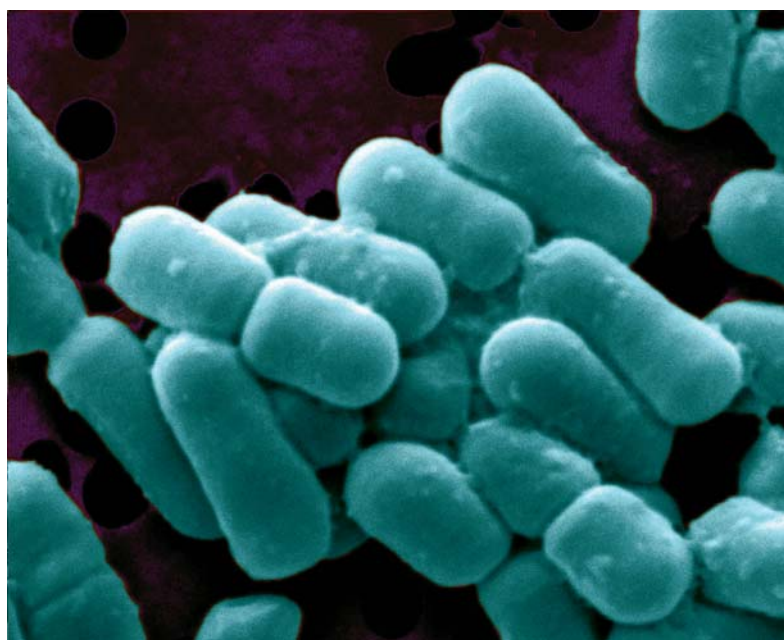
### Inflammatory bowel diseases

Patients with inflammatory bowel diseases, such as Crohn’s disease, ulcerative colitis and irritable bowel syndrome, may have an abnormal gut microflora in terms of both the organisms and their ability to adhere to the gut wall. Probiotics can potentially reduce the population of abnormal bacteria and reverse any problems of adhesion. Inflammatory bowel conditions are also associated with abnormalities in gastrointestinal immunity and restoration of a healthy flora may help to improve gut immune function.

Evidence of clinical benefit in clinical trials with probiotics in inflammatory bowel conditions is mixed. For Crohn’s disease the outcomes of most RCTs were not significant. For example, of five RCTs published between 2000 and 2006, only one small trial (n=32) showed decreased clinical relapse. For ulcerative colitis, however, the evidence is predominantly positive. Outcomes have included an increase in relapse free time and a reduction in inflammation. Furthermore, two relatively large trials (n=327 and n=116) showed that *E coli* Nissle 1917, used for a year, had an equivalent effect to mesalazine in maintaining remission.<sup>10,11</sup> Another RCT with 90 patients, showed that taking VSL#3 (a patented combination of eight probiotic strains, including bifidobacteria and lactobacillus) and low-dose balsalazide for eight weeks was more effective in achieving remission than drugs alone.<sup>12</sup>

For irritable bowel syndrome, the evidence is hopeful but not conclusive. For ex-

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### Lactobacillus species are used in probiotics and have been identified as reducing the risk of antibiotic-associated diarrhoea

ample, two RCTs were published in 2006. One indicated that symptoms of IBS decreased with four weeks of  $1 \times 10^8$  colony forming units of *Bifidobacterium infantis* compared with placebo, but not with higher or lower doses.<sup>13</sup> The other showed a decrease in abdominal pain but no significant difference in other symptoms.<sup>14</sup>

### Helicobacter gastritis

Evidence from laboratory and animal trials suggests that probiotic organisms are effective against *H pylori*. Clinical trials in humans have been conducted but many have been subject to limitations such as small numbers of participants and lack of placebo control. In some cases, probiotics were given along with standard *H pylori* eradication therapy with the aim of finding whether the probiotic could reduce the side effects of the eradication regimen rather than the efficacy of the probiotic.

A recent systematic review concluded that probiotics do not eradicate *H pylori* but maintain lower levels of the pathogen in the stom-

ach. In combination with antibiotics they may increase eradication rates or reduce adverse effects or both.<sup>15</sup> A more recent trial in 138 patients found that four-weeks' pretreatment with lactobacillus and bifidobacterium yogurt can improve the efficacy of quadruple therapy after triple therapy has failed.<sup>16</sup>

### Lactose intolerance

Lactose intolerance is a problem for a large number of people. If lactose is administered in yogurt containing live bacteria, the lactose is hydrolysed by bacterial lactase. This predigestion of lactose could potentially reduce the symptoms associated with lactose intolerance in susceptible individuals, but evidence from clinical trials is mixed.

A systematic review assessing the efficacy of oral probiotics in adults with lactose intolerance found that some probiotics may be effective in alleviating the signs and symptoms of this condition, but further trials of specific strains and concentrations are necessary.<sup>17</sup>

### Vaginal infections

Probiotics have been claimed to reduce the incidence of vaginal infections, particularly thrush. Lactic acid bacteria predominate in the normal flora of the vagina, generating an acid pH, which inhibits the growth of other organisms that can cause vaginal infections. A number of factors, such as pregnancy and diabetes, can contribute to changes in the vaginal microflora and cause vaginal infections.

There is limited evidence to support the effectiveness of probiotic preparations although several studies have shown that oral consumption of probiotics can alter vaginal microflora. The vaginal application of live yogurt has been recommended as a natural remedy for thrush but no RCTs have investigated the effects of topical application.

### Cholesterol

Probiotics have been evaluated for potential influence on serum cholesterol and other cardiovascular risk factors. However, evidence generated from studies so far has been mixed and if there is an effect at all, it appears to be weak.

### Bowel cancer

Regular, long-term consumption of probiotics has been suggested to protect against bowel cancer. The basis for this is that the acid pH in the colon generated by probiotics could prevent the growth of mutagen-generating bacterial species. However, there is no consistent evidence that probiotics prevent cancer in humans.

### Safety and quality

Side effects that have been recorded with the use of probiotics include abdominal bloating and flatulence. Although probiotics are largely safe, it may be wise not to recommend them for people who are severely immunocompromised.

Quality issues for probiotic products include:

## Panel 2: Examples of doses of probiotics in studies

Condition	Micro-organism(s)	Daily dose (number of organisms)
Diarrhoea in children	<i>Lactobacillus reuteri</i>	10–100 billion
Rotavirus diarrhoea	<i>Lactobacillus GG</i>	5–10 billion
Prevention of diarrhoea in children	<i>L GG</i>	12 billion
Prevention of antibiotic-associated diarrhoea	<i>L GG</i>	20 billion
Prevention of atopic allergy	Lactobacilli	20 billion
Irritable bowel syndrome	<i>B infantis</i>	1 billion
	<i>Lactobacillus plantarum</i>	20 billion
	VSL#3	450 billion
Ulcerative colitis	Lactobacilli/bifidobacteria	10 billion
<i>Helicobacter pylori</i> infection	<i>L acidophilus/B lactis</i>	5 billion

- **The bacterial content of the product** Does the product contain the bacterial species on the label? Does it contain any potentially pathogenic micro-organisms?
- **The viability of bacteria in the product** How many live organisms are present at the time of manufacture, the time of purchase and the time of consumption? Some products make no claim at all, while others claim the amount only at the time of manufacture. Some products, such as capsules, require the bacteria to be freeze-dried and such processes may also affect viability. A US study conducted by ConsumerLab.com found that among 26 probiotic products, eight contained less than 1 per cent of the claimed number of live bacteria or of the claimed minimum of 1 billion.

In addition, there has been debate about whether or not probiotic bacteria survive stomach acid and the journey along the gastrointestinal tract. According to a US review, evidence suggests that the bacteria can survive the gastrointestinal tract with survival rates of 20–40 per cent,<sup>18</sup> but the same review also stated that there is no evidence that orally administered probiotic organisms adhere to intestinal cells — they seem to pass into the faeces without adhering or multiplying, suggesting that, to produce benefit, the probiotic must be administered continually.

Another study, published by the UK Food Standards Agency in 2005,<sup>19</sup> involving 12 commercial products, found that most well known products matched their label claims in quality and content. However, not all the bacterial strains in the products had the ability to survive intestinal digestion. Overall the study showed that *Lactobacillus* species are resistant to the gastric environment but are sensitive to upper intestinal content, while bifidobacteria are more likely to be affected by gastric juice but survive well in the upper intestine. The researchers warned that this *in vitro* study of individual strains may not replicate the *in vivo* activity of a probiotic product containing several strains.

## Conclusion

There is promising evidence that probiotics could be beneficial in the prevention of diarrhoea, particularly antibiotic-associated diarrhoea, and the prevention of allergic disease. However, more research is needed to clarify findings.

The quality of some products in terms of claimed bacterial content and survival of micro-organisms in the intestine has been found wanting. Moreover, many people take these products for general gastrointestinal health and whether probiotics produce such benefits in healthy people is unclear.

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## Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Discuss with another pharmacist, whether or not you would recommend a synbiotic.
2. Do you stock probiotics? How can you assure the product's quality?
3. Train your staff on prebiotics and probiotics.

## Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

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