Harms Reporting in Randomized Controlled Trials of Interventions Aimed at Modifying Microbiota

A Systematic Review

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Background: Probiotics, prebiotics, and synbiotics are used increasingly, although the safety and potential harms of these interventions are poorly understood.

Purpose: To examine how harms-related information is reported in publications of randomized controlled trials (RCTs) of probiotics, prebiotics, and synbiotics.

Data Sources: Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and Web of Science (without language restrictions) from 1 January 2015 to 20 March 2018.

Study Selection: RCTs assessing the safety or efficacy of at least 1 intervention involving probiotics, prebiotics, or synbiotics alone or in combination with another intervention compared with any control (such as a placebo or an antibiotic) for any clinical condition.

Data Extraction: 4 reviewers independently assessed study characteristics, the reporting of harms, and the presentation of safety results.

Data Synthesis: Of 384 trials conducted in healthy volunteers (n = 136) or patients with any of several medical conditions (n = 248), 339 (88%) were published in specialty journals. Trials most often evaluated probiotics (n = 265 [69%]). Studies in persons with medical conditions enrolled outpatients (n = 195) and high-risk patients (n = 53). No harms-related data were reported for 106 trials (28%), safety results were not reported for 142 (37%), and the number of serious adverse events (SAEs) per study group was not given for 309 (80%). Of 242 studies mentioning harms-related results, 37% (n = 89) used only generic statements to describe AEs and 16% (n = 38) used inadequate metrics. Overall, 375 trials (98%) did not give a definition for AEs or SAEs, the number of participant withdrawals due to harms, or the number of AEs and SAEs per study group with denominators.

Limitation: Journal publication processes may have affected the completeness of reporting; only English-language publications were examined.

Conclusion: Harms reporting in published reports of RCTs assessing probiotics, prebiotics, and synbiotics often is lacking or inadequate. We cannot broadly conclude that these interventions are safe without reporting safety data.

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Probiotics are "live microorganisms that when administered in adequate amounts, confer a health benefit on the host" (1, 2). Prebiotics are "selectively fermented ingredients" that result in specific changes in the composition or activity of gut microbiota, providing health benefits to the host (2, 3). Probiotics and prebiotics are disseminated widely in our daily lives, particularly in the food industry, as ingredients in biscuits, cereals, chocolates, and dairy products (4). For example, most infant formulas are supplemented with probiotics and prebiotics, with the goal of creating a gut microbiota composition similar to that of a breast-fed infant (5).

Interest has been increasing in treatments that modify the microbiota to confer health benefits. During the past few years, probiotics have been among the most-studied interventions in neonatal medicine (6), and many clinical trials have investigated these microorganisms in a wide variety of diseases, including those outside the gastrointestinal tract (2, 6–10).

Despite some promising results, doubts and debate remain regarding the use of these interventions (11–18). One strong belief about probiotics and prebiotics is that they are safe, yet adverse events (AEs) arising from their use are poorly understood (18–20). Some authors have raised alarm about potential AEs with probiotics (18–21). In 2011, a report by the Agency for Healthcare Research and Quality (19) concluded that "the current literature is not well equipped to answer questions on the safety of probiotics in intervention studies with confidence." More worrying is that potential risks have been described in case reports and clinical trial results (19–23).

We believe that researchers must clearly describe the incidence and severity of AEs related to probiotics, prebiotics, and synbiotics, particularly when they are used to treat severe disease or are used by high-risk patients (such as preterm infants or persons who are receiving ventilation or are critically ill). To facilitate decision making by all stakeholders, the different issues related to harms reporting from studies of these interventions must be identified before their use expands (24–32). Therefore, we performed a methodological, systematic review of all published randomized controlled trials (RCTs) assessing probiotics, prebiotics, and synbiotics to examine how harms have been reported.

METHODS

We uploaded a prespecified protocol (20 March 2017) to a publicly accessible institutional Web site, and we followed standard procedures for systematic reviews and reported processes and results according

to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (33).

Data Sources and Searches

We systematically searched for eligible studies published between 1 January 2015 and 20 March 2018 in the following databases: Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and Web of Science. Search equations (which had no language restrictions) were developed for each database and were based partly on search terms used in previous studies on the topic (**Appendix Table 1**, available at Annals.org). The equations were based on MeSH (Medical Subject Headings) terms and specific free-text words pertaining to probiotics, prebiotics, and synbiotics.

Study Selection

We included all published reports of RCTs in humans that assessed the efficacy or safety of at least 1 intervention involving probiotics, prebiotics, or synbiotics (appropriate combinations of probiotics and prebiotics) alone or combined with another intervention, for any clinical condition. Studies of any probiotic, prebiotic, or synbiotic pharmaceutical formulation, food product, or dosage and duration of use were eligible, as were trials using any control (such as a placebo or an antibiotic).

We excluded preclinical studies (animal models or in vitro assays, studies using metagenomic methods only, and those assessing the mechanism of action of microbiota), observational studies, case reports and series, diagnostic or prognostic studies, analyses of medicoeconomics only, reviews, systematic reviews, meta-analyses, methodological publications, editorial-style pieces (such as editorials, letters, commentaries, and responses to articles), abstracts, posters, secondary analyses of trials, and studies not published in English.

Two reviewers (A.B. and M.K.) independently screened titles and abstracts and then selected full-text articles. Reasons for exclusion were documented, and disagreements regarding eligibility were resolved by consensus.

Data Extraction

Four reviewers (A.B., M.K., C.R., and Lina Ghosn El Chall [INSERM U1153; Assistance Publique-Hôpitaux de Paris, Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu; and Université Paris Descartes-Sorbonne Paris Cité, Paris, France]) independently extracted data from studies using a standardized form. Sources for the study data that were reviewed included published reports and the following if found: supplementary appendices, protocols, trial registration data reported by authors, and previous relevant publications mentioned by authors. Disagreements were resolved by discussion.

We collected the following study characteristics: journal type, year of publication, type of publication, country, centers involved, funding source, study design, type of microbiota intervention assessed and comparator used, number of patients randomly assigned, and clinical conditions (**Appendix Table 2**, available at Annals.org). We classified the clinical status of the study populations as healthy volunteers, outpatients, or hospitalized or critical care patients.

Data Synthesis and Analysis

For all sections (abstract, methods, results, and discussion) of each report, we determined whether any information related to harm (such as toxicity, AEs, side effects, or safety) was disclosed (even if no events occurred). Guided by the CONSORT (Consolidated Standards of Reporting Trials) statement extension for harms reporting (24) and other pertinent studies (28, 29, 34, 35), we evaluated how safety parameters were reported (such as through a list of addressed AEs and serious AEs [SAEs], with a definition for each; harms collection methods; a plan for the presentation and analysis of AEs; the number of participant withdrawals due to harms; or the number of AEs per study group, as well as grade and type, with separate information about SAEs). We also looked at information detailing unexpected and expected AEs, definitions of safety study population and time point of AEs, and any discussion of benefit–harm balance.

For studies reporting harms-related results, we described the format of the presentation and whether the authors used adequate or inadequate metrics (such as a mean without measures of precision or a percentage only). We assessed how safety data were mentioned per event (that is, the number of cases occurring for an event) or per patient (that is, the number of patients who had an event); data for AEs were combined per organ system (for example, gastrointestinal or neurologic events). We determined the type of inadequate reporting by identifying whether it used generic statements only; lumped the number of AEs without distinguishing grade or type; provided only the total number of AEs (not the number per group); gave results for only 1 group; restricted harms-related results to only common, unexpected, or serious events; provided results of global statistical tests only; or described AEs using only a figure.

Using parameters from previous studies (28, 29, 34, 35), we considered harms reporting in the abstract and discussion sections to be adequate if the authors discussed any limitations regarding harms. We considered reporting of methods to be adequate if the following items were included: a list of AEs and SAEs addressed, with definitions for each; mode of data collection; timing; and attribution methods. We considered reporting of results to be adequate if the following were reported: number of participant withdrawals due to harms; number of AEs per study group, as well as grade, type, and seriousness, with appropriate metrics; and definition of safety population.

Lastly, to summarize data, we built a composite outcome describing adequate reporting of key safety parameters on the basis of guidelines from Ioannidis and Lau (27). We considered reporting to be adequate if all 3 of the following items were reported and inadequate if 1 or more of the items were not reported: number of participant withdrawals due to harms, with reasons, per group and per type of AE; definition of AEs

and SAEs, with reference to standardized and validated definitions; and number of AEs per group, as well as grade, type, and seriousness, with denominators used for analysis.

Role of the Funding Source

No specific funding was received.

RESULTS

General Characteristics of RCTs

Figure 1 depicts the search and selection process that led to the identification of 384 RCTs for analysis (Appendix Table 3, available at Annals.org). Most trials (88%) were published in specialty journals, 154 (40%) were conducted in Europe, 269 (70%) were single-center trials, and 160 (42%) had at least 1 private funding source (Appendix Table 4, available at Annals.org). Study populations included healthy volunteers (n = 136) or patients with any of several medical conditions (n = 248). Gastrointestinal diseases and endocrine and metabolic conditions were studied in 134 RCTs (35%). Trials involving patients with medical conditions were conducted in outpatient (n = 195) and hospitalized or critical care (n = 53) settings. The median number of patients randomly assigned per study was 62 (interquartile range, 43 to 120). A total of 265 trials (69%) assessed probiotics, and 274 (71%) used a placebo as a comparator.

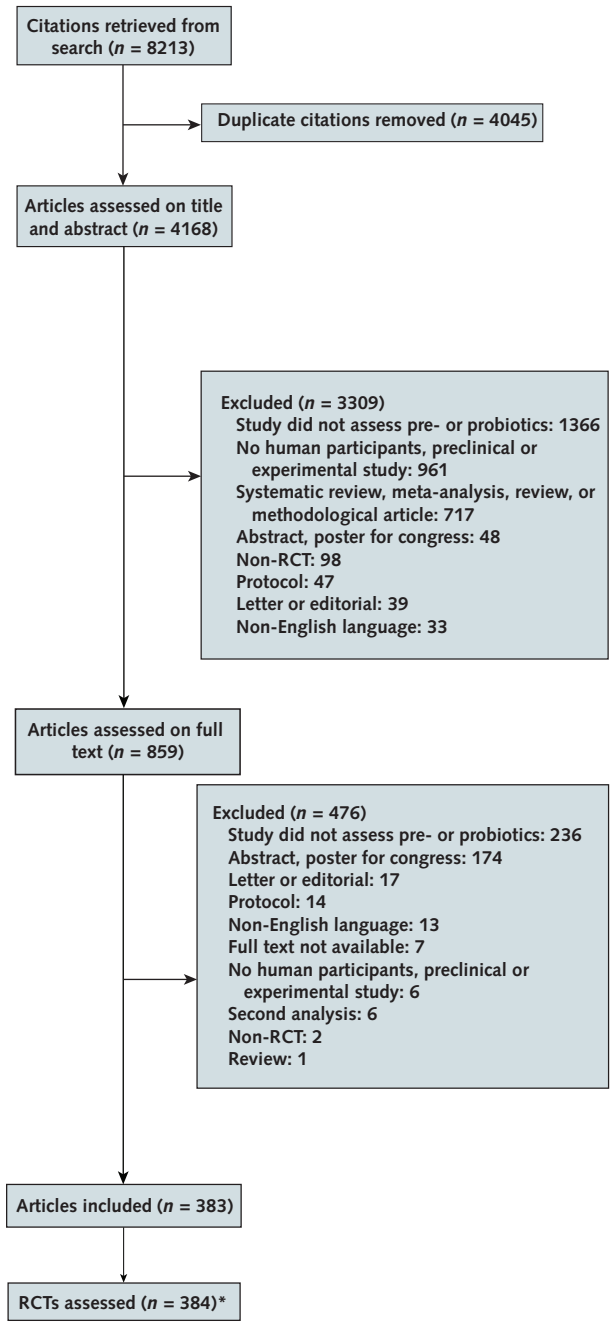
Reporting of Harms

Of the 384 trials, 106 (28%) did not give any information related to harms and 311 (81%) did not mention AEs in the abstract (Table 1 and Appendix Table 5, available at Annals.org). Definitions of AEs and SAEs were not provided for 347 studies (90%), and methods of collecting harms-related information were not described for 372 (97%). Although some safety results were reported in 242 trials (63%), few studies (18%) clearly identified the population included in the safety analysis. Few trials reported the number of participant withdrawals due to AEs (30%) or the number of AEs (21%) or SAEs (20%) per study group. Only 7 of the 53 studies involving hospitalized or critical care patients reported the number of SAEs per group.

Presentation of Harms-Related Results

When safety results were described (Table 2 and Appendix Table 6, available at Annals.org), AEs were often mentioned in the text (n = 205 of 242 trials [85%]). Adverse events were described at the level of the event for 57 (24%), the patient for 45 (19%), and both for 37 (15%) of 242 trials. The reporting was frequently inadequate: 37% of these RCTs used only generic statements; 16% used inadequate metrics; 8% gave only the global total number of AEs; 21% used some restrictions in reporting AEs (common, severe, unexpected); 7% lumped grade, type, and seriousness of AEs; and 5% provided only global statistical comparisons.

Figure 1. Evidence search and selection.



RCT = randomized controlled trial.
* One article reported 2 different RCTs.

Evaluation of Adequate Reporting of Harms

Nine trials (2%) adequately reported methods of harm assessment, mentioning the definitions of AEs, the mode used to collect data, the timing, and attribution methods (Figure 2 and Appendix Figure, available at Annals.org). Twenty-three (6%) adequately described safety results with the number of participant withdrawals due to harms, as well as the number of AEs and SAEs, with appropriate metrics and a denominator

Table 1. Reporting of Harms in RCTs Assessing Probiotics, Prebiotics, and Synbiotics, by Clinical Status of Population and Overall*

Item Reported	Overall (*n* = 384)	Healthy Volunteers (*n* = 136)	Outpatients (*n* = 195)	Hospitalized/Critical Care Patients (*n* = 53)
Harms-related data mentioned in publications	278 (72)	98 (72)	143 (73)	37 (70)
Abstract				
AEs mentioned in this section	73 (19)	29 (21)	32 (16)	12 (23)
Discussion of benefit–harm balance	49 (13)	24 (18)	18 (9)	7 (13)
Methods				
AEs mentioned in this section	152 (40)	61 (45)	75 (38)	16 (30)
List of AEs assessed with definition	34 (9)	20 (15)	9 (5)	5 (9)
Definition of SAEs	19 (5)	11 (8)	5 (3)	3 (6)
Definition of expected events	46 (12)	24 (18)	16 (8)	6 (11)
Definition of early and late AEs	10 (3)	6 (4)	3 (2)	1 (2)
Methods for collecting harms-related information	12 (3)	8 (6)	4 (2)	0 (0)
Mode for collecting data	111 (29)	49 (36)	53 (27)	9 (17)
Timing†	80 (21)	35 (26)	40 (21)	5 (9)
Attribution methods	46 (12)	24 (18)	18 (9)	4 (8)
Monitoring of harms-related and stopping rules if pertinent	27 (7)	14 (10)	13 (7)	0 (0)
Description of plan for presentation and analysis of harms	48 (13)	21 (16)	24 (12)	3 (6)
Results				
AEs mentioned in this section	242 (63)	85 (63)	122 (63)	35 (66)
Number of participant withdrawals for harms with reasons for discontinuations per group and grade and type of AEs (even if no participants withdrew)	117 (30)	41 (30)	61 (31)	15 (28)
AEs (even if no events occurred)	125 (33)	51 (38)	59 (30)	15 (28)
Number of AEs per group and grade and type (with numerical data)	80 (21)	32 (24)	39 (20)	9 (17)
SAEs (even if no events occurred)	85 (22)	33 (24)	43 (22)	9 (17)
Number of SAEs separately per group and grade and type (with numerical data)	75 (20)	30 (22)	38 (19)	7 (13)
Unattended and attended AEs separately per group	24 (6)	12 (9)	8 (4)	4 (8)
Population of safety analysis clearly identified (with denominator used for analysis)	70 (18)	29 (21)	33 (17)	8 (15)
Time point for analysis of harms	40 (10)	17 (13)	19 (10)	4 (8)
Discussion				
AEs mentioned in this section	126 (33)	42 (31)	61 (31)	23 (43)
Discussion of benefit–harm balance	110 (29)	39 (29)	52 (27)	19 (36)

AE = adverse event; RCT = randomized controlled trial; SAE = serious AE.
* Values are numbers (percentages).
† Length of follow-up and frequency of surveillance for AEs, as well as time of evaluation.

used for safety analysis. Nine trials (2%) adequately reported all guideline-recommended parameters (27) (that is, number of participant withdrawals due to harms; definition of AEs and SAEs; number of AEs per study group; and grade, type, and seriousness, with denominators used for analysis). Appendix Table 7 (available at Annals.org) lists examples of adequate harms reporting.

DISCUSSION

Our systematic review of 384 recently published RCTs assessing probiotics, prebiotics, or synbiotics found that harms reporting for these interventions often was missing, insufficient, or inadequate. One third of the trials gave no information on harms, and only 2% adequately reported key safety components. Most reports of harms-related results used generic statements (such as "well-tolerated") or inappropriate metrics (such as percentages only), or restricted AE reporting to common, severe, or unexpected events. The inadequacy in reporting harms-related results may lead to an inaccurate safety profile and erroneous decision making, with major consequences for patients. For example, a generic statement, such as "well-tolerated," may be misin-

terpreted as a lack of AEs reported for a trial, but the reader cannot determine whether no AEs occurred in any participants, the AEs were not measured or reported, or both. Readers should be able to estimate the number of AEs, even if no events occur.

Safety data may be omitted from RCT reports for several reasons. People have strong beliefs about the safety of probiotics, prebiotics, and synbiotics. Many researchers in this area think that a detailed evaluation of potential harms is not necessary (20). Caution is needed, however, particularly when considering these interventions for vulnerable or critically ill persons (23). The safety profile of an intervention should never be presumed; rather, it should be rigorously evaluated and reported. We need to promote more active implementation and endorsement of recommendations for standardizing evaluation and reporting methods, such as developing a reporting tool with specific templates (36–41).

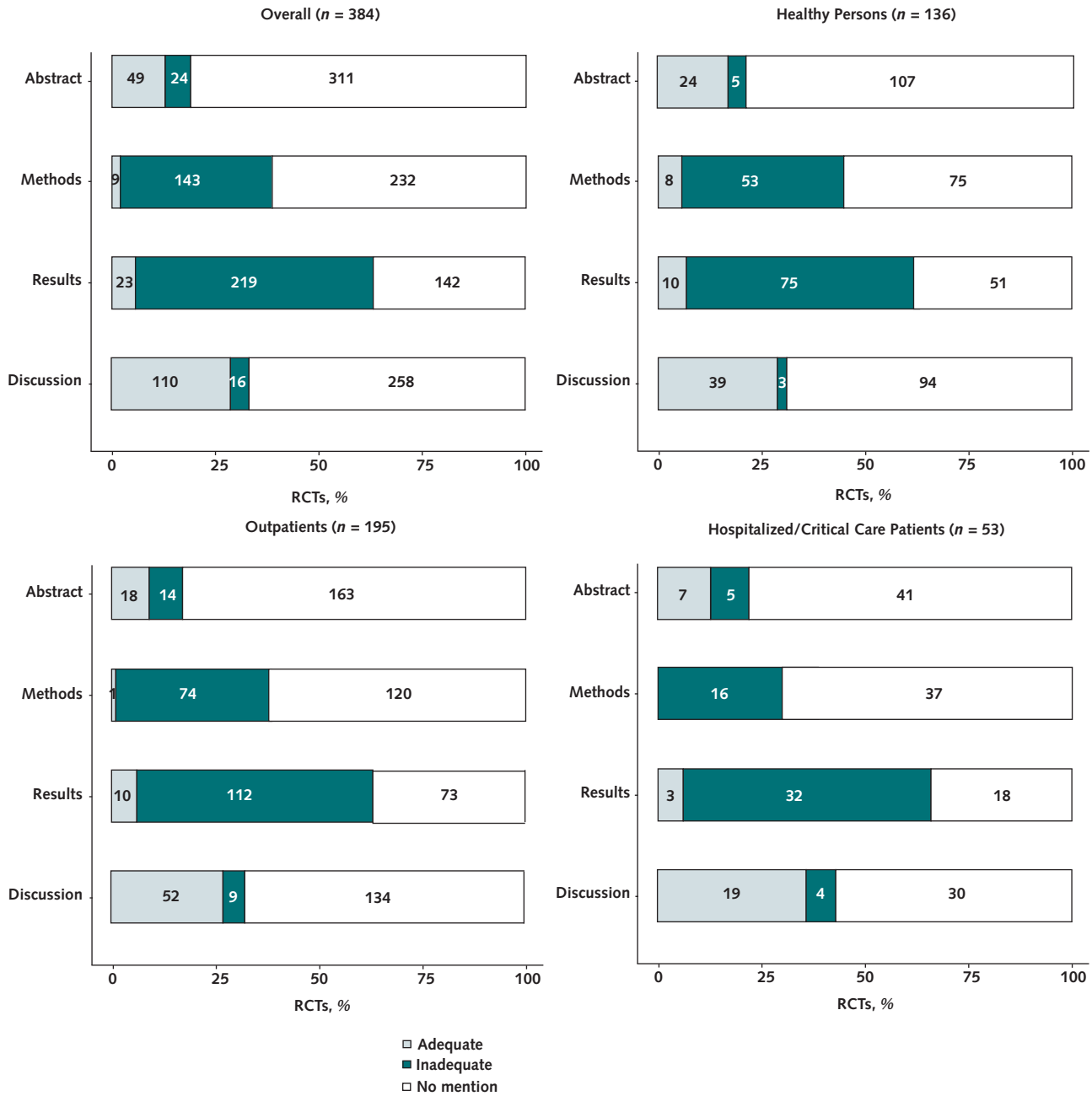
Several previous studies evaluating harms reporting in general found that clinical trials do not adequately report harms (27–29, 35, 37, 42–44). No previous reviews assessed the problem of harms reporting in probiotics, prebiotics, and synbiotics trials. We iden-

Table 2. Presentation of Harms-Related Results in RCTs Assessing Probiotics, Prebiotics, and Synbiotics, by Clinical Status of Population and Overall*

Item Reported	Overall (*n* = 242)	Healthy Volunteers (*n* = 85)	Outpatients (*n* = 122)	Hospitalized/Critical Care Patients (*n* = 35)
Format of results†				
Text	205 (85)	70 (82)	106 (87)	29 (83)
Table	56 (23)	19 (23)	28 (23)	9 (26)
Figure	9 (4)	4 (5)	5 (4)	0 (0)
Reporting of safety results				
Reporting of safety results with adequate metrics per group and grade, type, and seriousness (e.g., absolute risk for binary events and means [SDs] for continuous measures)	39 (16)	15 (18)	19 (16)	5 (14)
Reporting of safety data at level of events per group and grade and type	57 (24)	23 (27)	28 (23)	6 (17)
Reporting of safety data at level of patients (number of patients with ≥1 AE and/or SAE) per group and grade and type	45 (19)	19 (22)	24 (20)	2 (6)
Reporting of safety data at level of events and patients	37 (15)	15 (18)	16 (13)	6 (17)
Combining of different AEs per organ into 1 composite outcome	21 (9)	12 (14)	6 (5)	3 (9)
Type of inadequate reporting of safety results†				
Expression of AEs using only generic statements (e.g., "The treatment was well-tolerated.")	89 (37)	26 (31)	47 (39)	16 (46)
Reporting of AEs using inadequate metrics (e.g., only the percentage used or the mean without the measure of precision)	38 (16)	11 (13)	19 (16)	8 (23)
Reporting of global total number of AEs (not per group or grade or type)	19 (8)	9 (11)	8 (7)	2 (6)
Partial reporting of AEs (not for all AEs)	50 (21)	14 (16)	29 (24)	7 (20)
Restricted to common events	24 (48)	11 (79)	9 (31)	4 (57)
Restricted to severe events	18 (36)	2 (14)	15 (52)	1 (14)
Restricted to unexpected events	6 (12)	1 (7)	3 (10)	2 (29)
Restricted to common and unexpected events	2 (4)	0 (0)	2 (7)	0 (0)
Reporting of AEs per group but combination of grade, type, and seriousness	17 (7)	10 (12)	6 (5)	1 (3)
Reporting of AEs using only global statistical tests	12 (5)	4 (5)	7 (6)	1 (3)
Reporting of AEs of only 1 group	5 (2)	2 (2)	2 (2)	1 (3)
Reporting of AEs using only a figure	2 (1)	1 (1)	1 (1)	0 (0)

AE = adverse event; RCT = randomized controlled trial; SAE = serious AE.
* Values are numbers (percentages).
† Percentages do not sum to 100 because more than 1 answer was possible.

Figure 2. Evaluation of adequate harms reporting of RCTs assessing probiotics, prebiotics, and synbiotics, overall and by clinical status of population.



Data in boxes are numbers of studies. RCT = randomized controlled trial.

tified several systematic reviews, meta-analyses, and reviews focused on probiotics, prebiotics, and synbiotics (19, 20, 23, 45–50). Most of these studies evaluated the efficacy or safety of these interventions in 1 particular condition, but none evaluated the specific reporting of methods used to collect harms data, the definition of AEs, or the presentation of safety data. Our review explored not only the lack of harms reporting but also the many inadequacies in reporting harms in many trials assessing probiotics, prebiotics, and synbiotics for a wide range of clinical indications. These issues are important, especially because these interventions are increasingly being used. The different elements discussed may help authors better evaluate and describe any harms from these micro-organisms in future trials.

Our study had some limitations. The study authors may have omitted important details from their reports, or key information may have been deleted during the publication process (51). Nevertheless, most journals allow for an online appendix for extended descriptions

of methods and results, and we assessed all data from the original reports, previous publications, supplementary appendices, protocols, and trial registration data when available. We may not have identified all available studies because we did not use a validated search filter to retrieve studies assessing these interventions. We acknowledge that trials may be insufficiently powered to detect AEs and cannot be expected to detect and report all AEs, but our primary concern is that AE data, if available, should be reported, even if no AEs occur. Our results may not be generalizable to studies published in a language other than English. We did not contact the investigators for clarification of unclear methods.

In summary, most studies of probiotics, prebiotics, and synbiotics lack key safety parameters, raising doubts about the confidence we can have in conclusions about the safety of these interventions. Considering all these elements, a broad general conclusion that probiotics, prebiotics, and synbiotics are safe cannot be made without discussing safety and toxicology data. An evaluation of the benefit–risk balance should always be included in RCT reports. An international and collective effort is urgently needed.

From INSERM U1153 and Université Paris Descartes-Sorbonne Paris Cité, Paris, France (A.B., C.R.); Columbia University, New York, New York (M.K.); and INSERM U1153, Université Paris Descartes-Sorbonne Paris Cité, and French Cochrane Centre, Paris, France, and Columbia University, New York, New York (P.R.).

Note: All authors, external and internal, had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix Table 1. Search Terms and Equations

Variable	Number	PubMed	Cochrane Central Register of Controlled Trials	EMBASE	Web of Science
RCTs	1	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])		('(random$':ab,ti OR 'factorial$':ab,ti OR 'crossover$':ab,ti OR 'cross over$':ab,ti OR 'cross-over$':ab,ti OR 'placebo$':ab,ti OR 'doubl$ adj blind$':ab,ti OR 'singl$ adj blind$':ab,ti OR 'assign$':ab,ti OR 'allocat$)':ab,ti OR '(crossover-procedure' OR 'double-blind procedure'/exp/mj OR 'randomized controlled trial'/exp/mj OR 'single-blind procedure)') AND [embase]/lim	TOPIC: (("randomised controlled trial" OR "randomized controlled trial" OR RCT OR trial OR "clinical trial"))
Probiotics, prebiotics, synbiotics	2	(Probiotic*[Title/Abstract] OR lactobacill* [Title/Abstract] OR lactococc*[Title/ Abstract] OR Bifidobacter*[Title/ Abstract] OR Enterococc*[Title/ Abstract] OR Streptococc*[Title/ Abstract] OR "s thermophilus"[Title/ Abstract] OR Saccharomyces[Title/ Abstract] OR Bacillus [Title/Abstract] OR Pediococc*[Title/ Abstract]OR prebiotic*[Title/ Abstract]OR synbiotic* [Title/Abstract] OR symbiotic* [Title/Abstract])	'(Probiotic* OR lactobacill* OR lactococc* OR Bifidobacter* OR Enterococc* OR Streptococc* OR "s thermophilus" OR Saccharomyces OR Bacillus OR Pediococc*OR prebiotic*OR symbiotic* OR synbiotic*) in Title, Abstract, Keywords in Trials'	(probiotic*':ab,ti OR 'lactobacill*':ab,ti OR 'lactococc*':ab,ti OR 'bifidobacter*':ab,ti OR 'enterococc*':ab,ti OR 'streptococc*':ab,ti OR 'sthermophilus':ab,ti OR 'saccharomyces':ab,ti OR 'bacillus':ab,ti OR 'pediococc*or prebiotic*OR symbiotic* OR synbiotic*)':ab,ti "	TOPIC: ((Probiotic* OR lactobacill* OR lactococc* OR Bifidobacter* OR Enterococc* OR Streptococc* OR sthermophilus* OR Saccharomyces OR Bacillus OR Pediococc*OR prebiotic*OR symbiotic* OR synbiotic*))
Equation of search	–	1 and 2	2	1 and 2	1 and 2

RCT = randomized controlled trial.

Appendix Table 2. Classification of Conditions

Gastrointestinal diseases: Irritable bowel syndrome, inflammatory bowel diseases (Crohn disease and ulcerative colitis), constipation, *Clostridium difficile* infection, other diarrheal diseases, infantile colic, celiac disease, diverticular disease
Endocrinal and metabolic diseases: Diabetes, obesity, hypercholesterolemia, and nonalcoholic fatty liver disease, hyperoxaluria, hypothyroidism, polycystic ovary syndrome
Preterm neonates: Necrotizing enterocolitis, jaundice, sepsis and bacterial infections
Infectious diseases: Methicillin-resistant *Staphylococcus aureus*, infectious diseases of the digestive tract, impetigo, pharyngitis, rhinosinusitis, otitis
Periodontal diseases: Gingivitis, peri-implant, mucositis, periodontitis, oral candidiasis, active phase halitosis, caries
Eczema/atopic dermatis/allergy
Cancer: Colorectal cancer, gynecological cancer, pelvic
Neurologic, mental, and behavioral diseases: Parkinson disease, Alzheimer disease, multiple sclerosis, schizophrenia, major depressive disorder
Postoperative complications
Vaginal infections
HIV infection
Other: Burn injury, primary vesicoureteral reflux, preterm premature rupture of membranes, knee osteoarthritis, rheumatoid arthritis, severe acute malnutrition, dry eye syndrome, cystic fibrosis, chronic pulmonary symptoms due to sulfur mustard exposure

Appendix Table 3. Included Studies

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Appendix Table 3–Continued

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Zhao R, Wang Y, Huang Y, Cui Y, Xia L, Rao Z, et al. Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients: a prospective randomized and controlled trial. Medicine (Baltimore). 2017;96:e8418. [PMID: 29069041] doi:10.1097/MD.0000000000008418

Appendix Table 4. General Characteristics of Trials

Item and Subcategory	Trials (*n* = 384)*
Year of publication	
2015	150 (39)
2016	68 (18)
2017	157 (41)
2018	9 (2)
Journal	
Specialized	339 (88)
General	45 (12)
Location of studies†	
Iran	63 (16)
United States	36 (9)
Italy	35 (9)
Spain	24 (6)
India	18 (5)
United Kingdom	16 (4)
Japan	16 (4)
Sweden	14 (4)
Brazil	13 (3)
South Korea	12 (3)
Turkey	11 (3)
Australia	10 (3)
China	10 (3)
Germany	10 (3)
Canada	8 (2)
Denmark	7 (2)
Poland	7 (2)
Other (<7 studies/country, 32 countries)	92 (24)
Number of countries	
Single country	373 (97)
Multiple countries	11 (3)
Number of centers	
Single-center	269 (70)
Multicenter	72 (19)
Not reported	43 (11)
Funding sources	
Public	126 (33)
Private	117 (30)
Both	43 (11)
None	18 (5)
Not reported	80 (21)
Study design	
Parallel group	343 (89)
Crossover	37 (9)
Factorial	3 (1)
Cluster	1 (1)
Type of microbiota intervention assessed	
Probiotics	265 (69)
Prebiotics	55 (14)
Synbiotics	34 (8)
Several types of microbiota (pro-prebiotics, synbiotics)	11 (3)
Combination of probiotics with another intervention	15 (4)
Combination of synbiotics with another intervention	3 (1)
Combination of prebiotics with another intervention	1 (1)

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Appendix Table 4–Continued

Item and Subcategory	Trials (*n* = 384)*
Control group	
Placebo	274 (71)
Food product	57 (14)
Pharmacologic treatment	26 (7)
Probiotics or prebiotics	11 (3)
No treatment	2 (1)
Other	6 (2)
Not clear	8 (2)
Condition	
Healthy volunteers	136 (35)
Endocrinal and metabolic diseases	69 (19)
Gastrointestinal diseases	65 (17)
Preterm neonates	20 (5)
Infectious diseases	19 (5)
Eczema/atopic dermatitis/allergy	15 (4)
Periodontal diseases	13 (3)
Cancer	8 (2)
Neurologic, mental, and behavioral diseases	9 (2)
Postoperative complications/surgery	6 (2)
HIV	5 (1)
Vaginal infections	4 (1)
Other (<3 studies/condition, 9 conditions)	15 (4)
Status of population	
Outpatients	195 (51)
Healthy volunteers	136 (35)
Hospitalized or critical care patients	53 (14)
Age of population	
Adults (18 to 65 y)	151 (39)
Children (<18 y)	121 (31)
Adults and seniors	81 (21)
Seniors (>65 y)	8 (2)
Adults and children	8 (2)
All ages	1 (1)
Not reported	14 (4)
Sample size	
Median patients randomly assigned per study (interquartile range), *n*	62 (43-120)
Reporting of trial registration	248 (65)
Results posted	8 (3)
AEs posted	7 (3)
Publication with appendix	81 (21)
Protocol available	22 (6)
Type of publication	
Full original article	383 (99)
Research letter	1 (1)

AE = adverse event.
* Values are numbers (percentages) unless otherwise indicated.
† More than 1 answer was possible, so the total does not equal 100.

Appendix Table 5. Reporting of Harms, by Intervention Type*

Items Reported	Probiotics (*n* = 265)	Prebiotics (*n* = 55)	Synbiotics (*n* = 34)	Other (*n* = 30)
Harms-related data mentioned in publication	192 (72)	39 (71)	25 (74)	22 (73)
Abstract				
AEs mentioned in Abstract section	50 (19)	11 (20)	4 (12)	8 (27)
Discussion of benefit–harm balance	33 (12)	9 (16)	2 (6)	5 (17)
Methods				
AEs mentioned in Methods section	101 (38)	25 (45)	12 (35)	14 (47)
List addressed AEs with definition	20 (8)	8 (15)	3 (9)	3 (10)
Definition of SAEs	13 (5)	3 (5)	2 (6)	1 (3)
Definition of expectedness events	23 (9)	11 (20)	5 (15)	7 (23)
Definition of early and late AEs	6 (2)	2 (4)	1 (3)	1 (3)
Methods for collecting harms-related information	7 (3)	1 (2)	3 (9)	1 (3)
Mode for collecting data	71 (27)	22 (40)	8 (24)	10 (33)
Timing (follow-up period and frequency of surveillance for AEs, and time of evaluation)	54 (20)	14 (25)	5 (15)	7 (23)
Attribution methods	27 (10)	9 (16)	6 (18)	4 (13)
Monitoring of harms-related and stopping rules if pertinent	19 (7)	2 (4)	4 (12)	2 (7)
Description of plan for presentation and analysis of harms	27 (10)	9 (16)	6 (18)	6 (20)
Results				
AEs mentioned in Results section	162 (61)	35 (64)	23 (68)	22 (73)
Number of participant withdrawals for harms with reasons for discontinuations per group and type of AEs (even if no participant withdrawals)	78 (29)	21 (38)	10 (29)	8 (27)
Reporting of AEs (even if no events occurred)	85 (32)	19 (35)	12 (35)	9 (30)
Reporting of number of AEs per group and grade and type (with numerical data)	58 (22)	9 (16)	7 (21)	6 (20)
Reporting of SAEs (even if no events occurred)	58 (22)	14 (25)	6 (18)	7 (23)
Reporting of no. of SAEs separately per group and grade and type (with numerical data)	53 (20)	12 (22)	5 (15)	5 (17)
Reporting of unattended and attended AEs separately per group	16 (6)	5 (9)	1 (3)	2 (7)
Population of safety analysis clearly identified (denominator used for analysis)	51 (19)	8 (15)	6 (18)	5 (17)
Time point for analyses on harms	25 (9)	7 (13)	3 (9)	5 (17)
Discussion				
AEs mentioned in Discussion section	86 (32)	19 (35)	8 (24)	13 (43)
Discussion of benefit–harm balance	76 (29)	15 (27)	7 (21)	12 (40)

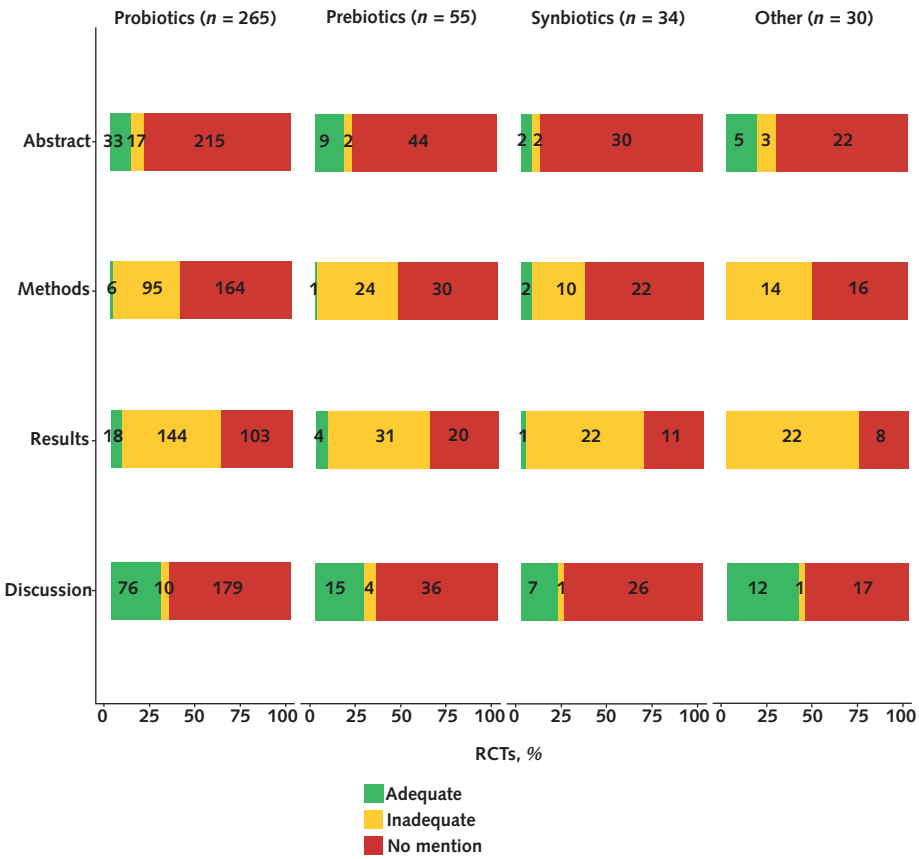
AE = adverse event; SAE = serious AE.
* Values are numbers (percentages).

Appendix Table 6. Presentation of Harms-Related Results, by Intervention Type*

Items Reported	Probiotics (*n* = 162)	Prebiotics (*n* = 35)	Synbiotics (*n* = 23)	Other (*n* = 22)
Format of results†				
Text	136 (84)	28 (80)	20 (87)	21 (95)
Table	41 (25)	8 (23)	4 (17)	3 (14)
Figure	6 (4)	2 (6)	0	1 (5)
Reporting of safety results				
Reporting of safety results with adequate metrics per group and grade, type, and seriousness (e.g., absolute risk for binary events, mean and standard deviation for continuous measures)	31 (19)	4 (11)	2 (9)	2 (9)
Reporting of safety data at level of events per group and grade and type	38 (23)	10 (29)	6 (26)	3 (14)
Reporting of safety data at level of patients (number of patients with ≥1 AE and/or SAE per group and grade and type)	26 (16)	7 (20)	6 (26)	6 (27)
Reporting of safety data at level of events and patients	27 (17)	5 (14)	3 (13)	2 (9)
Combining of different AEs per organ into 1 composite outcome	13 (8)	4 (11)	1 (4)	3 (14)
Type of inadequate reporting of safety results†				
Expression of AEs using only generic statements (e.g., the treatment was well-tolerated)	61 (38)	11 (31)	7 (30)	9 (41)
Reporting AEs using inadequate metrics (e.g., only percentage use, mean without measure of precision)	21 (13)	11 (31)	3 (13)	3 (14)
Reporting of global total number of AEs (not per group or grade or type)	11 (7)	5 (14)	1 (4)	2 (9)
AEs partially reporting (not for all AEs)	31 (19)	5 (14)	9 (39)	5 (23)
Restriction to common events	13 (42)	3 (60)	5 (56)	3 (60)
Restriction to severe events	13 (42)	1 (20)	4 (44)	
Restriction to unexpected events	4 (13)	1 (20)		1 (20)
Restriction to common events and unexpected events	1 (3)			1 (20)
Reporting AEs per group but lumping grade, type, and seriousness	11 (7)	4 (11)		2 (9)
Reporting of AEs using only global statistical tests	8 (5)	2 (6)		2 (9)
Reporting of AEs of only group	4 (2)			1 (5)
Reporting of AEs using only a figure	2 (1)			

AE = adverse event; SAE = serious AE.
* Values are numbers (percentages).
† Multiple answers were possible, so the total does not equal 100.

Appendix Figure. Evaluation of adequate harms reporting, by intervention type.



Data in boxes are numbers of studies. RCT = randomized controlled trial.

Appendix Table 7. Examples of Adequate Reporting of Harm

Domain	Example	Reference
Describe list addressed AEs		
Comprehensive list with definitions	Methods section: "An adverse event (AE) is any untoward medical occurrence that may arise during the study period . . . Fever: Sustained axillary >37.50 Hypothermia: Sustained axillary < 35 0 C measured for 3 minutes. Convulsion: Visible convulsion (reported by parents) but confirmed by study personnel . . . Vomiting: three or more episodes a day, any projectile, bloody or bilious vomiting. Diarrhea: Change in consistency of stool with more water content as reported by the mother."	**Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, et al.** A randomized synbiotic trial to prevent sepsis among infants in rural India. Nature. 2017;548:407-12. [PMID: 28813414] doi:10.1038/nature23480
Definition of SAEs	Methods section: "A serious AE was defined as cause of death, life threatening, requiring inpatient hospitalization, producing disability or incapacity persistent or significant or threatening the patients."	**Montané E, Barriocanal AM, Arellano AL, Valderrama A, Sanz Y, Perez-Alvarez N, et al.** Pilot, double-blind, randomized, placebo-controlled clinical trial of the supplement food *Nyaditum resae*® in adults with or without latent TB infection: safety and immunogenicity. PLoS One. 2017;12: e0171294. [PMID: 28182700] doi:10.1371/ journal.pone.0171294
Reference to standardized and validated definitions and grading	Methods section: "Laboratory abnormalities were graded following the Toxicity Grading Scale Guidance provided by the Food and Drug Administration."	**Montané E, Barriocanal AM, Arellano AL, Valderrama A, Sanz Y, Perez-Alvarez N, et al.** Pilot, double-blind, randomized, placebo-controlled clinical trial of the supplement food *Nyaditum resae*® in adults with or without latent TB infection: safety and immunogenicity. PLoS One. 2017;12: e0171294. [PMID: 28182700] doi:10.1371/ journal.pone.0171294
Reporting of expected events	Methods section: "It is expected that these adverse events will manifest as diarrhea, vomiting, sepsis and, in severe cases, lactobacillemia."	**Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, et al.** A randomized synbiotic trial to prevent sepsis among infants in rural India. Nature. 2017;548:407-12. [PMID: 28813414] doi:10.1038/nature23480
Describe mode for collecting data	Methods section: "Record of adverse events, both gastrointestinal and non-gastrointestinal, being reported by the subject either spontaneously or after questioning or looking at the Volunteer's Diary, during the first 4 weeks of the monitoring . . . AE detected by the investigator through interrogation or reported by the subject during the defined period of collection were recorded."	**Montané E, Barriocanal AM, Arellano AL, Valderrama A, Sanz Y, Perez-Alvarez N, et al.** Pilot, double-blind, randomized, placebo-controlled clinical trial of the supplement food *Nyaditum resae*® in adults with or without latent TB infection: safety and immunogenicity. PLoS One. 2017;12:e0171294. [PMID: 28182700] doi:10.1371/ journal.pone.0171294

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Appendix Table 7–Continued

Domain	Example	Reference
Timing: Follow-up period and frequency of surveillance for AEs, and time of evaluation	Methods section: "safety were assessed by asking and recording all reported adverse events (including changes in medications/OTC products and health) at visit 2 (end of run-in period) and visit 3 (end of intervention period)."	**Ringel-Kulka T, Kotch JB, Jensen ET, Savage E, Weber DJ.** Randomized, double-blind, placebo-controlled study of synbiotic yogurt effect on the health of children. J Pediatr. 2015;166:1475-81. [PMID: 25841539] doi:10.1016/j.jpeds.2015.02.038
Attribution methods	Methods section: "The investigators determined the relationship between the study treatment and the AE as `not related', `unlikely', `possibly', `probably', and `definite' according to a predefined algorithm based on the modified Karch and Lasagna algorithm used by the Spanish Pharmacovigilance System and after a consensus reached between the clinical pharmacologists study investigator . . . The CRO of the study (FLS Research Support) monitored all the study in order to ensure the use of standard terminology and the collection of accurate, consistent, complete and reliable data."	**Montané E, Barriocanal AM, Arellano AL, Valderrama A, Sanz Y, Perez-Alvarez N, et al.** Pilot, double-blind, randomized, placebo-controlled clinical trial of the supplement food *Nyaditum resae*® in adults with or without latent TB infection: safety and immunogenicity. PLoS One. 2017;12:e0171294. [PMID: 28182700] doi:10.1371/journal.pone.0171294
Monitoring of harms-related and stopping rules if pertinent	Methods section: "Serious ill health and severe stress, for example, hospitalisation, were grounds for withdrawal from the trial and reported as serious adverse events."	**Harnett J, Myers SP, Rolfe M.** Probiotics and the microbiome in celiac disease: a randomised controlled trial. Evid Based Complement Alternat Med. 2016;2016:9048574. [PMID: 27525027] doi:10.1155/2016/9048574
	Methods section: "Furthermore, stopping rules for study termination included reports of adverse events resulting from participation that posed unnecessary risk to the participant. Adverse events that were reported to the study physician were determined to add no serious risk of harm. The institutional research board determined that no changes were needed and that the study could continue as approved."	**Ringel-Kulka T, Kotch JB, Jensen ET, Savage E, Weber DJ.** Randomized, double-blind, placebo-controlled study of synbiotic yogurt effect on the health of children. J Pediatr. 2015;166:1475-81. [PMID: 25841539] doi:10.1016/j.jpeds.2015.02.038
Description of plan for presentation and analysis of harms	Methods section: "The frequency and severity of the adverse events were described using frequencies and percentages. . . . The frequencies of adverse and serious adverse outcomes were compared using Fisher's exact test. No adjustments for multiple comparisons were used."	**Tan TP, Ba Z, Sanders ME, D'Amico FJ, Roberts RF, Smith KH, et al.** Safety of *Bifidobacterium animalis* subsp. *lactis* (*B. lactis*) strain BB-12-supplemented yogurt in healthy children. J Pediatr Gastroenterol Nutr. 2017;64:302-9. [PMID: 28114246] doi:10.1097/MPG.0000000000001272
Number of participant withdrawals for harms: With reasons for discontinuations per group and grade and type of AEs, even with no participant withdrawals	Results section: "Thirty-three patients (eight women) were randomized. One patient accomplished the first visit but decided to withdraw early in the study due to nausea to the probiotics."	**Bengtsson J, Adlerberth I, Östblom A, Saksena P, Öresland T, Börjesson L.** Effect of probiotics (*Lactobacillus plantarum 299* plus Bifidobacterium Cure21) in patients with poor ileal pouch function: a randomised controlled trial. Scand J Gastroenterol. 2016;51:1087-92. [PMID: 27150635] doi:10.3109/00365521.2016.1161067

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Appendix Table 7–Continued

Domain	Example	Reference
	Results section: "There were no participant withdrawals from the study due to adverse event."	**Merenstein DJ, Tan TP, Molokin A, Smith KH, Roberts RF, Shara NM, et al.** Safety of *Bifidobacterium animalis* subsp. *lactis* (*B. lactis*) strain BB-12-supplemented yogurt in healthy adults on antibiotics: a phase I safety study. Gut Microbes. 2015;6:66-77. [PMID: 25569274] doi:10.1080/19490976.2015.1005484
Number of AEs per group as well as grade and type	Results section: The author report in table the number of patients adverse events per group and grade and type see table 1.	**Tan TP, Ba Z, Sanders ME, D'Amico FJ, Roberts RF, Smith KH, et al.** Safety of *Bifidobacterium animalis* subsp. *lactis* (*B. lactis*) strain BB-12-supplemented yogurt in healthy children. J Pediatr Gastroenterol Nutr. 2017;64:302-9. [PMID: 28114246] doi:10.1097/MPG.0000000000001272
Number of SAEs per group as well as grade and type	Results section: The author report in table the number of patients serious adverse events per group and grade and type see table 4.	**da Costa Ribeiro H Júnior, Ribeiro TC, de Mattos AP, Pontes M, Sarni RO, Cruz ML, et al.** Normal growth of healthy infants born from HIV+ mothers fed a reduced protein infant formula containing the prebiotics galacto-oligosaccharides and fructo-oligosaccharides: a randomized controlled trial. Clin Med Insights Pediatr. 2015;9:37-47. [PMID: 25788839] doi:10.4137/CMPed.S17841
	Results section: "No patient experienced a serious, severe."	**Cremon C, Guglielmetti S, Castellazzi AM, Pagano I, Bellini M, Cicala M, et al.** Effect of *Lactobacillus paracasei* CNCM I-1572 in patients with irritable bowel syndrome: a pilot, multicenter, randomized, double-blind, placebo-controlled, study. United European Gastroenterol J. 2017:9-10.
Number of unintended AEs per group as well as grade and type	Results section: "Regarding safety, no unexpected adverse events were observed during the course of the study."	**Dilli D, Aydin B, Fettah ND, Özyazici E, Beken S, Zenciroglu A, et al.** The Propre-Save study: effects of probiotics and prebiotics alone or combined on necrotizing enterocolitis in very low birth weight infants. J Pediatr. 2015;166:545-51. [PMID: 25596096] doi:10.1016/j.jpeds.2014.12.004

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Appendix Table 7–Continued

Domain	Example	Reference
Definition of safety population: with denominator used for analysis	Results section: The author report in table the number of patients included in analysis of harm see table 5.	**Boyle RJ, Tang ML, Chiang WC, Chua MC, Ismail I, Nauta A, et al; PATCH study investigators.** Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: a randomized controlled trial. Allergy. 2016;71:701-10. [PMID: 27111273] doi:10.1111/all.12848
Time of AEs	Results section: "Regarding the primary study variable, i.e. safety assessment, in the whole sample, a total of 15 and nine AEs were reported at visits 2 and 3, respectively. At visit 2, nine AEs (14.75% of patients) were reported in the active group and six (10.00%) in the placebo group, without statistically significant differences in AE prevalence between both groups (p=0.1533). At visit 3, the occurrence of AEs decreased, with four events (6.67%) in the active group and five (8.47%) in the placebo group, with statistically significant differences between both groups (p=0.0361)."	**Alexea O, Bacarea V, Piqué N.** The combination of oligo- and polysaccharides and reticulated protein for the control of symptoms in patients with irritable bowel syndrome: results of a randomised, placebo-controlled, double-blind, parallel group, multicentre clinical trial. United European Gastroenterol J. 2016;4:455-65. [PMID: 27403313] doi:10.1177/2050640615615050

AE = adverse event; CRO = clinical research organization; FLS = Fundació per la Lluita contra la Sida; OTC = over-the-counter; SAE = serious AE.