Probiotic acute and long term safety: where do we stand in 2022?

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Commonly marketed probiotics are often presumed to be safe. Ten years ago, a large review published by the RAND Corporation found 11,977 publications, of which 622 studies were reviewed. In 235 studies, only nonspecific safety statements were made ("well tolerated"); the remaining 387 studies reported the presence or absence of specific adverse events. The review concluded, "The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence." However, RCTs do not represent the totality of evidence on probiotic safety. There have been large cohort studies without serious adverse events reported. Further, global consumption of probiotics (dominated by *Lactobacillaceae* and *Bifidobacterium* probiotics), estimated at about $40 billion USD retail sales in 2017, suggests that large amounts of common probiotics are being consumed without safety issues.

However, theoretical and proven adverse events from probiotic consumption exist and probiotic safety has recently come under attack in several high profile publications (here, here and here). Additionally, there are probiotics under development that do not have the long history of safe use and qualified presumption of safety (QPS) status applicable to common *Bifidobacterium* and *Lactobacillaceae* probiotics.

Therefore, further examination of probiotic safety is warranted. We will examine both acute and long-term potential risks. Probiotic safety encompasses properties inherent to the probiotic, to the consumer/patient, and to how the product is manufactured (contaminated probiotics products represent a safety concern). Issues such as target population (e.g., age, clinical condition), mode of administration (e.g., oral, naso-jejunal), and exposure (dose) are all relevant factors to this discussion.

Note: Safety of probiotics has been addressed previously in 2 ISAPP discussion groups. The outcome of one is published here; the other was not published. Also, a USP expert panel, under ISAPP leadership, published on quality, purity, quantification and identity issues important in probiotic manufacturing (here).

Objectives

1. Are there additional **acute adverse events, beyond what is required by good clinical study practice,** which should be monitored in human probiotic trials? It is agreed that all trials should follow CONSORT and widely accepted adverse event reporting practices. However, are there additional acute safety monitoring that are specific to probiotics? For example, bacteremia, fungemia, antibiotic resistance gene transmission, D-lactate production, microbiome alteration? Or are there probiotic-specific concerns for certain age groups (e.g., neonates) or clinical conditions (e.g., short bowel, critically ill, immunocompromised). Also, are there concerns about acute adverse events that differ for probiotics with the long history of safe use and qualified presumption of safety (QPS) status versus newer generation probiotics?
    a. Are there population groups where extra monitoring is indicated or where additional safety studies should be considered?

   b. Are there microbiota changes that should be monitored, including the risk of antibiotic resistance gene transfer from a probiotic to the resident microbiota?
   c. How to approach safety for strains of qualified presumption of safety (QPS) status versus newer generation probiotics?
   d. Manufacturing issues related to probiotic quality, purity, and identity.
2. Are there **long-term adverse events** from probiotic administration that should be monitored?
   a. What long term safety tracking is typically required (how long, what is tracked)?
   b. What long-term adverse events may result *from probiotic-mediated microbiome alteration* that should be monitored?
      i. Should we hold probiotics to a standard that many microbiome-altering drugs (antibiotics, metformin, PPIs, etc) are not held to or will those drugs in the future be held to? Brief summary of studies that have tracked long term effects? Should hypothetical (long term) microbiome alteration disqualify a strain for use by certain populations, specifically infants and young children?
      ii. What type of microbiome assessment is currently expected for microbiome-altering drugs (antibiotics, metformin, PPIs, etc)?