Orally ingested probiotic micro-organisms do not exert health effects exclusively in the intestine. Some strains can alleviate or prevent bacterial, fungal or viral infections in other organs by stimulation of the immune system. By preservation or improvement of the barrier function of the intestinal mucosa, they may inhibit translocation of potential pathogens and thus prevent infections of the blood stream and other tissues and organs. Modulation of the intestinal microflora can affect the local microflora of the urogenital tract and possibly of the oral cavity. Finally, some strains of orally ingested bacteria reach target organs like the urogenital tract in a viable state; alternatively they can be applied locally.

Despite the infection-preventing properties of probiotic bacteria, lactic acid bacteria have rarely been identified in infections of the blood stream, heart valves and other organs, usually only in patients with severe disease. It is the general opinion that in most cases the source of infection was the commensal microflora of the intestine or the oral cavity. Until now only one case of infection associated with administration of a probiotic strain has been published.

The most promising health-promoting effects have been seen in vaginosis, urinary tract infections, Helicobacter pylori gastritis and infections of the respiratory tract in children. More controlled clinical trials with sufficient numbers of participants are needed to determine the scientific basis for the use of probiotic bacteria in infections in locations of the body other than the intestine.

**Probiotics: Non-intestinal infections**

**Introduction**

Many of the widespread older definitions of the term ‘probiotic’, for example Fuller (1989): ‘a live microbial feed supplement which beneficially affects the host (animal) by improving its intestinal microbial balance’, confine probiotic effects to modulation of the microflora and/or immune system of the intestine. In contrast to this, the definition of Schrezenmeir & de Vrese (2001), namely ‘a probiotic is a preparation or product containing viable, defined microorganisms in sufficient numbers, which alters the microflora in a compartment of the host and by that exerts health effects in this host’ emphasises that besides the intestine, other compartments of the body may be targets for probiotic micro-organisms, where an alteration of the microflora may exert health effects.

However, the ‘natural’ target of ingested probiotics is the intestine, its microflora and the associated immune system, and therefore investigations and clinical studies of non-intestinal infections are rather scarce. Possible applications for probiotics outside the intestine are bacterial and fungal infections of the oral cavity, the upper respiratory tract and the lungs, the stomach and the urogenital tract. Common viral infections like the common cold or influenza are another target for probiotics. This would be of relevance to a large number of otherwise healthy subjects.

**Urogenital tract infections**

Bacterial and fungal infections of the urogenital tract are the most promising field of application for probiotics other than the intestine. Bacterial vaginosis, candida vaginitis and infections of the urethra, bladder, ureter, kidney or cervix affect 300 million women per year world-wide. They are due to microbial invasion or an imbalance of the urogenital microflora (Reid, 2001).

The flora of the vagina and the urinary tract consists of a well-balanced system of about fifty bacterial strains. Lactobacilli dominate the healthy flora of premenopausal women. They are believed to protect the host against infections by means of several mechanisms, including: (1) occupation of specific adhesion sites at the epithelial surface of...
the urinary tract; (2) stabilisation of a low pH and the production of antimicrobial substances like acids, hydrogen peroxide and bacteriocines; (3) the degradation of polyamines; and (4) the production of surfactants, which have anti-adhesive properties against the adhesion of pathogens (Reid, 2001). The balance can be disturbed by the overgrowth of indigenous bacteria of the vagina like Gardnerella, Bacteroides, Peptostreptococcus, Prevotella spp. or aerobic cocci, or by the invasion of foreign micro-organisms, such as Escherichia coli, Enterococcus faecalis, enterobacteriaceae, staphylococci or candida.

An obvious goal is to attempt to restore an unbalanced urogenital flora by adding protective ‘probiotic’ lactobacilli. Indeed, some efforts have been made to select lactobacilli strains that show the above protective properties to a high degree. Both pathogenic and probiotic microorganisms may enter the urogenital tract by a variety of different routes. They come mainly from the colon and rectum via the perineum. However, when the immune system is stressed, translocation of gut bacteria through the intestinal wall is possible. Probiotic lactobacilli can act via immunostimulation or inhibition of bacterial translocation. After entering the colon, they may alter the colonic microflora positively, and certain strains may reach the vagina and the urinary tract in a viable state (Reid et al., 2001). Alternatively, probiotics can be applied locally using appropriately treated tampons or gel beads, for example.

For many decades anecdotal reports rather than controlled studies have been published which show promising results of the oral or local application of yoghurt in vaginosis. However, studies showing eradication of pathogens, reduction of symptoms or fewer episodes of recurrent bacterial vaginosis were usually open, and the numbers of subjects were small (Table 1).

Comparable results were obtained in open and placebo-controlled studies, in which lyophilised Lactobacillus acidophilus was applied locally (Hallen et al. 1992; Parent et al. 1996) or L. acidophilus yoghurt was given orally (Hilton et al. 1992). In these studies success rates for bacterial vaginosis or candida-vaginitis ranged from 57 to 88 % in the probiotic group and from 0 to 22 % in the control group. A rationale for the efficacy of orally ingested yoghurt was given by Reid and co-workers (2001), who proved using molecular typing that orally ingested probiotics reach the vagina in a viable state. Overall, more controlled clinical trials are needed to determine the scientific basis for the use of probiotic bacteria instead of or in conjunction with antibiotics in vaginosis and vaginitis.

Only a small number of human studies show positive health effects of probiotics in urinary tract infections (Table 2). Much of the work in this field was done by Reid and co-workers (2001). Since 1988 they have identified promising strains of Lactobacillus rhamnosus, L. acidophilus or Lactobacillus fermentum. These strains showed tight adhesion to epithelial surfaces, hydrogen peroxide production, or the release of biosurfactants. In a human study with forty-nine subjects, the local application of L. rhamnosus reduced the rate of urinary tract infections by 73 % (Reid & Bruce, 1995). This corresponds to in vitro and animal studies showing inhibitory effects of L. acidophilus and L. rhamnosus strains on growth and adhesion of some potentially pathogenic bacteria and Candida strains (Table 2). The possible importance of immunological mechanisms is underlined in a study where Lactobacillus casei Shirota inhibited the growth of E. coli and decreased inflammation in E. coli-infected mice, even when the bacteria were heat-killed (Asahara et al. 2001). More controlled clinical trials are needed.

**Helicobacter pylori infections**

The role of *Helicobacter pylori* in the aetiology of gastritis, gastric ulcer and gastric carcinomas and lymphomas is well established. More than 70 % of the ulcers of the gastric mucosa and duodenum are considered a consequence of *H. pylori* infection. Although it has been demonstrated that some strains of lactic acid bacteria inhibit the growth of *H. pylori* in vitro (Bhatia et al. 1989; Cocomnier et al. 1998) and show adhesion to CaCo-2 cells (Brassart et al. 1993), results from investigations in gnotobiotic

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**Table 1. Studies in vaginosis/vaginitis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study*</th>
<th>n</th>
<th>Probiotic</th>
<th>Application</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>O</td>
<td></td>
<td>Yoghurt</td>
<td>local</td>
<td>Non-specific vaginitis ↓, trichomonas vaginitis ↓</td>
<td>Gunston &amp; Fairbrother (1975)</td>
</tr>
<tr>
<td>1992</td>
<td>R, P, dB</td>
<td>57</td>
<td>L. acidophilus (lyophilised)</td>
<td>local</td>
<td>Cure rate sixteen out of twenty-eight (probistic) v. zero out of twenty-nine (placebo)</td>
<td>Hallen et al. (1992)</td>
</tr>
<tr>
<td>1995</td>
<td>O</td>
<td></td>
<td>Yoghurt</td>
<td>local</td>
<td>Symptoms ↓, pH ↓, eradication 54 %</td>
<td>Chimura et al. (1995)</td>
</tr>
<tr>
<td>2001</td>
<td>O</td>
<td>10</td>
<td>L. rhamnosus, L. fermentum in milk</td>
<td>oral</td>
<td>Orally administered probiotics were identified in the vagina by molecular typing. Cure rate 60 %</td>
<td>Reid et al. (2001)</td>
</tr>
</tbody>
</table>

mice (Kabir et al. 1997) and man have been somewhat surprising. Although, by definition, probiotics should reach the intestine to exert health effects — ingestion of Lactobacillus salivarius, L. acidophilus or Lactobacillus johnsonii prevented H. pylori infection, reduced the activity of H. pylori in the stomach and attenuated H. pylori gastritis (Table 3), indicating an effect on the stomach as well.

Helicobacter ‘activity’ is measured by means of the cleavage of the marker 13C-urea and the resulting increase in the ratio of 13CO2 to 12CO2 in the exhaled air. Human studies have shown that the outcome of the urea-breath test correlates significantly with mucosal concentrations of H. pylori (estimated from biopsies) or the degree of gastritis, respectively (correlation r = 0.32 and r = 0.53, respectively; Hilker et al. 1996). Perri et al. (1998) concluded that the urea-breath test is an appropriate measure to estimate both H. pylori concentration and gastritis.

Studies involving the effect of L. acidophilus, L. rhamnosus or Bifidobacterium longum on antibiotic-induced diarrhoea have been performed in Helicobacter-infected subjects during eradication therapy (de Vrese et al. 2001a). The ingestion of these probiotics as a yoghurt for four weeks significantly decreased Helicobacter activity even before Helicobacter eradication. This effect was independent of whether the probiotic bacteria were viable or heat-killed (Fig. 1; de Vrese & Schrezenmeir, 2000a). This makes it probable that the effect on Helicobacter activity was caused by a component of the milk or the bacterial cell wall or by a fermentation product in the yoghurt.

### Table 2. Studies in urinary tract infections

<table>
<thead>
<tr>
<th>Year</th>
<th>Study/model*</th>
<th>n</th>
<th>Probiotic</th>
<th>Application</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>Screening</td>
<td>29</td>
<td>B. longum</td>
<td>oral</td>
<td>– 70 % candida infections in urethras (responders)</td>
<td>Tomoda et al. (1988)</td>
</tr>
<tr>
<td>1996</td>
<td>Screening 50</td>
<td>Fifteen strains of lactobacilli</td>
<td>local</td>
<td>Urinary tract infection rate – 73 %</td>
<td>Reid &amp; Bruce (1995)</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Mice†</td>
<td>L. fermentum in agarose beads</td>
<td>in vitro</td>
<td>Biosurfactant production ↓ ; E. faecalis adhesion ↓</td>
<td>Velraads et al. (1996)</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Mice‡</td>
<td>(Heat-killed) L. casei Shirota</td>
<td>local</td>
<td>Moderately effective, E. coli ↓</td>
<td>Silva de Ruiz et al. (1996)</td>
<td></td>
</tr>
</tbody>
</table>

* Study type: O, open; R, randomised; P, placebo-controlled; dB, double-blind; X, cross-over design; M, multicentre.
† The urinary tract of the mice was infected with E. coli, and low-doses of ampicillin were given.
‡ The urinary tract of the mice was infected with E. coli.

### Table 3. Effects of probiotics on Helicobacter pylori (Hp) activity and gastritis

<table>
<thead>
<tr>
<th>Year</th>
<th>Study/model*</th>
<th>n</th>
<th>Probiotic</th>
<th>Application</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>CaCo-2 cells</td>
<td>Preinoculation with L. johnsonii</td>
<td>Hp adhesion to CaCo-2 cells ↓</td>
<td>Brassart et al. (1993)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>gnotobiotic mice</td>
<td>L. salivarius</td>
<td>Prevention of Hp infection and gastritis ↓</td>
<td>Kabir et al. (1997)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Study type: O, open; R, randomized; P, placebo-controlled.
Respiratory tract infections

Very little is proven concerning the effects of probiotic bacteria in respiratory tract infections. It has been shown in animal experiments, when *Lactobacillus plantarum* and *Lactobacillus fermentum* were administered intranasally to mice, that the mucosa of the respiratory tract is an appropriate area for probiotics to induce immune stimulation. In clinical studies, ingestion of *Bifidobacterium longum* or yoghurt bacteria increased the number of macrophages in the lungs, and administration of a bifidobacteria preparation to children with respiratory tract infections stimulated immunological parameters (Table 4b). However, it is not clear if and to what degree this immunostimulation led to attenuated or shorter infections (Lykova *et al.* 1996; Moineau & Goulet, 1997; Cangemi de Gutierrez *et al.* 2000; Grangette *et al.* 2001).

Miscellaneous infections

The use of probiotics in bacterial infections of other organs has been studied to a limited extent (Table 4c). Some authors have published open studies, in which the ingestion of probiotics reduced or enhanced *Candida* concentrations in liver, spleen and the lungs or inhibited translocation of pathogenic bacteria from the intestine into internal organs in subjects with a sub-optimal immune system (Tomoda *et al.* 1988).

An unusual finding is that the administration of *Lactobacillus casei* to *Trichinella*-infected mice increased interferon gamma and decreased significantly the number of trichinae in the muscles. This was due to an eradication of the adult trichinae in the intestine due to immunostimulation (Bautista-Garfias *et al.* 1999).

Common viral infections

The mechanisms by which probiotics exert effects against viral infections is considered to be by immunostimulation and not by direct competition with the infectious agent in the gut. Therefore, probiotics with proven immunostimulatory properties may be appropriate candidates for the prevention or treatment of viral infections. This has been investigated in rotavirus infections and also for viruses whose target organ is not the intestine. Examples include polio, hepatitis and the group of viruses involved in common viral diseases (Table 5).

The effect of orally administered strains of *L. rhamnosus*...
Bifidobacterium and L. paracasei during oral infection with an enterovirus, namely polio I, II and III, was investigated in a randomised, double-blind, placebo-controlled clinical study (de Vrese et al. 2001b). For this purpose sixty-six subjects in three groups ingested one of two probiotic yoghurt products or a chemically acidified milk product as the placebo for 8 weeks. One week after the beginning of the yoghurt period, the subjects were vaccinated orally with live attenuated polioviruses. Ingestion of both probiotic yoghurts enhanced significantly the vaccination-induced increase in poliovirus-neutralising antibody concentration in serum. Neutralising antibody titres — mainly immunoglobulin (Ig)A — were measured as the potency of a stepwise diluted serum to protect cultured cells against a lethal poliovirus infection.

The increase in polio-specific IgG and IgA in serum after vaccination was also significantly enhanced by factors of about 2.2 or 4, respectively, in volunteers consuming probiotic yoghurts compared with placebo. The study showed that probiotics induce an immunological response and provide protection from polioviruses by increased production of virus-neutralising antibodies.

The evidence that the consumption of certain probiotics can reduce the risk of some common viral infections like the common cold or influenza would be of great interest because a great number of otherwise healthy subjects regularly suffer from common virus diseases. The first evidence that some probiotic strains could be effective in this way came from experiments in influenza (and rotavirus) infected mice. In the group that received a probiotic strain of Bifidobacterium breve more mice had anti-influenza-IgG concentrations above 400 U and had a higher survival rate (Yasui et al. 1999). The first controlled study which showed that long-term consumption of probiotic bacteria had positive effects on common gastrointestinal and respiratory tract infections in an otherwise healthy population was performed in Finland. Three hundred and seventy-one children (aged 1–6 years) from day-care centres consumed milk with or without the probiotic L. rhamnosus strain daily for seven months. In the probiotic group fewer children had respiratory tract infections (17% reduction compared to the placebo group). These children also had fewer days away from the centres because of gastrointestinal and respiratory tract illnesses (4.9 versus 5.8 days) and needed less antibiotic administration. However no differentiation was made in the study between viral and microbial infections (Hatakka et al. 2001).

### Infectivity of probiotic bacteria

With one exception no probiotic micro-organisms have been identified in isolates from clinical infections. Therefore the rest of this section deals with the infectivity of lactobacilli and bifidobacteria in general.

Lactobacilli and bifidobacteria, which include most of the probiotic micro-organisms used in the food industry, are generally considered safe because they are common components of the commensal microflora of humans and many lactic acid bacteria have a long history of consumption without harmful effects. In Germany, for example, lactobacilli and bifidobacteria are assigned to risk group 1 — no

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**Table 5. Probiotics in virus infections**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study*</th>
<th>Probiotic Application</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>mice</td>
<td>* oral</td>
<td>B. breve</td>
<td>Anti-rotavirus IgA</td>
</tr>
<tr>
<td>2000</td>
<td>R, P; oral polio vaccination</td>
<td>L. rhamnosus, L. paracasei oral (yoghurt)</td>
<td>Anti-poli IgA</td>
<td>de Vrese et al. (2001b)</td>
</tr>
<tr>
<td>2001</td>
<td>R, P; oral polio vaccination</td>
<td>L. rhamnosus, L. acidophillus, B. bifidum oral (lyophilisate)</td>
<td>NS</td>
<td>de Vrese &amp; Schrezenmeir (2000b)</td>
</tr>
<tr>
<td>2001</td>
<td>R, P; 371 healthy children</td>
<td>L. rhamnosus for seven months oral</td>
<td>- 17% respiratory tract-infected children; 4-9 days of illness (control) v. 5.8 days (placebo)</td>
<td>Hatakka et al. (2001)</td>
</tr>
</tbody>
</table>

* Study type: R, randomized, P, placebo-controlled.

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**Table 6. Infectivity of lactic acid bacteria and yeasts**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Strain</th>
<th>Isolated from</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oakey et al. (1995)</td>
<td>Lb spp., Sc spp. (eF)</td>
<td>Endocarditis</td>
<td>&lt;0.6%</td>
</tr>
<tr>
<td>Brook &amp; Frazier (1993)</td>
<td>Bb spp., Lb spp. (eF)</td>
<td>Abdominal abscesses</td>
<td>0.24%</td>
</tr>
<tr>
<td>Saxelin et al. (1996)</td>
<td>L. casei (LGG)</td>
<td>Blood cultures</td>
<td>2%</td>
</tr>
<tr>
<td>Adams (1999)</td>
<td>L. rhamnosus, casei, L. reuteri, L. acidophilus (kP)</td>
<td>Infections*</td>
<td>2%</td>
</tr>
<tr>
<td>Adams (1999)</td>
<td>Ec spp.</td>
<td>Endocarditis</td>
<td>1-6%</td>
</tr>
<tr>
<td>Rogasi et al. (1998)</td>
<td>L. casei</td>
<td>Pneumonia and sepsis*</td>
<td>1-6%</td>
</tr>
<tr>
<td>Piarroux et al. (1999)</td>
<td>Saccharomyces bouardii (sometimes a wrongly identified S. cerevisiae)</td>
<td>Fungemia</td>
<td>1-6%</td>
</tr>
<tr>
<td>Rautio et al. (1999)</td>
<td>L. rhamnosus (undistinguishable from LGG)</td>
<td>Liver abscesses</td>
<td>One case</td>
</tr>
</tbody>
</table>

*Immunodefficient subjects.

Bb, Bifidobacterium; Lb, Lactobacillus; Sc, Streptococcus; Ec, Enterococcus; eF, from the endogenous intestinal flora; nP, no probiotics.
health risk — by the ‘Professional Association of the Chemical Industry’ (Berufsgenossenschaft der Chemischen Industrie, 1997). Only L. rhamnosus strains and Bifidobacterium dentium are placed in group 2 — small risk. Although lactobacilli, bifidobacteria or the probiotic yeast Saccharomyces boulardii have been identified in infections of the blood stream (bacteraemia), heart valves (infectious endocarditis), the cerebral membrane (meningitis), the urinary tract, the liver and other organs (Aguirre & Collins, 1993; Oakey et al. 1995; Adams, 1998; Rogasi et al. 1998; Piarroux et al. 1999), infections by lactobacilli, lactococci and bifidobacteria, especially those strains which include food probiotics, are rare. Examples are given in Table 6. Gasser (1994) reported that lactic acid bacteria accounted for 0.05–0.4% of cases of infective endocarditis, whereas streptococci and staphylococci accounted for nearly 80%. Among 3317 blood culture isolates from southern Finland analysed between 1989 and 1992 (Saxelin et al. 1996) lactobacilli were identified in only eight samples. This was equivalent to a prevalence of lactobacilli-induced blood-stream infections of 0.24%; in France, 0.1% of cases of bacteraemia were caused by Lactobacilli (Gasser, 1994).

A prerequisite of lactic acid bacteria infection is impaired host health. These infections are probably opportunistic infections, e.g. due to skin lesions or injuries of internal organs. For example, the starting point of infectious endocarditis is frequently a (transient) bacteraemia caused by micro-organisms from the oral cavity, which entered the blood stream through lesions of the oral mucosa or following dental surgery. Bacterial translocation through the intestinal mucosa and subsequent invasion via mesenteric lymph nodes or the portal vein also plays an important role in bacteraemia, which may progress to septicaemia and infections of other inner organs. Translocation is promoted by many conditions which decrease the intestinal barrier: injuries of the intestinal mucosa, infections or inflammatory diseases of the gut, abdominal surgery, intestinal bacterial overgrowth, massive antibiotic treatment and/or host immunodeficiency, i.e. after chemotherapy, radiation or in HIV-infected patients. There is no proven difference between the commensal microflora of the host and (probiotic) lactic acid bacteria administered orally with respect to the above mechanisms. However, it is still unclear to what extent orally ingested bacteria and food probiotics actually translocate, particularly as most of the existing studies have not recorded the dietary habits of the patients.

Investigations in germ-free mice have shown that after oral mono-association of the mice with a probiotic Bifidobacterium longum strain, bifidobacteria translocated and were found in the mesenteric lymph nodes, liver and kidneys one week later. Translocation of probiotic bacteria had no harmful effects but increased the barrier function of the intestinal mucosa and inhibited translocation of the other bacteria. After a latency period of 4 weeks no further bacterial translocation was observed, neither of B. longum nor of other (potentially pathogenic) bacteria administered to the mice (Yamazaki et al. 1982).

In most cases the source of clinical infections by lactobacilli and bifidobacteria is thought to be the commensal microflora of the intestine or the oral cavity, and not orally ingested probiotic micro-organisms. To confirm this, the identification of specific strains by molecular biological methods is required. Until now only one case of a probiotic infection has been published, which probably was caused by probiotic lactobacilli. This was in 1999, when Rautio and colleagues isolated a L. rhamnosus strain from a liver abscess that was indistinguishable from the probiotic L. rhamnosus strain GG (Rautio et al. 1999).

Comparing the scarcity of infections by lactobacilli and bifidobacteria with the quantity of probiotic ingested, probiotic lactobacilli and bifidobacteria can be regarded as safe. There is no indication that reduced consumption of probiotic bacteria would decrease the number of such infections.

References


Cangemi de Gutierrez RC, Santos de Araoz VS & Nader-Macias ME (2000) Effect of intranasal administration of Lactobacillus


