



# Probiotic Safety—No Guarantees

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For centuries, people have consumed live bacteria in many foods, such as yogurt, cheese, kimchi, and sauerkraut. The mass-marketing of isolated live bacteria for their purported beneficial or “probiotic” properties, however, is a relatively recent phenomenon. The World Health Organization defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” Yet to be sold as a probiotic supplement in the United States, a live microorganism does not require evidence of efficacy or even safety.

Certain live microorganisms do have well-defined health benefits, and an emerging literature supports the use of select strains of bacteria and yeast to treat specific medical conditions.(1) The yeast *Saccharomyces boulardii*, for example, reduces the rates of antibiotic-associated diarrhea in children and can decrease rates of recurrent *Clostridium difficile* infections in adults, when combined with antibiotics.(1) Most microorganisms used in the production of food, however, do not have proven health benefits, and their safety when sold as probiotic supplements has not been fully established.

Hundreds of small studies whose results are spun as favorable, creative advertising and enthusiasm for the microbiome have contributed to increased popular and professional interest in commercial probiotics; between 2002 and 2012 consumption of probiotic supplements more than doubled in the US.(2) Consumption is highest among college-educated adults with 3.5% reporting the use of probiotic supplements within the past 30 days.(2) Probiotics are frequently prescribed by clinicians as well; a survey of 145 US hospitals found that 2.6% of patients had received probiotics during their hospitalizations.(3)

Although preliminary evidence supports the use of specific strains of probiotics in certain clinical settings, such as preventing *C. difficile* and antibiotic-associated diarrhea, widespread use, particularly among people who are healthy, has greatly outpaced the science. Probiotics are promoted to assist healthy adults, adolescents and children to maintain normal intestinal function and to sustain cardiovascular, respiratory, immunologic, reproductive and even psychological health.(4) Despite the advertised indications, there are no large, long-term clinical trials proving that probiotics offer clinical benefits for people who are already healthy.(4) The lack of robust evidence does not limit US manufacturers' ability to promote supplements to improve health. There are few restrictions on structure/function claims, such as "boosts digestive health" or "supports the immune system", on supplement labels, while information about potential adverse effects is not required. As a result, consumers are unlikely to appreciate that probiotic supplements may also present risks, such as opportunistic infections and allergic reactions.(5,6)

Probiotic supplements, given the inherent infective qualities of the microorganisms they contain, may pose risks to certain people. Serious adverse events, such as fungemia and bacteremia, have been described in dozens of case reports, especially among immune-compromised individuals. However, as a result of a lack of structured reporting of adverse events in most probiotic clinical trials, and a lack of effective systems to detect post-marketing harm from supplements, the actual rates of opportunistic infections from probiotic supplements are not known.(5-7)

Poor quality probiotic supplements raise additional safety concerns. Although the US Food and Drug Administration (FDA) has established current good manufacturing practices for all dietary supplements, including that firms "conduct all manufacturing operations in accordance with

adequate sanitation principles”, manufacturers are often not compliant with them. For example, the FDA inspected 656 facilities producing a wide variety of dietary supplements in fiscal year 2017 and found violations in more than half of the inspected facilities. These violations were not trivial: Most commonly, companies had failed to establish the identity, purity, strength or composition of their final product. The FDA also requires that supplements be tested for contaminants; nonetheless, studies have found commercial probiotics that contain live microorganisms not listed on their labels.(6) These contaminants can pose life-threatening risks as was tragically illustrated by the death of an 8-day-old premature infant from fulminant gastrointestinal mucormycosis.(8) Epidemiologists at the Centers for Disease Control and Prevention eventually traced the source of the infection to fungal contamination of a probiotic supplement used to treat the infant.(8)

Full compliance with FDA manufacturing standards for supplements would prevent products from containing contaminants and incorrect species of bacteria, but still would not ensure the safety of probiotic supplements because the FDA’s requirements do not address several of the unique risks that probiotics may pose, such as the potential to introduce new genes into consumers’ microbiomes.(6) Of particular concern are genes that may confer antibiotic resistance. Bacteria sold as probiotics, like all bacteria, may have intrinsic as well as acquired resistance to antibiotics. Intrinsic resistance refers to each strain’s typical resistance pattern. These qualities are not easily transferrable to other bacteria in the human gut; thus, they pose health risks only in instances in which individuals develop opportunistic infections from the probiotic and require treatment. Intrinsic resistance to antibiotics may, in fact, be a desirable trait

as probiotics may be administered concomitantly with antibiotics to prevent diarrhea or other conditions, and resistance to the administered antibiotic could enhance the probiotic's efficacy.

In contrast, atypical or acquired resistance patterns in probiotics may signal the presence of a mobile gene capable of transferring antibiotic resistance to pathogenic bacteria. This has been established under experimental conditions both *in vitro* and in rodent models. For example, *in vitro* the probiotic *Lactobacillus plantarum* M345 can transfer erythromycin resistance genes to *Listeria monocytogenes*. To date, however, only limited resources – and to my knowledge just one study involving 7 subjects – have been dedicated to determining whether such transfers might occur within the human intestine.(9)

Until more data are available regarding the transfer of probiotic genes in humans, modern manufacturing techniques should be used to ensure that mobile resistance genes are not contained in the probiotics consumed by millions of people in the US. Standards designed to decrease exposure to mobile resistance genes have been implemented in Canada and several European countries. The FDA, however, does not require these safeguards in the US. In fact, in 2005, the agency permitted the sale of infant formula that included a probiotic strain with a potentially transferrable tetracycline resistance gene.

In the US, live bacteria, yeast and other microorganisms may be sold as food, dietary supplements or drugs, with differing regulatory requirements for each category. A better approach would be to create a consistent regulatory framework under which all probiotic-type microorganisms could be safely marketed to improve health. High quality microorganisms with

a long track record of safety should be accurately labeled and readily available to consumers, and labels should only advertise health claims if robust clinical evidence has demonstrated efficacy. Such a framework would require new laws, and Congress would seem unlikely to tackle probiotics in the foreseeable future.

The FDA has recently released a draft guidance that, if implemented, would give firms the option of listing the number of colony forming units in the Supplement Facts label.<sup>(10)</sup> The agency should go further and require manufacturers, as Canadian authorities already do, to provide the specific strain or strains, and the number of live microorganisms per serving, on every bottle of probiotic supplements. This should be a routine part of ingredient disclosure.

The FDA should also revise its current good manufacturing practices for live microorganisms and include additional safety testing, such as identifying and eliminating potentially transferrable antibiotic resistance genes, for all bacterial strains prior to marketing, as is currently required in Canada. In the meantime, the underdeveloped regulatory framework in the US and inadequate compliance of manufacturers with the existing laws and regulations remain substantial problems. Consumers and physicians should not assume that the label on probiotic supplements provides adequate information to determine if consuming the live microorganism is worth the risk.

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