What is a probiotic?
For centuries living microorganisms, particularly lactic acid bacteria (producers of lactic acid from sugar) have been used in food preservation so there has been a long term awareness of the beneficial effects of microorganisms. However, the first reports of beneficial effects on human health linked to lactobacilli and bifidobacteria appeared in the late 19th/early 20th century (Tannock, 2003).

In 1965, Lilly and Stillwell proposed the term “probiotics” to refer to ‘substances produced by microorganisms which promote the growth of other microorganisms’ and the characteristics and properties of probiotics (Sanders, 2009) are listed in Table 1. The most widely adopted definition of probiotics is ‘live microorganisms which, when administered in adequate amounts, confer health benefits on the host’ (Joint FAO/WHO Expert Consultation, 2001). Health Canada (2009) suggests one possibility for probiotics to confer a health benefit would be by modulating the microbiota indigenous to humans. Organisms included in probiotic preparations are lactic acid bacteria (such as Lactobacillus acidophilus, L. casei, L. reuteri, L. rhamnosus, Lactococcus lactis, among others), bifidobacteria (e.g. Bifidobacterium animalis subsp. lactis, B. bifidum, B. infantis, B. longum), the yeast Saccharomyces boulardii, Enterococcus faecium and Enterococcus faecalis, Escherichia coli Nissle 1917 and Bacillus coagulans (L. sporogenes). Figure 1 provides examples of probiotic products.

Where do probiotics come from?
The human gastrointestinal (GI) tract has co-evolved with a very complex, stable microbial population (known as the gut microbiota) of more than 100 trillion (100,000,000,000,000) microorganisms comprising several hundred different species that has led to the development and optimization of complex immune mechanisms that control this ecosystem. The gut microbiota plays an important role in nutrition and metabolism (digestion, absorption, fermentation, vitamin synthesis and energy production), regulation of immune function (by stimulation of immunoglobulin and cytokine production), and protection
(colonisation resistance and production of antimicrobial substances). The genomes of the gut microbiota encode for metabolic activities distinct from those of the human microbiota, thus contributing directly to human physiology. Many factors, such as diet, food poisoning, infections, antibiotic therapy, stress and ageing can impact on the balance of the gut microbiota and gastrointestinal disturbances can range from mild to life threatening. There is a growing awareness of the importance of the relationship between the gut microbiota and human health and the potential for the manipulation of this relationship to achieve therapeutic effects.

**What are the benefits of probiotic use?**

The use of the probiotic strains has been widely investigated for a range of conditions, namely, diarrhoea in children, antibiotic-associated diarrhoea, *Clostridium difficile*-associated diarrhoea, traveller’s diarrhoea, Irritable bowel syndrome, Inflammatory bowel diseases (Crohn’s disease, Ulcerative colitis, Pouchitis), pancreatitis, necrotizing enterocolitis, colon cancer, allergic diseases including atopic dermatitis (eczema), urogenital infections, *Helicobacter pylori* gastric infection, prevention of common cold, winter infections, absences from work, lactose intolerance and oral health. The well-characterised immunomodulatory properties of probiotic bacteria have been used as a tool to alleviate intestinal inflammation, normalize gut mucosal dysfunction and down-regulate hypersensitivity reactions (Collado et al., 2009). In addition, recent work is identifying the role of probiotic organisms in energy metabolism.

**Safety of Probiotics**

Reports of infection due to lactobacilli and bifidobacteria (the most abundant probiotic strains) are extremely rare and have been estimated to represent only between 0.05-0.4% of cases of infective endocarditis and bacteraemia, and these mostly in immunocompromised patients. There is no evidence that ingested probiotic lactobacilli or bifidobacteria pose any risk of infection greater than that associated with commensal strains (Borriello et al., 2003). There is a general consensus of opinion that probiotics such as Lactobacilli and Bifidobacteria are suitable and well tolerated. To our knowledge, there are no reports of serious adverse events attributable to probiotics in healthy individuals.
Applications of Probiotics

Probiotic usage is being advocated within all areas of the gastrointestinal tract and the following is a summary of the range of applications with particular reference to our own studies with antibiotic resistance and probiotics and the Irritable Bowel Syndrome (IBS).

Mouth

The oral cavity is very densely populated with a complex microbiota, where many species have not yet been identified. It is known that 70% of dental plaque (biofilms) contains up to 10 billion bacteria (Teughels, 2009) but it is only recently that probiotics have been found to have a potential role in oral health in the prevention and treatment of oral infections, including dental caries (potential to alter colonisation of cariogenic bacteria), gingivitis and periodontitis. Krasse et al. (2006) found reduction in plaque levels and gingival inflammation with the application of *L. reuteri*. Furthermore, it has been suggested that there is an association between the oral microbiota and systemic disease, such as cardiovascular disease and complications during pregnancy (Allaker et al., 2009). Indirect probiotic actions within the oral cavity include the modulation of aspects of both innate and specific immune function.

Stomach

It is known that about half of the human population carries *Helicobacter pylori* in the stomach which is acquired in childhood (before the age of 10) and, in the absence of antibiotic therapy, will persist for life (Cover et al., 2009). *H. pylori* is associated with an increased risk of developing peptic ulcers, gastric cancer and mucosa-associated lymphoid tissue lymphoma and therapy involves use of a proton-pump inhibitor combined with two antibiotics (clarithromycin, amoxicillin or metronidazole). This therapy is frequently associated with adverse events but the use of probiotics in conjunction with the triple therapy has been found to reduce the frequency of the adverse events; with regard to *H. pylori* eradication, differences in the effectiveness have been observed depending on the strains used (Lenoir-Wijnkoop et al., 2007; Sullivan et al., 2005).
Intestine

Within the intestine, the best results relating to the use of probiotics have been obtained for the prevention and treatment of acute diarrhoea, including antibiotic-associated and *Clostridium difficile*-associated diarrhea (Lomax et al., 2009; Lenoir-Wijnkoop et al., 2007). There is also growing evidence for the capacity of probiotics to modulate immune function and reduce intestinal permeability.

One of the growing concerns relating to the use of antibiotics is the emergence of antibiotic resistant microorganisms in response to exposure of the gut microbiota to the antibiotics. On treatment with antibiotics, the balance of the gastrointestinal microbiota is disturbed and the numbers of organisms present in the gut decreases. However, any antibiotic resistant strains comprising part of the indigenous microbiota will be able to thrive under such conditions and the re-growth population is often dominated by the antibiotic resistant strains. In a placebo controlled double blind study it has been found that supplementation with probiotics during and post antibiotic therapy reduces the extent of disruption to the intestinal microbiota with a reduction in the incidence and total numbers of antibiotic-resistant strains in the re-growth population (Plummer et al., 2005; Madden et al., 2005).

The intestinal microbiota is considered a positive health asset that exerts a conditional effect on intestinal homeostasis with resident bacteria delivering regulatory signals to the epithelium to instruct mucosal immune responses. The composition of the gut microbiota is believed to influence the development of the immune response. Kelly et al. (2005) suggest that an imbalance between aggressive and protective bacterial species, or loss of gut bacteria that promote tolerance and Treg cell polarization could lead to excessive Th1 or Th2 responses, thus promoting inflammatory or allergic diseases. The recognition of the involvement of the gut microbiota (and more specifically lactobacilli and bifidobacteria) in the development of allergic diseases has led many researchers to develop strategies to modify gut microbiota. Several studies have shown a benefit in the prevention of atopic dermatitis in infants and older children, with a clear effect only for the prevention of eczema (Osborn, 2007; Reid, 2007). Benefits of probiotic supplementation on the symptoms of allergic rhinitis have also been observed.
(Vliagoftis et al., 2008) but not for asthma treatment, but, the modulation of immune response and inflammatory markers following probiotic administration has been widely recorded.

Within the intestine it has been found that probiotics supplementation shows promise with the Irritable Bowel Syndrome (IBS), a complex, multifactorial gastrointestinal disorder characterized by abdominal discomfort or pain and altered bowel habit with impact on quality of daily life and is a female dominated condition with female: male ratio of 2-2.5:1 (Adeyemo et al., 2008). The prevalence of IBS in the general population varies from 3% to 25%, in USA IBS affects 15 million adults, in Canada more than 2 million people and in UK 10-15% of adult population (McFarland et al., 2008; Clement, 2008). IBS pathogenesis is far from clearly defined and most hypotheses focus on one or more of the following: altered intraluminal milieu, immune activation, enteric neuromuscular dysfunction and/or brain-gut axis dysregulation. The pharmacological therapy for IBS can involve antidiarrhoeals, laxatives, antispasmodics, antidepressant and serotonergic agents (Hammerle et al., 2008) but success with these drugs has been limited (some are associated with safety issues) and, hence, it is not surprising that many IBS sufferers are turning to complementary and alternative therapies, such as probiotics, peppermint oil, soluble fibre, hypnotherapy and cognitive-behavioural therapy (Shen et al., 2009). An overview of studies performed with probiotics in IBS treatment is shown in Table 2.

IBS may result from a dysfunctional interaction between the indigenous flora and the intestinal mucosa leading to immune activation in the colonic mucosa and changes in the colonic microbiota could result in the proliferation of gas-producing organisms or in organisms that facilitate deconjugation of bile acids impacting upon water and electrolyte transport within the colon. Quigley et al. (2007) reviewed the use and efficacy of probiotics in IBS and suggested a clear rationale for probiotic usage in response to a dysfunctional relationship between the indigenous microbiota and the host. The authors further suggested the feasibility of probiotics for bacterial displacement and alteration of luminal content. However, clarification is required regarding the need for clear definition of strains, dosage and viability of the probiotic organisms in use. Kassinen et al. (2007) have shown lower numbers of both lactobacillus spp. and bifidobacteria in the microbiota of IBS sufferers suggesting the need for a product comprising both organisms.
In our own experience, the use of a probiotic comprising both *Lactobacillus acidophilus* and *Bifidobacterium* spp. (LAB4) in a double blind placebo controlled trial (Williams et al., 2009) resulted in a significantly greater improvement in the Symptom Severity Score of IBS and in scores for Quality of Life, Days with Pain and Satisfaction with Bowel Habit over the 8 week intervention period in the volunteers receiving the probiotic.

**Conclusion:**
The scope of probiotics seems endless! It seems that more and more applications for the involvement of probiotic supplements are being identified, almost on a daily basis. There are inconsistencies in the results that have been obtained but much of that relates to the testing of a diversity of products with different compositions and potencies. It is apparent that there are benefits from probiotics across a broad spectrum of conditions, many of which are linked with antibiotic therapy. As our knowledge of the value of the gastrointestinal microbiota is growing, so is the awareness of the potential for probiotics and as the mechanistic details of the mode of action of probiotics becomes clearer, further developments will occur. Overall, the message for probiotics and the gastrointestinal tract is “watch this space”.

**References**


Borriello SP et al. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis* 2003; 36: 775-780.


Table 1 Characteristics and properties of probiotic

<table>
<thead>
<tr>
<th>Probiotic characteristics</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Microorganism</strong></td>
<td>Live bacteria or yeasts, when administered with proven health benefit on the host. Dead bacteria, live vaccine are not considered to be probiotics.</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td>Human or animal intestinal tract</td>
</tr>
<tr>
<td><strong>Identification</strong></td>
<td>Must be identified at the genus, species and strain levels using current recommended genetic and phenotypic methods and correctly named according current nomenclature</td>
</tr>
<tr>
<td><strong>Properties</strong></td>
<td>Non-pathogenic and non-toxic; resistant to gastric acid, digestive enzymes and bile acids in small intestine, if the target site is large intestine; adherence to mucus, intestinal cells; transient colonisation of the intestinal tract; remain viable during transport and retain stability during the guaranteed shelf life of the product.</td>
</tr>
<tr>
<td><strong>Safety assessment</strong></td>
<td>Antibiotic resistance profile and potential horizontal transfer of antibiotic resistance genes to other more pathogenic microorganisms; virulence factors; adverse immunological effects; assessment of certain metabolic activities (e.g., D-lactate production), the route and dose of administration; health status of the consumers; assessment of adverse events during human intervention studies; post-market surveillance of adverse incidents in consumers.</td>
</tr>
<tr>
<td><strong>Mechanism of actions</strong></td>
<td>Antimicrobial activity against potentially pathogenic bacteria (production of bacteriocins and organic acids); ability to reduce pathogen adhesion to surfaces; modulate immune responses; improve gut mucosal barrier function; modulate epithelial cell gene expression; promote recovery of commensal microbiota when perturbed.</td>
</tr>
</tbody>
</table>
Figure 1 Range of probiotic formats available on market and scanning electron micrographs of *Lactobacilli* cells
### Table 2 Summary of selected double-blind randomised controlled studies on probiotics and IBS treatment times and dosages.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Probiotic</th>
<th>Duration</th>
<th>Dose</th>
<th>(No. of subjects)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kajander 2005</td>
<td>L. rhamnosus GG, L. rhamnosus LC705, B. breve Bb99, Propionibacteriumfreudenreichii ssp. shermanii</td>
<td>6 months</td>
<td>8-9x10⁹ cfu/day</td>
<td>81</td>
<td>Significant difference in Total symptom score (abdominal pain +distension +flatulence + borborygmi).</td>
</tr>
<tr>
<td>Niv 2005</td>
<td>L. reuteri ATCC 55730</td>
<td>6 months</td>
<td>2x10⁸ cfu/day</td>
<td>(39)</td>
<td>No significant difference in relieving IBS symptoms between the groups</td>
</tr>
<tr>
<td>Kajander 2008</td>
<td>L. rhamnosus GG, L. rhamnosus LC705, B. animalis ssp.lactis Bb12 and Propionibacteriumfreudenreichii ssp. shermanii JS</td>
<td>5 months</td>
<td>4.8x10⁹ cfu/day</td>
<td>(86)</td>
<td>Significant difference between groups in symptom score (abdominal pain +distension +flatulence + rumbling).</td>
</tr>
<tr>
<td>Williams 2009</td>
<td>L. acidophilus CUL21 (NCIMB 30156) L. acidophilus CUL60 (NCIMB 30157) B. bifidum CUL20 (NCIMB 30153) B. lactis CUL34 (NCIMB 30172)</td>
<td>8 weeks</td>
<td>2.5x10¹⁰ cfu/day</td>
<td>(48)</td>
<td>Significant improvement in the Symptom Severity Score (abdominal pain, days with pain, bloating, satisfaction with bowel habits and quality of life) in probiotic group compared to placebo.</td>
</tr>
<tr>
<td>O'Mahony 2005</td>
<td>B. infantis 35624 or L. salivarius UCC4331</td>
<td>8 weeks</td>
<td>2x10¹⁰ cfu/day</td>
<td>(67)</td>
<td>B. infantis 35624 was more effective in the relief of IBS symptoms and improvement of IL-10/IL-12 ratio than L. salivarius UCC4331.</td>
</tr>
<tr>
<td>Enck 2008</td>
<td>ProSymbioflor: E. faecalis (DSM 16440) E. coli (DSM 17252).</td>
<td>8 weeks</td>
<td>3-9x10⁷ cfu/day</td>
<td>(264)</td>
<td>Significant difference in global symptom score between two groups.</td>
</tr>
<tr>
<td>Guyonnet 2007</td>
<td>Fermented milk ActiviaDanone: B. animalis DN-173010, S. thermophilus, L. bulgaricus</td>
<td>6 weeks</td>
<td>2.74x10¹⁰cfu/d</td>
<td>(267)</td>
<td>No significant difference in Health-related quality of life (HRQoL) discomfort score between two groups.</td>
</tr>
<tr>
<td>Bausserman 2005</td>
<td>L. rhamnosus GG</td>
<td>6 weeks</td>
<td>2x10¹⁰/day</td>
<td>(50)</td>
<td>Significant difference in abdominal distention between groups.No significant effect in relieving abdominal pain between groups.</td>
</tr>
<tr>
<td>Kim 2005</td>
<td>VSL#3 product: B. longum, B. infantis, B. breve, L. acidophilus, L. casei, L. delbrueckii ssp. bulgaricus, L. plantarum and Streptococcus salivarius ssp. thermophilus</td>
<td>4 weeks</td>
<td>4.5x10¹¹ cfu/day</td>
<td>(48)</td>
<td>No significant difference in abdominal pain or bloating between two groups. Significant reduced flatulence and colonic transit time.</td>
</tr>
<tr>
<td>Drouault-Holowacz 2008</td>
<td>B. longum LA 101, L. acidophilus LA 102, L. lactis LA 103, S. thermophilus LA 104</td>
<td>4 weeks</td>
<td>1x10¹⁰ cfu/day</td>
<td>(100)</td>
<td>No significant difference in relieving symptoms of IBS between two groups.</td>
</tr>
<tr>
<td>Whorwell 2006</td>
<td>B. infantis 35624</td>
<td>4 weeks</td>
<td>3 xDose: 1x10⁶ cfu/ml, 1x10⁸ cfu/ml, 1x10¹⁰ cfu/ml</td>
<td>(362)</td>
<td>Dose 1x10⁸ cfu/ml: Significant difference in overall assessment of IBS symptoms. Doses 1x10⁶ cfu/ml and 1x10⁸ cfu/ml were not significant different from placebo, 1x10¹⁰ dose was associated with significant formulation problems.</td>
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