

The Safety of Probiotics Considerations Following the 2011 AHRQ Report



The Safety of Probiotics: Considerations following the 2011 U.S. Agency for Health Research and Quality Report¹

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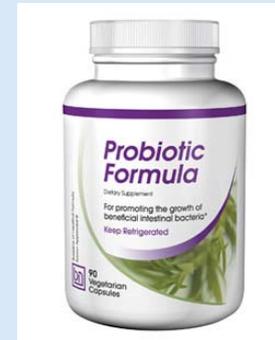
The authors offer this commentary to *The Journal of Nutrition* in response to the recently published report, "The Safety of Probiotics to Reduce Risk and Prevent or Treat Disease" by the U.S. Agency for Healthcare Research and Quality (AHRQ) Southern California Evidence-Based Practice Center. This robust systematic review of randomized controlled trial (RCT) includes data on the safety of probiotics used in research to reduce the risk of, prevent, or treat disease (1). In short, the authors set out to answer the question: are probiotics safe? The report cataloged data concerning the safety of interventions containing organisms from 6 genera: *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* spp. alone or in combination (1). After systematic review of over 11,941 articles identified and 622 included studies on probiotics, the report found that there was only limited evidence to address the questions that the review set forth to answer (1). Although the review included a large number of RCT, most of them were not designed specifically to address and report safety findings. The study concluded that despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence. It is important for the scientific community to recognize that this conclusion should not put the safety of these microorganisms into question but provide further evidence to advance the notion that the 6 genera included in the study have minimal safety concerns, because no adverse events were reported.

The overarching goal of the AHRQ report is to perform an evidence-based review that will help inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. Although evidence-based reviews can be powerful tools to identify and synthesize all relevant data, they are limited when available data are not designed with the same research question as the review intends to address. It is incumbent, to achieve the goal of informing the health care community and consumers about the safety of commonly consumed food components with an established history of safe use, that we use a scientific framework that is fit for the purpose. To explore the question "are probiotics safe?" using a drug-based framework assumes that the literature will include drug-

like safety and toxicology data. The scientific community and authors of the AHRQ report need to consider that traditional foods and food components are not studied in the same way as drugs. If the AHRQ intended to answer the question "are apples safe?" it would likely come to the same conclusion, which is that the current literature is not well equipped to answer questions on the safety of apples with confidence. The research community should recognize that in the absence of drug-like safety data, the safety of traditional foods should be based on the totality of evidence in healthy populations. Totality of evidence in this instance can be defined as a history of safe use, as well as RCT, epidemiological data, animal studies, and in vitro cell work that all contribute to the general understanding of the safety and efficacy of probiotics. Although the AHRQ report is a robust compilation of RCT that monitor the presence or absence of participants' adverse health outcomes, the evidence-based report does not address the totality of evidence in relationship to the safety of probiotics. The limited nature of published data available that are specifically designed to assess safety of probiotics should not come as a surprise to the scientific community, given that very few traditional foods/food ingredients that have been widely consumed for centuries have been the subject of systematic toxicological and safety assessment (2). Many microorganisms to which we ascribe probiotic effects have origins in dairy/fermented foods and have long been consumed as constituents of these foods without any apparent ill effect for centuries. Despite their widespread use in foods and dietary supplements, the incidence of bacteremia attributable to probiotic strains remains extremely low (3). The data available in the AHRQ report and literature strengthen the conclusion that the majority of probiotics strains (excluding those new and recently engineered probiotic strains that have not been clinically evaluated for safety and do not have a long history of safe use) in foods and dietary supplements should be considered generally safe. Additionally, many probiotics pose a low risk in the general population, as shown by their native colonization in the gastrointestinal tract of humans. If the question is "are probiotics safe?" and the answer is intended to inform the healthcare community and consumers, then the conversation is incomplete without a discussion concerning the other types of evidence demonstrating that the probiotics covered in the AHRQ report are in fact safe. To properly inform the health care community about the safety of probiotics and other nutritional substances, scientists may be required to modify the current paradigm away from evidence-based reviews that are focused on evidence from RCT while giving little consideration to other forms of evidence. It is imperative to note that the authors of this commentary in no way wish to suggest that the scientific community should

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Disclosures



- Council for Responsible Nutrition
- Developing Solutions, LLC
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- Steering Committee - JACN



AHRQ Report on Probiotics



- April 2011 – AHRQ Report released.
 - Robust systematic review of RCTs specifically focused on the safety of probiotic interventions.
- The report reviewed over **11,981 articles** identified and **622 studies** included on probiotics.
- *“Only limited evidence to address questions the review set forth to answer.”*

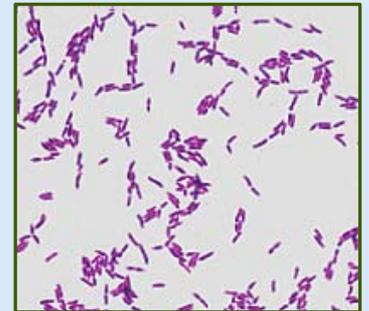
Conventional Foods: History of Safe Use



Probiotics: Theoretical Side Effects



- Systemic infections
- Deleterious metabolic activities
 - Deconjugation or dehydroxylation of bile salts → **Diarrhea**
- Excessive immune simulation in susceptible individuals
 - Stimulation of cytokine production → **Fever, arthritis, etc.**
- Gene transfer
 - **E.g. antibiotic resistance**



Probiotics: Theoretical Side Effects



- Historically probiotics associated with food and supplements have been considered safe as they are normal commensals of the GI tract.

(Adams & Marteau. 1995. J Food Micro. 27:263)

- Despite their use in foods and supplements the incidence of bacteremia attributed to probiotic strains remains extremely low.

(Salminen et al. 2002. Clin Infect Dis. 35:1155)

General Comments



- We do NOT suggest that the scientific community discontinue researching the safety of probiotics.
- However, in the absence of drug-like safety data, health care authorities and policy-makers should consider a risk-benefit analysis that utilizes all available evidence pertaining to the potential for benefit or harm.

Was Evidence-Based Review Appropriate?



- Evidence-based reviews can be powerful tools to identify and synthesize relevant data, they are limited when available data are not designed with the same research question as the review intends to address. It is essential that we use a scientific framework that is fit for the purpose.
- Using evidence-based reviews assumes the literature will include drug-like safety and toxicological data.

Was Evidence-Based Review Appropriate?



- Foods, food components and dietary supplements are not studied the same way as drugs.

Parameter	Drugs	Nutrients
True Placebo	Yes	No
Systematic Function	Isolated	Complex networks
Effect Size	Large	Small
Nature of Effect	Therapeutic	Preventive
Side Effects	Large	Small

Conclusions



- While it is important that safety not be presumed, the specific nature of any probiotic should be considered during a safety evaluation.
- Given the increasingly wide-spread use of probiotic foods and supplements with few adverse events reported in clinical trials and/or the general public, a risk-benefit assessment and discussion of totality of evidence should be considered when judging safety.

Conclusions



- Growing public interest in probiotics calls for appropriate regulatory and policy action.
- The lack of adverse events reported throughout the AHRQ report should strengthen the argument that probiotics are safe.
- The totality of evidence supports that probiotics interventions in both healthy and some diseased populations can be considered safe.

Thank You!... Questions?

