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Commentary

Probiotics for diarrhoea

Probiotics (literally, "for life") are microorganisms purported to have a health benefit on the host organism. Defining probiotics is challenging because of the limits in our understanding of the mechanism of action through which the organisms may benefit the human host. The genera of bacteria and fungi that have been employed in research studies for their probiotic properties are most commonly species of *Lactobacillus* and *Bifidobacterium*; other bacterial genera, such as *Streptococcus*, *Enterococcus*, and *Bacillu*s, and species of the yeast genus *Saccharomyces* have also been studied[1]. As it currently stands, the term "probiotic" is better understood as referring to the intention, rather than the effect, of the preparation given that establishing the beneficial properties of the intervention is often the goal of the research study.

The intentional use of microorganisms in the preparation of foods as well as the belief in their health-promoting properties has a long history. Species of the lactic acid bacterium genus *Lactobacillus* have been used for thousands of years to preserve dairy products by converting milk to yogurt. Mixtures of microorganisms have been used to treat infections topically and systemically since ancient times. The use of probiotics to prevent and treat gastrointestinal disorders in particular has been advocated since the beginning of 20th Century[2].

Depending on the form and the country in which probiotics are administered or used, probiotic products are classified as any one of several different entities: dietary supplements, foods, food components, or pharmaceuticals. Each of these categories is subject to entirely different regulations and burdens of proof regarding the demonstration of a health benefit as well as safety, and these regulations and guidelines differ by country. The European Food Safety Authority (EFSA) determined in 2009 that none of the claims for specific probiotic strains submitted to that date were adequately substantiated by the scientific data that were provided as evidence of support[3]. The Indian Council of Medical Research (ICMR) in collaboration with the Department of Biotechnology has recently formulated guidelines for the regulation of probiotic products that define a set of parameters required for a preparation to be termed as "probiotic". This includes, among many reporting requirements, a demonstration of the efficacy in human participants[4,5].

Empirical evidence for the clinical effectiveness of probiotics has shown mixed results and we still know very little about which probiotics work for which indication and group of patients. In order to be of informational value, the effectiveness of probiotics needs to be demonstrated in strong research designs, such as randomized controlled trials, that hold up to scientific scrutiny. Furthermore, there is a need to use measurable and symptomatic or clinically relevant outcomes, rather than relying on intermediate and *in vitro* outcomes, when assessing the effectiveness of probiotics in clinical studies.

Although probiotics have been applied to a large number of clinical indications, only selected applications may robustly demonstrate empirically measurable and clinically relevant beneficial effects. A substantial amount of research has, in particular, been dedicated to the prevention and/or treatment of diarrhoea. A meta-analysis on probiotics for the prevention and treatment of antibiotic-associated diarrhoea showed encouraging results[6]. The pooled relative risk across 63 randomized controlled trials indicated a significant association of probiotic administration with reduction in antibiotic-associated diarrhoea (RR 0.58; 95% CI, 0.50 to 0.68; $P<0.001$).

The study by Aggarwal and colleagues[7] in this issue shows an application of probiotics that has

increasingly become the subject of research interest for the treatment of acute childhood diarrhoea. Diarrhoea in small children can have severe consequences, hence finding effective interventions to reduce the duration or the severity of symptoms is pertinent. A recent systematic review on probiotics for acute diarrhoea has reported that probiotics decrease the duration of diarrhoea and fever significantly in children[8]. The 2013 World Gastroenterology Organization (WGO) Guidelines stress upon the need for human studies to identify beneficial the effects of specific probiotics and that effects shown for one microorganism strain are unlikely to be generalizable to all probiotic interventions[9]. Furthermore, whether probiotics are useful from a global perspective has been the subject of much debate. The WGO guidelines state that the use of probiotics may not be appropriate in resource-constrained settings; other recent initiatives stress that successful models can be established and sustained[10].

Probiotic microorganisms are characterized by their genera, species, and strains, and research studies vary in additional intervention characteristics such as the dose, potency, and treatment duration, viability of the organism, as well as the combination of strains. Although many research studies have tested probiotics, it is important to characterize each intervention in detail, reporting as a minimum the species and the investigated strain, in order to be able to identify successful applications. Furthermore, many commercial products change over time. Huys *et al*[11] conducted a survey of commercial probiotic strains and found that 28 per cent of the strains intended for use in humans as probiotics were misidentified at the genus or species level. Other reports show that products can contain more species than noted on the product labels[12,13]. As technology and methods develop, this should also entail a more reliable, DNA-based validation of the characteristics of the included microorganisms, that is, the valid identification of the studied organism and the purity or the identification of all included microorganism in the study product.

A further characteristic of probiotics is that in most cases the definition is reserved for live organisms. Presumably the organisms need to remain live to be fully functional and it is recommended that the investigators demonstrate that they were indeed able to maintain the evaluated organisms in a live and robust state. More guidance for the conducting and reporting research on probiotics has been published elsewhere[14]. As outlined, there is a need for more reliable information on the identity, potency, and viability of the included microorganisms given to participants at the time of the intervention as this may depend on the storage and delivery vehicles chosen for interventions.

A substantial number of probiotic intervention studies is available in the literature and the research volume is increasing exponentially. However, given the frequency of poor reporting, the evidence base is still limited. In addition, many probiotic studies do not test one product but instead investigate blends of organisms, *e.g.*, combining several different genera, species, or strains, making it impossible in individual studies to identify the active ingredient (or ingredients), and making it very difficult in meta-analytic studies to establish the comparative effectiveness of probiotic products. Furthermore, a substantial amount of research is based on adult participants that exclude the elderly and children. More research is needed to establish whether effects found in one patient group are generalizable to other patient groups.

Many existing probiotics studies, including the present study[7] report no adverse events associated with the probiotic intervention. Unfortunately, many intervention studies do not mention the safety of probiotics at all, and many existing publications do not specify what exactly was monitored in terms of adverse events when they state that "no adverse events" were found. This practice severely hinders the evidence base of probiotics.[1] It is not possible to extrapolate from the lack of mention of adverse events that no adverse events occurred, *e.g.* the adverse events may just not have been associated with the intervention. Vague safety statements such as "the intervention was well tolerated" are only informative if the authors report what was monitored or how "well tolerated" was defined. Although it may appear plausible to assume that such statements mean at least no death or hospitalizations occurred, this assumption is problematic for evidence-based medicine and cannot replace actual empirical evidence on the safety of probiotics. The safety of probiotics has only recently been considered as an issue warranting further investigation. Authors may not have thought to associate specific harms with an intervention traditionally considered "completely harmless". Many case studies have described fungaemia and some bacteraemia potentially associated with administered probiotic organisms. Safety reviews focus on toxicity, the potential for translocation, and antibiotic resistance or other virulence factors[15-17]. Again, more effort is needed to routinely monitor for probiotic-specific

adverse events and studies should monitor and report the presence and also the absence of specific harms.

Finally, it should be noted that the study by Aggarwal and colleagues[7] reported a statistical power analysis prior to undertaking the research. Power analyses are especially important in fields where the treatment effect has yet to be established and where large effects cannot be assumed. The above mentioned meta-analysis[6] on the prevention of antibiotic associated diarrhoea (ADD) estimated that only 10 per cent of the included probiotics trials were adequately powered.

More research studies are needed that provide sufficient detail on interventions and outcomes and are sufficiently powered to increase the evidence based on the effectiveness of probiotics for the treatment of acute childhood diarrhoea in global settings.

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