Introduction
Interest in probiotics has grown over the past two decades, particularly as a result of recent research investigating the role gut microbiota play in the development of chronic diseases.

**KEY MESSAGES**
- The clinical use of probiotics has benefitted from recent quality randomised clinical trials (RCTs).
- Cochrane review supports the beneficial effects of specific probiotic strains in the treatment of antibiotic-associated diarrhoea in children and adults.
- Prevention of necrotising enterocolitis (NEC) with probiotics in preterm infants is widely accepted, with supportive evidence from South African studies in HIV-exposed premature infants.
- Probiotics show potential in the prevention of chronic disorders (obesity, metabolic disorders, non-alcoholic fatty liver disease).
- A South African probiotic developed at the University of Stellenbosch has passed the key hurdles of safety and efficacy studies in both in vitro and in vivo systems. Further clinical studies are warranted.

Probiotics are defined as ‘live microorganisms that beneficially affect the host by improving microbial balance’.\(^1\)
A recent WHO Food and Agricultural Organisation definition has redefined this to include the need for adequate levels of probiotics to be administered. This definition states that ‘probiotics are live organisms which, when administered in adequate amounts, confer health benefits to the host.’

Probiotics have been shown to provide beneficial effects by replenishing natural gastrointestinal flora. In African culture, fermented milk is regarded as having health benefits for the gastrointestinal tract. The popularity of probiotics is reflected in the fact that many of today’s ‘functional foods’ contain probiotics.

In pharmaceutical medicine, probiotics are classified as ‘nutraceuticals’ and offer a more concentrated form of the probiotic or probiotic combination.

Initial trials of probiotics suffered from many shortcomings, similar to those of dietary supplements. In the last decade, however, a large number of scientific studies have addressed the mechanism of action of probiotic strains. Increasingly, clinical trials are undertaken to support ‘health claims’ and to provide a better understanding of which probiotics are beneficial and to define their evidence-based use.
Major micro-organisms considered to be probiotics

Lactic acid bacteria are the major group of bacteria suitable for use as probiotics. They are Gram-positive and catalase-negative, and produce lactic acid as the main end product from the fermentation of carbohydrates. The most important genera are *Lactobacillus* and *Bifidobacterium*, which are used in food products and nutraceuticals. *Enterococcus* is also an important lactic acid bacterium, which is often used in combination with either *Lactobacillus* or *Bifidobacterium*. Table 1 provides a list of species used and cited in clinical research.2

### Table 1. Micro-organisms considered to be probiotics

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
<th>Bifidobacterium species</th>
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</thead>
<tbody>
<tr>
<td><em>L. acidophilus</em></td>
<td><em>B. adolescentis</em></td>
</tr>
<tr>
<td><em>L. casei</em></td>
<td><em>B. animalis</em></td>
</tr>
<tr>
<td><em>L. crispatus</em></td>
<td><em>B. bifidum</em></td>
</tr>
<tr>
<td><em>L. gallinarum</em> (Mainly used in animals)</td>
<td><em>B. breve</em></td>
</tr>
<tr>
<td><em>L. gasseri</em></td>
<td><em>B. infantis</em></td>
</tr>
<tr>
<td><em>L. johnsonii</em></td>
<td><em>B. lactis</em> (Recently reclassified as <em>B. animalis</em> subsp. <em>lactis</em>)</td>
</tr>
<tr>
<td><em>L. paracasei</em></td>
<td><em>B. longum</em></td>
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<tr>
<td><em>L. plantarum</em></td>
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<tr>
<td><em>L. reuteri</em></td>
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<tr>
<td><em>L. rhamnosus</em></td>
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### Essential probiotic properties

Probiotics need to be able to withstand the harsh gastric environment to reach the intestine and adhere to the mucosal and epithelial surfaces. *In vitro* tests are used to determine the following desirable properties:
1. Acid and bile tolerance; essential for oral administration
2. Adhesion to mucosal and epithelial surfaces to compete with and exclude pathogenic bacteria from the receptor
3. Production of antimicrobial activity against pathogenic bacteria (so that the probiotic can compete even more successfully with pathogenic bacteria)
4. Bile salt hydrolase activity
5. Resistance to certain antibiotics, so that the probiotic is able to restore the microbial balance and prevent antibiotic side-effects
6. Quantity of viable micro-organisms, although not precisely defined, should reach a minimum total of $10^8$ – $10^9$ colony forming units (CFUs). Viability should also be maintained under normal storage conditions.

### Mechanisms of action

Probiotics have various mechanisms of action. These include the production of bacteriocins (antibacterial peptides) and short-chain fatty acids, lowering of gut pH, stimulation of mucosal barrier function and immunomodulation. There is considerable evidence that probiotics influence the acquired and innate immune response by inducing phagocytosis and IgA secretion, modifying helper T-cell response and the release of cytokines in a strain-specific manner.3

### Evaluating the benefits of probiotics in the perinatal period and early childhood

#### Maternal probiotic supplements

A recent double-blind randomised clinical trial (RCT) of probiotic supplementation during pregnancy (two months prior to delivery) and breastfeeding found the supplementation safe and effective in reducing the risk of eczema in infants of allergic mothers positive for skin-prick tests.4 The strains used in this trial were *Lactobacillus rhamnosus* LPR and *Bifidobacterium* BL999, also *Lactobacillus* GG.5 A recent Cochrane review6 from the Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada, conducted a meta-analysis of 29 RCTs and supported this outcome, but pointed out that the certainty of the evidence for various probiotic strains is still low.
Probiotics of *Lactobacillus* and *Bifidobacterium* species were evaluated to be safe when administered to healthy pregnant women in the last trimester of pregnancy. As probiotics are rarely systemically absorbed, they are not expected to transfer into breast milk. Ingestion of viable probiotic bacteria (*Bifidobacterium* and *Streptococcus thermophiles*) in infant formula over a six-month period has also been shown to be well-tolerated, safe and conducive to adequate growth.

Prevention of antibiotic-associated diarrhoea (AAD) in otherwise healthy children

A recent Cochrane review of 23 studies using a diverse selection of probiotics (bifidobacteria, lactobacilli, lactococci, streptococci, *Clostridium butyricum*, *Bacillus* species) has shown a protective effect of probiotics in preventing AAD with a number-needed-to-treat (NNT) of 10. The report singled out a benefit of *Lactobacillus rhamnosus* / *Saccharomyces boulardii* and noted that probiotics should not be used in severely debilitated or immune-compromised children.

A large study was recently concluded, but results are not yet available. It aimed to determine the changes in intestinal microbiota composition after antibiotic treatment in early life. These types of studies will become more frequent as gene analysis of microbiota is applied to clinical settings and will provide a further basis for probiotic intervention.

Prevention of *Clostridium difficile*-associated diarrhoea in children (and adults)

A meta-analysis of 23 randomised trials suggests that when probiotics are administered with antibiotics, they reduce the risk of *Clostridium difficile*-associated diarrhoea by 64%. The most common side-effects (abdominal cramping, nausea, fever, flatulence and taste disturbance) were also reduced by concomitant probiotic administration. The probiotic species most used were *Lactobacillus*, *Bifidobacterium*, *Saccharomyces* and a combination of these strains.

Prevention of necrotising enterocolitis (NEC) in preterm infants

The American Pediatric Surgical Association supports the use of prophylactic probiotics in preterm infants weighing less than 2.5 kg to reduce the incidence of NEC, as well as the use of breast milk rather than formula where possible. A South African study using a daily probiotic therapy consisting of $1 \times 10^9$ colony forming units (CFUs) of *Lactobacillus GG* and *Bifidobacterium infantis* in HIV-exposed premature infants showed that this combination safely reduced the incidence and severity of NEC in these infants at risk of HIV.

Probiotics in adults

Irritable bowel syndrome (IBS)

Several trials and meta-analyses have shown that probiotics (particularly lactobacilli and bifidobacteria) reduce abdominal pain and symptom severity in IBS. IBS is, however, a heterogeneous functional disorder, which is still incompletely understood, and evidence is growing that it may be a post-inflammatory and stress-related condition. Probiotics appear to be a useful option in terms of both efficacy and safety, but until the pathophysiology of the condition is clear, evidence of probiotic benefit will remain elusive.
Prevention of chronic disorders (obesity, metabolic disorders, non-alcoholic fatty liver disease)

As the understanding of the role of the gut microbiota in the development of chronic diseases unfolds, a potential role for probiotics emerges as a therapeutic tool to reduce the prevalence of these serious chronic conditions.

South African probiotics (Enterococcus munditii ST4SA and Lactobacillus plantarum 423) – safety and efficacy data

- Adhesion of Enterococcus munditii ST4SA and Lactobacillus plantarum 423 compared well to that recorded for the probiotic Lactobacillus rhamnosus GG.14
- Using an in vitro gastrointestinal model (GIM), Enterococcus munditii ST4SA and Lactobacillus plantarum 423 used in combination survived well at conditions that mimic those in the duodenum and ileum.16
- Using an in vivo system (rats) with a fluorescent marker to tag the probiotic, the Enterococcus munditii ST4SA and Lactobacillus plantarum 423 combination was shown to colonise the caecum and colon, persisting for at least 24 hours.17
- Lactobacillus plantarum 423, isolated from sorghum beer, produces a bacteriocin, an antibacterial peptide.
- Adhesion of this probiotic combination displaced 81% of cells of Clostridium sporogenes and 91% of cells of Enterococcus faecalis, reducing their bacterial pathogenic action.18
- Using rat models, the probiotic combination showed no signs of perforating epithelial cells.19
- The strain Lactobacillus plantarum 423 exhibited no virulence factors, while Enterococcus munditii ST4SA contains a few non-functional genes. Safety has been confirmed.

References