



Probiotics: issues of credibility and safety

People have believed for more than a century that live microorganisms in foods may benefit human health. More recently, probiotics have appealed to consumers who want nutritional products with added health attributes. The demonstration of efficacy in probiotics thus offers vast opportunities for the development of human and veterinary products.

However, the addition of novel bacterial strains to foods and therapeutic products presents a challenge in safety assessment for regulatory authorities. Probiotic products which claim specific nutritional, functional or therapeutic characteristics blur the boundaries of what is a food, a diet supplement or a medicine.

The introduction of a new probiotic culture demands that it be at least as safe as its conventional counterparts. Suggested safety criteria have included, but not been limited to, unequivocal identification of species and strain, with candidate strains lodged in culture collections for reference and comparison; a profile of intrinsic properties of the organism such as metabolic and enzyme activities, antibiotic resistance and the potential for its transference; host-specific behaviour of the strain; as well as host factors predisposing to infection¹.

The most commonly used probiotic organisms belong to the genera *Lactobacillus* and *Bifidobacterium* and are specifically adapted to survive in the gastrointestinal (GI) tract. They are generally regarded as safe because of their long history of use as dairy starters. They have only rarely been associated with disease, usually as opportunistic infections in people with predisposing conditions¹.

Enterococci are commensal microflora of the GI tract and occur naturally in some

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foods. They have been used in commercial preparations for years and are common in veterinary probiotics. However, several species are pathogens and have recently been isolated in nosocomial and other infections. They demonstrate resistance to antibiotics, including vancomycin, and have the ability to transfer antibiotic resistances¹. The potential of enterococci species for pathogenicity, together with their tendency to exchange genetic material and acquire antibiotic resistance determinants, renders their use in foods or probiotics questionable.

Novel probiotics may be from other genera of the lactic acid bacteria (LAB) group e.g. *Lactococcus* and *Leuconostoc* or from food-associated genera such as *Propionibacterium*. Other genera and species such as *Clostridia* and *Bacillus* are proposed as potential probiotics¹. Rigorously designed studies are needed to characterise and demonstrate the safety and efficacy of such probiotic bacteria. Consumer resistance to genetically modified organisms (GMO) is such that GMO probiotics are unlikely in the near future.

Animal probiotics have the potential to transfer to humans and need to be assessed as safe, in both animals and humans. Transferable antibiotic resistance determinants from strains of animal probiotics potentially harbouring these

genes may in theory enter the human food chain¹.

Evidence for the safety and efficacy of probiotic organisms has, until recently, been largely anecdotal or based on relatively little, often poorly designed research. LAB and yeasts intrinsic to the production of traditional foods have been accepted as safe without any real scientific criteria, partly because they exist as normal commensal flora, but also because of their presence for generations without obvious adverse effect. The same cannot be assumed for novel organisms intended for probiotic use.

For many consumers the term probiotic is a new concept and they are reliant on the manufacturers' label for appropriate information. The consumer is entitled to expect that the label on a probiotic product accurately reflects its contents; the organism is what it purports to be; it is viable in a specified concentration range for a stated period; and the suggested serving size contains sufficient organisms to achieve the claimed benefit. The persistent use of incorrect or non-existent species and strain names on product labels despite taxonomic re-assignment is an issue for the safety and credibility of probiotics.

Studies by Temmerman *et al.*² showed that, of isolates from 55 European probiotic products, 47% of food supplements and 40% of dairy products were mislabelled. The food supplements yielded either no viable bacteria (37%) or significantly lower counts than the dairy products, which is inconsistent with the claim that health benefits derive from the presence of a minimum concentration of live probiotic bacteria.

In only six products did all species isolated conform to the label description; in 19 products they differed from those



listed. *Enterococcus faecium*, followed by *Lactobacillus rhamnosus*, were found most frequently in food supplements. *E. faecium* was isolated in such high numbers that contamination was unlikely to be the source. *Lactobacillus acidophilus* was present in only two of the 22 cultures purporting to contain it. Bifidobacteria were isolated from five of 27 products claiming to contain them, despite the use of different selective media. The organism most frequently claimed to be in, and isolated from dairy products was *L. acidophilus*, though it was not necessarily found where claimed. The study by Temmerman *et al.*² on the incorrect identification and mislabelling of probiotic products corroborates earlier findings^{3,4}.

It is essential that a probiotic should not have the ability to invade the host cells and cause infection. We need to know its pathogenic potential. Do other strains or related species cause clinically important infections or produce toxins? Probiotic organisms must be sensitive to broad spectrum and commonly used antibiotics. This is a significant issue where the intestinal barrier is immature, as in infants; where its integrity is impaired from radiotherapy, antibiotic treatment or disease; and in immuno-compromised states. With advances in medical care, an increasing proportion of the community may be immuno-compromised at some time and at risk of opportunistic infection.

The study also found 68.4% of probiotic isolates were resistant to two or more antibiotics². Strains of lactobacilli were found resistant to kanamycin (81%), tetracycline (29.5%), erythromycin (12%) and chloramphenicol (8.5%). Systematic screening for antibiotic resistance in probiotic strains is not undertaken at present.

The potential exists for viable probiotics to colonise the intestinal tract and transfer genetic material. Of concern is the potential for genetic transfer of antibiotic resistance to previously

susceptible species. It is difficult to assess what level of gene transfer, if any, may be considered acceptable by the community. This is a significant reason to select strains lacking the potential to transfer genetic determinants of antibiotic resistance.

Tests of bacteria to find a putative probiotic often yield conflicting data, sometimes for the same organism. Comparisons between studies and organisms cannot be readily made because of non-standardised dosing procedures, particularly for the number of bacteria and the duration of dosing. Pharmacokinetics, pharmacodynamics, safety and the risk of acquisition of antimicrobial resistance have usually not been evaluated⁵.

Probiotic effects are strain-specific, which illustrates the need to characterise the relationship between the dose, its duration and effect on a strain by strain basis. When considering the pharmacokinetics of the probiotic organism we need to know whether the bacterial strain modifies intestinal flora. In determining the dose-response relationship, is the failure to elicit an effect because the organisms failed to reach effective levels at the site, or is it due to rapid elimination of the bacteria, or non-persistence, or destruction?

It is also unclear whether proposed consumption of a probiotic should be on a regular daily basis for whole of life, or irregular and dependent on symptoms. Information is not readily available on the equivalence or comparability of formulations in different preparations; on the distinction between spore or vegetative forms, powders, granules, tablets, liquids and yoghurts; or on adult and paediatric products. Nutritional studies may be needed in addition to toxicological studies depending on the nature of the product; its intended use; its anticipated intake; the impact of dietary intake on the spectrum of colonic flora, their metabolic functions and bioavailability of nutrients⁶.

Clinical studies in humans have investigated the effect of oral administration of probiotics on the balance of intestinal microflora and in a variety of disorders. Many of the studies were inadequate, having an absence of a patient control group; small treatment groups; undefined treatment groups; a wide age range within a treatment group; a diversity of antibiotic treatments; an absence of dosing criteria such as dose and duration; or subjects with symptoms of concurrent disease with the potential to confound an observation of adverse effects. The gold standard is a controlled study with randomised, blind assignment to treatment, placebo and untreated groups.

After market release of a novel probiotic, epidemiological surveillance for any associated adverse effects, particularly infection, is important. Characterisation of clinical isolates for comparison with endogenous and probiotic strains is integral to confirming its safety. Deposition of probiotic strains in a recognised international culture collection for access by manufacturers, scientists and regulators would ensure organisms could be monitored for genetic drift and comparison with clinical isolates.

References

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