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EED INTERVENTIONS 3.0

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Agenda

- Project Background and Objectives
- Approach & Rationale
- Methods
- Results
- Discussion and Next Steps

Work Order to the UW START Team

Background

The Enteric and Diarrheal Disease Team of the Bill & Melinda Gates Foundation previously engaged the START team to conduct a landscape analysis of intervention trials for Environmental Enteric Dysfunction (EED). During the course of this analysis, an additional track of work was identified to do a similar landscape analysis focusing on the safety and tolerability of prebiotic and probiotic interventions in children under 5 living in LMICs and/or immunosuppressed children.

Work Order to the UW START Team

Objectives

Diagnosis of EED by gut biopsy is an invasive and resource-intensive process and is often not feasible in vulnerable populations. Having previously focused on EED biomarkers in Phase I, Phase II examined upstream microbiome endpoints and downstream outcomes related to growth. Phase III will expand upon the work completed in Phase II and will examine the following areas:

1. Safety measures in papers for probiotics in kids under 5 in LMICs for other primary aims besides growth.
2. Safety with probiotic use in pre-term premature birth cohorts regardless of indication.
3. Look at safety measures in papers for probiotics in kids under 5 on immunosuppression. (May consider increasing to 18 years)

Probiotic Safety in targeted populations

- Analyze safety and efficacy of probiotics in children
  - Adverse events
  - Infection
  - Tolerability

Prioritize:

- Kids under 5 in LMICs for other primary aims besides growth
- Pre-term/premature birth cohorts regardless of indication
- Kids under 5 on immunosuppression.
  - (May consider increasing to 18 years)

Targeted Database and Search

Phase 1 efficacy and safety

- Database: Embase
- 'phase 1 trial'/exp OR 'phase 1 trial' OR 'safety' OR 'safety'/exp OR safety OR ('safety' OR 'safety'/exp OR safety AND efficacy) AND ('probiotic'/exp OR 'probiotic' OR 'prebiotic'/exp OR 'prebiotic' OR 'lactobacillus'/exp OR 'lactobacillus' OR 'vsl3'/exp OR 'vsl3' OR 'bacillus'/exp OR 'bacillus' OR 'bifidobacterium'/exp OR 'bifidobacterium' OR 'escherichia coli nissle 1917' OR 'e. coli nissle 1917' OR 'streptococcus thermophilus'/exp OR 'streptococcus thermophilus' OR 'saccharomyces'/exp OR 'saccharomyces') AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim) AND [humans]/lim AND [english]/lim
- 403 hits

Inclusion and Exclusion Criteria

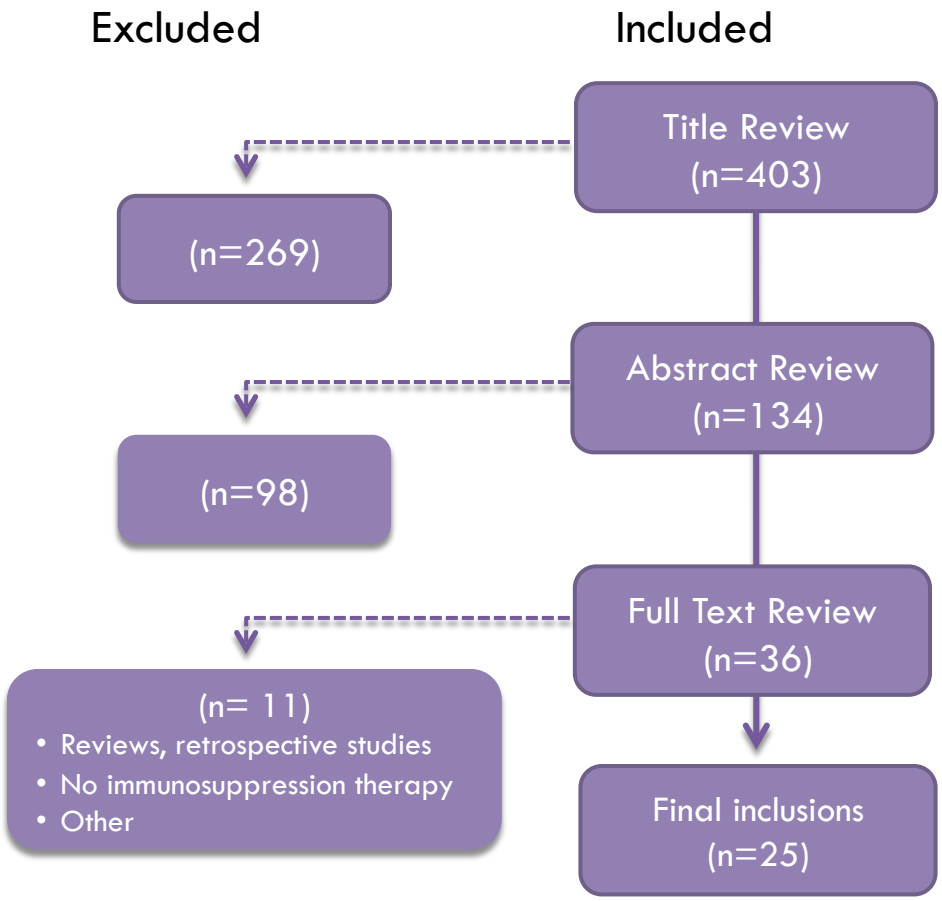
Inclusion

- Prospective studies and RCTs investigating probiotics (and/or prebiotics)
- Human Subjects
- Children <5
  - LMICs
  - Immunosuppression
- Safety and efficacy trials
  - Key words: tolerability, safety, adverse events
- Premature birth cohorts regardless of indication

Exclusion

- Retrospective studies, editorials and reviews
- Animal models/in vitro studies
- Adults, including provision to pregnant mothers
- Oral health, potentially non-ingested
- Healthy children
- No indication of safety or tolerability

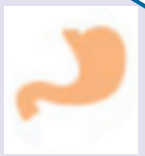
Literature Review Flowchart



Embase Search Results:

- ~ 9% of articles pulled for full text review
  - Probiotics n=21
  - Synbiotics n=4
- Inclusion criteria
  - Preterm n=10
  - LMICs n=11
  - Immunosuppression n=4

Safety concerns with probiotic administration

Potential safety concerns with probiotics:

- They can become opportunistic and translocate through the gastrointestinal barrier
- Toxicity
- Adverse immunologic effects, i.e., spread antibiotic resistance to pathogenic species

Case reports of safety concerns with probiotic administration:

- Three ***Lactobacillus* sepsis** cases after administration of *L. rhamnosus GG* in infants with short-bowel syndrome (De Groote et al., 2005; Kunz et al., 2004)
- **D-lactic acidosis** in children with short-bowel syndrome after probiotic supplementation (Munakata et al., 2010; Ku et al., 2006)
- Two case reports of **bacteremia** and **sepsis** attributable to Lactobacillus species in two medically compromised children (Land et al., 2005)

Summary of systematic review

Beneficial Microbes, 2015; 6(5): 615-630

Safety of probiotics and synbiotics in children under 18 years of age

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RESEARCH ARTICLE

Abstract

This study aimed to systematically evaluate safety of probiotics and synbiotics in children ageing 0-18 years. This study is the third and final part in a safety trilogy and an update is provided using the most recent available clinical data (2008-2013) by means of the Common Terminology Clinical Adverse Events (CTCAE version 4.0) classification. Safety aspects are represented and related to number of participants per probiotic strain/culture, study duration, dosage, clinical condition and selected afflictions. Analysis of 74 clinical studies indicated that probiotic and/or synbiotic administration in children is safe with regard to the specific evaluated strains, dosages and duration. The population of children include healthy, immune compromised and obese subjects, as well as subjects with intestinal disorders, infections and inflammatory disorders. This study revealed no major safety concerns, as the adverse events (AEs) were unrelated, or not suspected to be related, to the probiotic or synbiotic product. In general the study products were well tolerated. Overall, AEs occurred more frequent in the control arm compared to children receiving probiotics and/or synbiotics. Furthermore, the results indicate inadequate reporting and classification of AEs in the majority of the studies. In addition, generalizability of conclusions are greatly limited by the inconsistent, imprecise and potentially incomplete reporting as well as the variation in probiotic strains, dosages, administration regimes, study populations and reported outcomes.

Keywords: probiotics, synbiotics, children, safety, prebiotics

1. Introduction

The human gut microbiota is of major importance in metabolic and physiological processes (Vyas and Ragnanathan, 2012). Additionally, the microbiota is proposed to play a key role in development, maturation and maintenance of the immune system (Alonso and Guarner, 2013; Buccigrossi *et al.*, 2013; Kamada *et al.*, 2013). Indeed, when individuals fail to acquire a 'normal' microbiota it is associated with illnesses and other complications (Buccigrossi *et al.*, 2013; Hickey *et al.*, 2012). For instance, the increasing prevalence of allergies in the developed world could be partially explained by the 'hygiene hypothesis' (Strachan, 1989). This hypothesis postulates that improved hygiene, healthcare and smaller families leads to a decrease in antigen exposure, including bacteria and fungi, thereby affecting immune development of infants and children (Van der Aa *et al.*, 2010). The lack of bacterial exposure skews the immune response to a more IgE-mediated T_H2-response, which is associated with allergies and other pathologies. The early microbial colonisation is not only important in polarising the appropriate T_H1/T_H2 balance; it is also suggested to play a role in regulatory mechanisms (Pan *et al.*, 2010). This colonisation by microorganisms recognised as harmless by the immune system, also called 'old friends', drive regulatory T-cell polarisation and thereby down regulate auto- and allergic-immune responses (Guarner *et al.*, 2006). Indeed, insufficient exposure to these 'old friends' might lead to a dysfunctional immune regulation. For instance, the risk of asthma is inversely related to the

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Systematic literature review: *Safety of probiotics and synbiotics in children under 18 years of age*

By M van den Nieuwboer et al., 2015

Review included:

- 74 interventional studies
- Among over 15,000 participants, aged 0 to 18 years
- Published between 2008 and 2013

Conclusions:

- A clear general safety conclusion cannot be made due to inconsistent and imprecise documentation of AEs, variety of supplemented strains, doses, and target population
- However, in a controlled clinical trial setting, probiotic and symbiotic administration appears safe
- Standardized AE reporting is needed in future studies; most studies do not provide the incidence of AE and fail to report on common AEs while favoring reporting more irregular AEs.

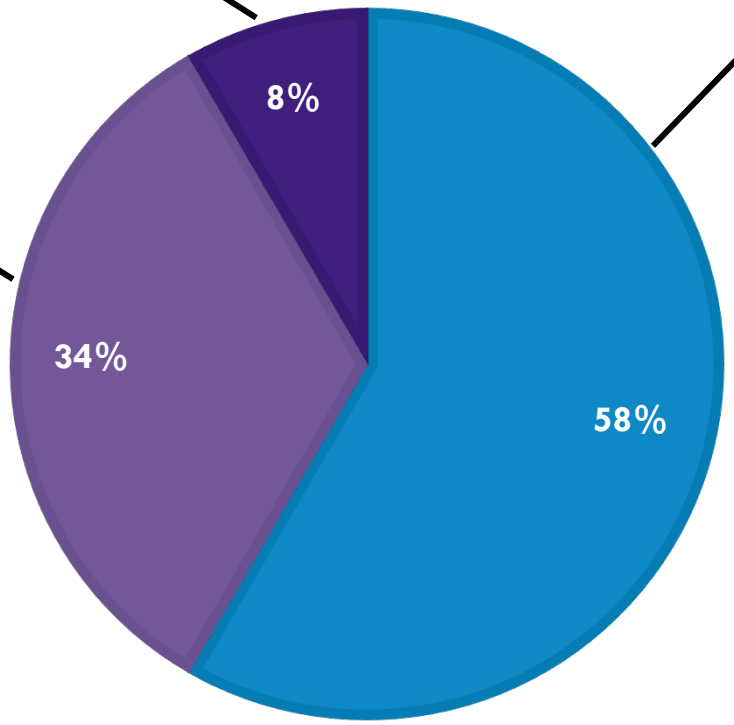
Included articles (n=25)

Immunosuppressed children (n=2)

- US (n=2)

Preterm infants (n=8)

- Australia (n=1)
- France (n=2)
- Ireland (n=1)
- Italy (n=1)
- Japan (n=1)
- US (n=2)



Children from LMICs (n=14)

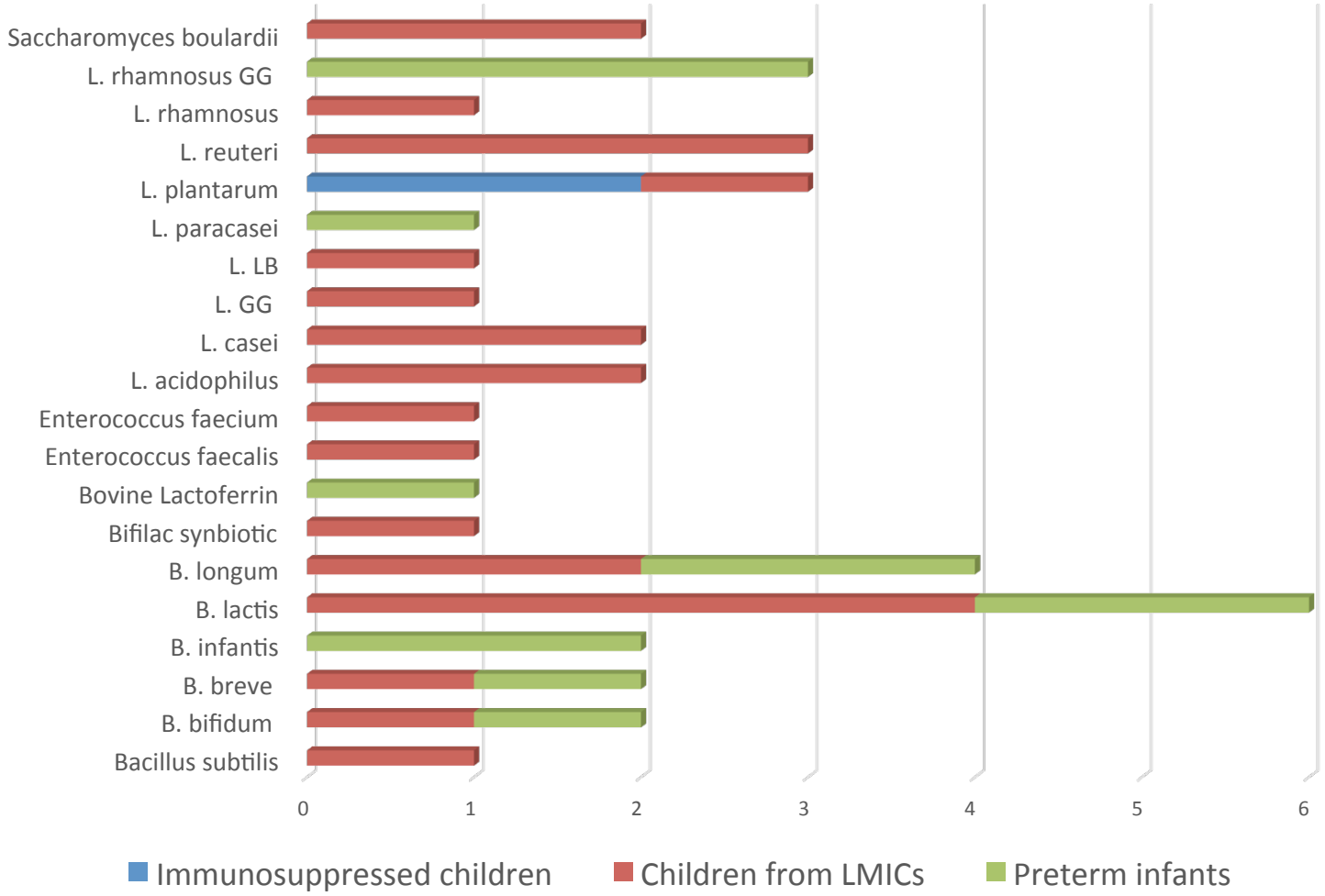
Lower middle income:

- Bangladesh (n=2)
- Egypt (n=1)
- India (n=4)
- Indonesia (n=1)
- Pakistan (n=1)

Upper middle income:

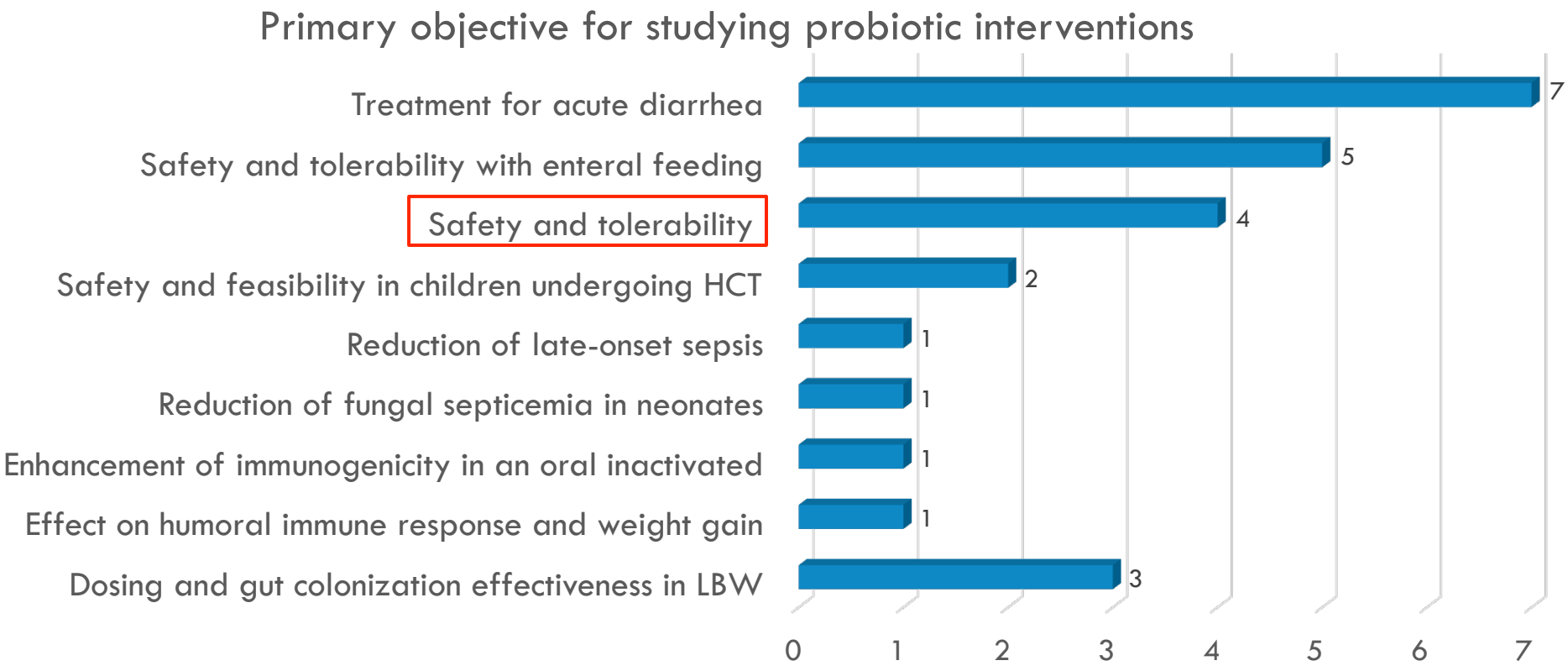
- China (n=1)
- Peru (n=1)
- Thailand (n=1)
- Turkey (n=2)

Probiotic strains studied



Primary study objectives of included articles

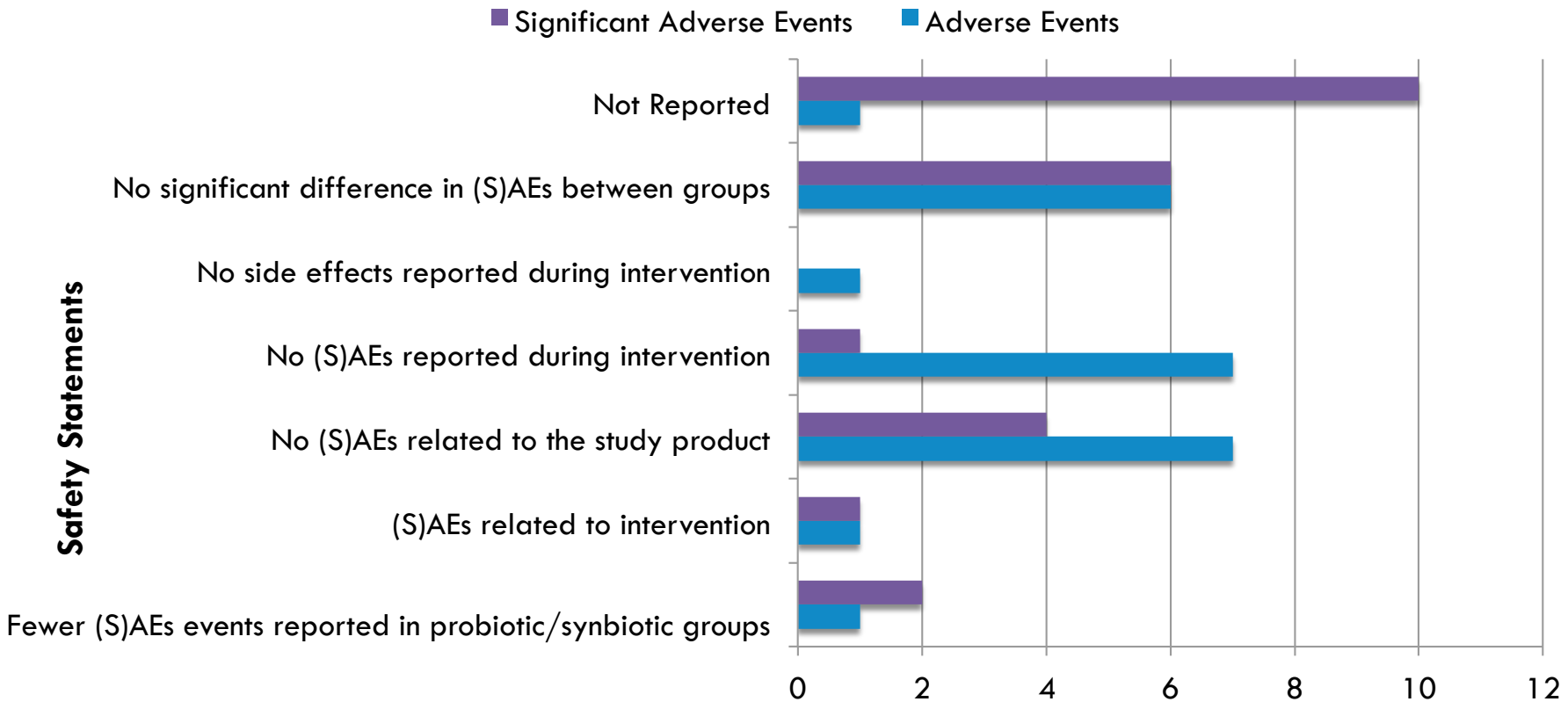
Evaluating the safety and tolerability of probiotics was not the primary objective of most studies



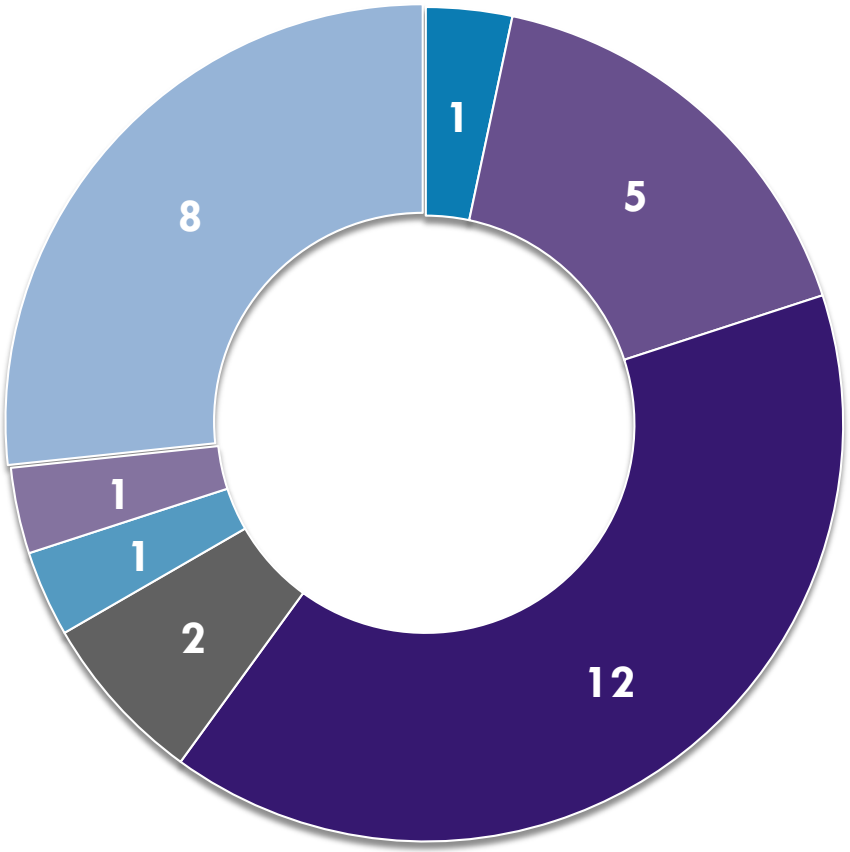
HTC = hematopoietic cell transplantation

Reporting Safety Outcomes

Frequency of safety statements for Significant Adverse Events and Adverse Events (S)AEs

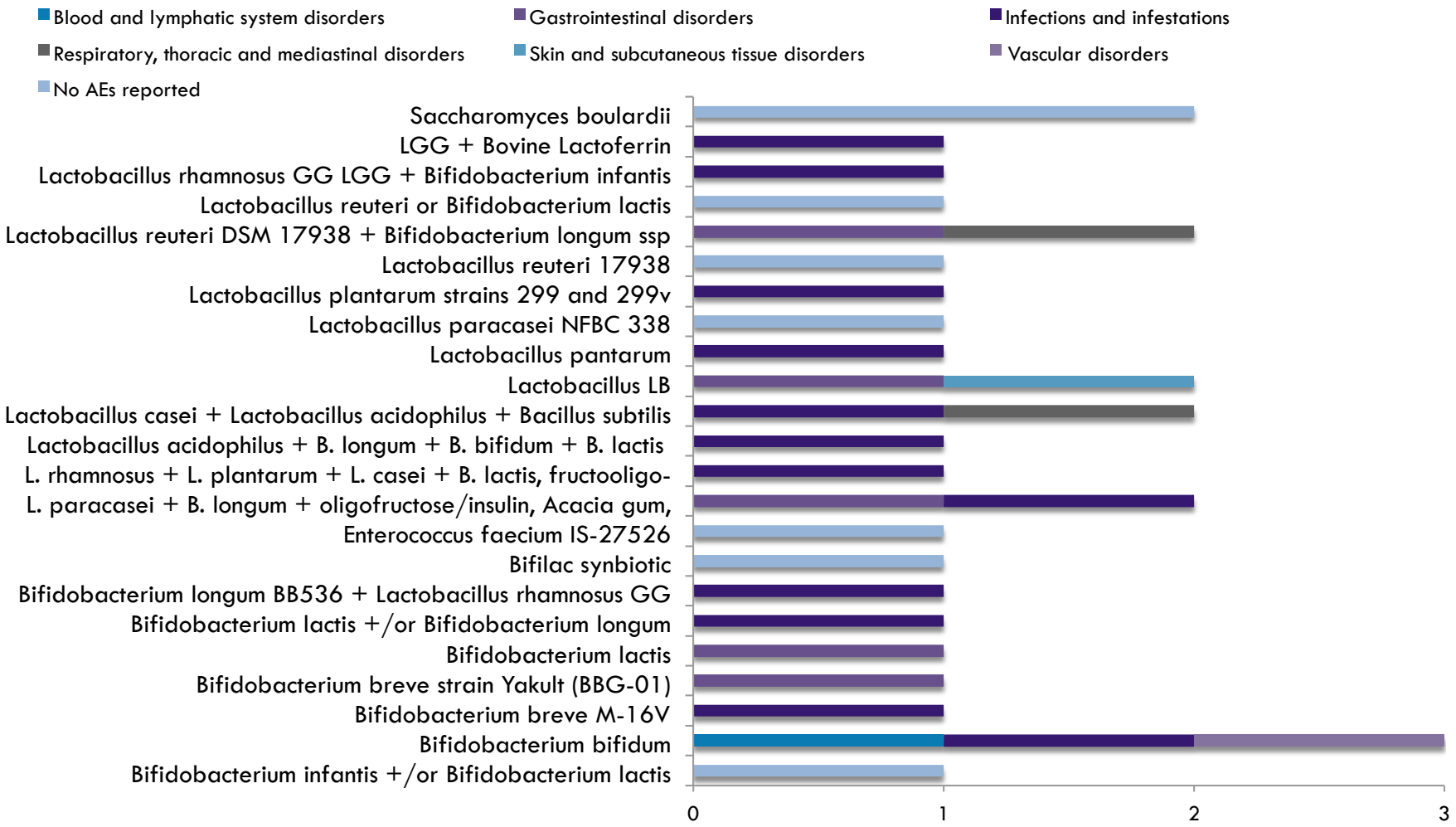


Reported Adverse Events using Common Terminology Criteria for Adverse Events Version 4.0

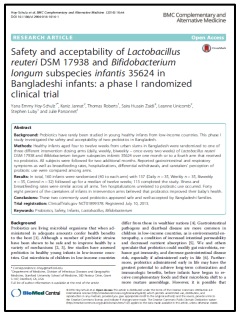


- Blood and lymphatic system disorders
- Gastrointestinal disorders
- Infections and infestations
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Vascular disorders
- No AEs reported

Adverse Events observed among probiotic and synbiotic strains



Stand-out studies



Safety and acceptability of *Lactobacillus reuteri* DSM 17938 and *Bifidobacterium longum* subspecies *infantis* 35624 in Bangladeshi infants: a phase I randomized clinical trial

By YE Hoy-Schulz et al., 2016

Study objective: to evaluate the safety and acceptability of two probiotics in healthy infants from low-income countries

Geography: Bangladesh

Probiotics:

- L. reuteri DSM 17938 (10^8 CFU)
- B. longum subspecies infantis 35624 (10^9 CFU)

Study population: healthy children 4-12 weeks*

Infants likely to be affected by EE, GI infections, malnutrition and stunting were targeted for selection

Intervention period: 1 month treatment plus 12 weeks follow-up

Intervention arms:

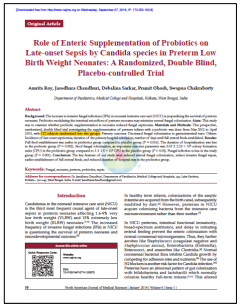
- Arm 1: 29 daily doses (n=31)
- Arm 2: 5 weekly doses (n=29)
- Arm 3: 3 bi-weekly doses (n=29)
- Arm 4: control (n=24)

Serious adverse events: 8 infants hospitalized for pneumonia and diarrhea; not probiotic related

Other: No significant differences in treatment arms for symptoms: diarrhea, watery stool, vomiting, poor feeding, colic, cough, congestion, difficulty breathing

Conclusion: L. reuteri and B. longum in combination, are safe and well-tolerated in very young infants

Stand-out studies


Role of Enteric Supplementation of Probiotics on Late-onset Sepsis by Candida species in Preterm Low Birth Weight Neonates: A Randomized, Double Blind, Placebo-controlled Trial

Role of enteric supplementation of Probiotics on late-onset sepsis by Candida species in preterm low birth weight neonates: A randomized, double blind, placebo-controlled trial

By A Roy et al., 2014

Study objective: to examine whether probiotic supplementation in neonates reduced fungal septicemia

Geography: India

Probiotics: Combined preparation:

- L. acidophilus (1.25 x 10^9 CFU)
- B. longum (0.125 x 10^9 CFUl)
- B. bifidum (0.125 x 10^9 CFUl)
- B. lactis (1.0 x 10^9 CFUl)

Study population: Preterm low birth weight infants aged <2 weeks

Intervention period: 6 weeks

Intervention arms:

- Arm 1: 6 x 109 CFU/day of probiotics (n=56)
- Arm 2: control (n=56)

Serious adverse events: 2 infants in each arm developed NEC. 7 infant deaths in occurred in probiotics arm while 8 infant deaths in control arm. Bacterial infections occurred among 18 infants in control arm and 9 infants in probiotic arm.

Other: Abdominal distension, vomiting, and diarrhea

Conclusion: Use of combined probiotic preparation reduced gastrointestinal symptoms among treated preterm neonates. Probiotics were safe and well-tolerated in.

Summary Findings

- Majority of probiotics and synbiotics were safe and well tolerated
  - No association seen between LMICs and adverse events
- Systemic Infections
  - 3 studies cited cases of bacteremia not related to intervention probiotic
    - Nieder et al. 2012 children undergoing HCT
    - Ladas et al. 2016 children and adolescents undergoing HCT
    - Hays et al. 2016 preterm infants in Peru
  - 7 studies reporting sepsis
    - 6 report NS between study arms
    - 1 found fewer cases of late onset sepsis in probiotic group
  - Mixed Preterm cohorts
    - 6 studies document improved outcomes in probiotic/synbiotic groups
    - 3 studies found NS difference among treatment arms
    - 1 discontinued due to VRE outbreak

Critical Gaps

- Lack of standard reporting limits generalizability
  - (S)AEs and severity of adverse events
  - Bacterial strains
  - Dosages