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Perioperative Probiotics or Synbiotics in Adults Undergoing Elective Abdominal Surgery

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Objective: To define the impact of perioperative treatment with probiotics or synbiotics on postoperative outcome in patients undergoing abdominal surgery.

Background: Postoperative surgical infection accounts for a third of all cases of sepsis, and is a leading cause of morbidity and mortality. Probiotics, prebiotics, and synbiotics (preparations that combine probiotics and prebiotics) are nutritional adjuncts that are emerging as novel therapeutic modalities for preventing surgical infections. However, current evidence on their effects is conflicting.

Methods: A comprehensive search of the PubMed, Embase, and WHO Global Index Medicus electronic databases was performed to identify randomized controlled trials evaluating probiotics or synbiotics in adult patients undergoing elective colorectal, upper gastrointestinal, transplant, or hepatopancreaticobiliary surgery. Bibliographies of studies were also searched. The primary outcome measure was incidence of postoperative infectious complications. Secondary outcomes included incidence of noninfectious complications, mortality, length of hospital stay, and any treatment-related adverse events. Quantitative pooling of the data was undertaken using a random effects model.

Results: A total of 34 randomized controlled trials reporting on 2723 participants were included. In the intervention arm, 1354 patients received prebiotic or symbiotic preparations, whereas 1369 patients in the control arm received placebo or standard care. Perioperative administration of either probiotics or synbiotics significantly reduced the risk of infectious complications following abdominal surgery [relative risk (RR) 0.56; 95% confidence interval (CI) 0.46–0.69; $P < 0.00001$, n = 2723, $I^2 = 42\%$]. Synbiotics showed greater effect on postoperative infections compared with probiotics alone (synbiotics RR: 0.46; 95% CI: 0.33–0.66; $P < 0.0001$, n = 1399, $I^2 = 53\%$ probiotics RR: 0.65; 95% CI: 0.53–0.80; $P < 0.0001$, n = 1324, $I^2 = 18\%$). Synbiotics but not probiotics also led to a reduction in total length of stay (synbiotics weighted mean difference: −3.89; 95% CI: −6.60 to −1.18 days; $P = 0.005$, n = 535, $I^2 = 91\%$ probiotics RR: −0.65; 95% CI: −2.03–0.72; $P = 0.35$, n = 294, $I^2 = 65\%$). There were no significant differences in mortality (RR: 0.98; 95% CI: 0.54–1.80; $P = 0.96$, n = 1729, $I^2 = 0\%$) or noninfectious complications between the intervention and control groups. The preparations were well tolerated with no significant adverse events reported.

Conclusions: Probiotics and synbiotics are safe and effective nutritional adjuncts in reducing postoperative infective complications in elective abdominal surgery. The treatment effects are greatest with synbiotics.

Keywords: elective abdominal surgery, meta-analysis, outcomes, probiotics, synbiotics

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Sepsis is a major problem for health care organizations around the world and continues to be a leading cause of morbidity and mortality, especially in postoperative patients.[1,2] The frequency of sepsis is increasing despite advances in antibiotic therapy and the implementation of infection control policies.[2–5] The limitations of infection control strategies, as well as the increasing global concern about antimicrobial resistance, has led to the demand for novel or alternative strategies to reduce the risk of infection in surgical patients.

Probiotics are defined by the World Health Organization[6] as live microorganisms which confer beneficial effects to the host when given in sufficient quantities. They survive transit through the gastrointestinal tract with the majority of their activity being in the colon.[7] Prebiotics are food ingredients, which escape digestion in the upper gastrointestinal tract to stimulate the growth or activity of selective bacterial genera in the colon.[8] When prebiotics and probiotics are combined in a single preparation they are known as synbiotics.[9] These nutritional adjuncts have emerged as potential treatments that could help reduce the incidence of postoperative infection.

Probiotics have been shown to be useful in the treatment of gastrointestinal infections; they are effective along with oral rehydration therapy in treating acute infectious diarrhea in children,[10–13]

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traveller's diarrhea,[14] and antibiotic-associated diarrhea in both children[15–17] and adults.[18–21] Mechanisms of action for probiotics include competitive exclusion of potentially pathogenic bacteria and direct antimicrobial effects.[22] Probiotics alter the pH of intestinal mucosa, produce bacteriocins which inhibit pathogenic epithelial adherence and production of virulence factor, and prevent bacterial translocation via tight junctions.[22,23] Furthermore, probiotic bacteria have also been shown to promote anti-inflammatory cytokine production.[22,24] The proliferation of probiotic bacteria can be enhanced by the co-administration of prebiotics; and certain bacterial genera are stimulated selectively by these compounds which supply nutrients for their growth.[25]

A number of randomized controlled trials (RCTs) have examined the value of prebiotics and probiotics in reducing postoperative complications with mixed results, most likely due to variations in methodological quality and endpoints. Serious adverse effects of probiotics are uncommon in those who are well, but it is theorized that these may occur in patients with impaired immunity. In patients with severe pancreatitis, administration of probiotics was associated with an increased frequency of bowel ischemia.[26,27] This potential for adverse effects of probiotics warrants systematic review before their use in the perioperative setting can be recommended. This systematic review and meta-analysis of RCTs evaluated the effect of perioperative probiotics or synbiotics on postoperative infections in adult patients undergoing elective abdominal surgery.

METHODS

The methodology for this meta-analysis was approved by the Cochrane Collaboration and the protocol was published in the Cochrane Library: *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD009246. DOI: 10.1002/14651858. CD009246. This strategy was amended since publication of the protocol to extend the search dates to 2018.

Search Strategy

RCTs were identified from PubMed (1966–2018), Embase (1980–2018), and World Health Organization (WHO) Global Index Medicus. Search terms were used and connected by Boolean operators AND/OR and included Population: Adults Intervention: Probiotic, Probiotic, Synbiotics, Individual species/preparations. Disease condition: Abdominal Surgery, Operation, Laparotomy, Colorectal resection, Pancreatic Surgery, Infection, Sepsis, Collection, Abscess. References from relevant articles were scanned and primary authors consulted for additional information as necessary. Bibliographies of RCTs, meta-analyses, and systematic reviews were hand-searched for studies that were not captured by the initial search. Unpublished or ongoing studies were identified by checking clinical trials registers. The complete strategy for identifying RCTs is described in the Supplementary Document, http://links.lww.com/SLA/B774.

Inclusion and Exclusion Criteria

Only RCTs evaluating perioperative probiotics or synbiotics in patients aged 18 years and older having elective abdominal surgery (including laparoscopic surgery) were included. Studies which included patients younger than 18 years of age or pregnant women were excluded.

The perioperative administration of probiotics or synbiotics given by any route, duration, combination or preparation was accepted. Control groups were defined as those that did not receive any probiotics or synbiotics and received either placebo or standard care.

Outcome Measures

The primary outcome was incidence of postoperative infectious complications as defined by the trial authors in each of the studies included, with a pre-planned subgroup analysis based on the type of preparations (probiotics and synbiotics). Secondary outcome measures included incidence of non-infectious postoperative complications, primary length of hospital stay (LOS), 30-day mortality, and any other reported adverse events. A further analysis based on the source of funding as reported in the individual studies, was undertaken to assess the role of this on outcome of studies.

Selection of Studies

The studies identified from the electronic searches were evaluated independently by 2 reviewers (A.H.C. and A.A.) using a study eligibility form based on the inclusion criteria. Titles and abstracts were initially screened for relevance. The full texts of potential studies were then retrieved, assessed independently and any discordance adjudicated by a third reviewer (D.N.L.).

Data Extraction and Management

Two reviewers (A.H.C. and .A.A.) extracted data independently from the full text publications of the RCTs that met the inclusion criteria using a standardized data extraction form and data were validated by a third reviewer (D.N.L.).

Data Analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement methodology[28] was adhered to. Studies were appraised critically and the risk of bias of all included studies assessed according to the guidelines of The Cochrane Collaboration.[29] Relative risk (RR) was reported along with 95% confidence intervals (CIs) to estimate treatment effects or discrete numerical variables. Weighted mean difference (WMD) was used for reporting continuous outcomes. Pooled data were analyzed using the random-effects model with the inverse variance or Mantel-Haenszel method as appropriate. As studies may have used different lengths of treatment, studies were subjected to metaregression to determine the most effective duration of treatment. Heterogeneity was quantified using the I^2 statistic, with the values of 25%, 50%, and 75% signifying the limits of low, moderate, and high statistical heterogeneity, respectively.[30] A funnel plot was used to explore publication bias for the studies included. All statistical analyses were performed using RevMan 5.3 software.[31]

RESULTS

The initial literature search identified 196 potential studies for inclusion in this analysis. Following application of exclusion criteria, 34 studies were deemed appropriate for full analysis (Fig. 1).

A large proportion of studies were excluded because they did not fulfill criteria for human RCTs, for example, they were not randomized, were performed as retrospective analyses, or were animal studies. Additional studies were excluded on the basis that they did not use probiotics, prebiotics, or synbiotics or were not undertaken in patients undergoing elective abdominal surgery. Eleven studies were excluded as they did not report infectious complications. An attempt to contact the authors (n = 8) was made for publications that qualified for analysis but did not contain the required information in the manuscript, but the responses were limited.

Studies Included

Of the 34 studies[32–65] included in the final analysis, 16 used probiotics[33,34,37,38,42–48,58,60,62,63,65] as the sole intervention with the remaining 18 studies using synbiotic preparations[32,35,36,39–41,49–57,59,61,64] in comparison with placebos or standard care. All the studies identified were published after the year 2000. In total, 2723 participants were included in this analysis, of whom 1354

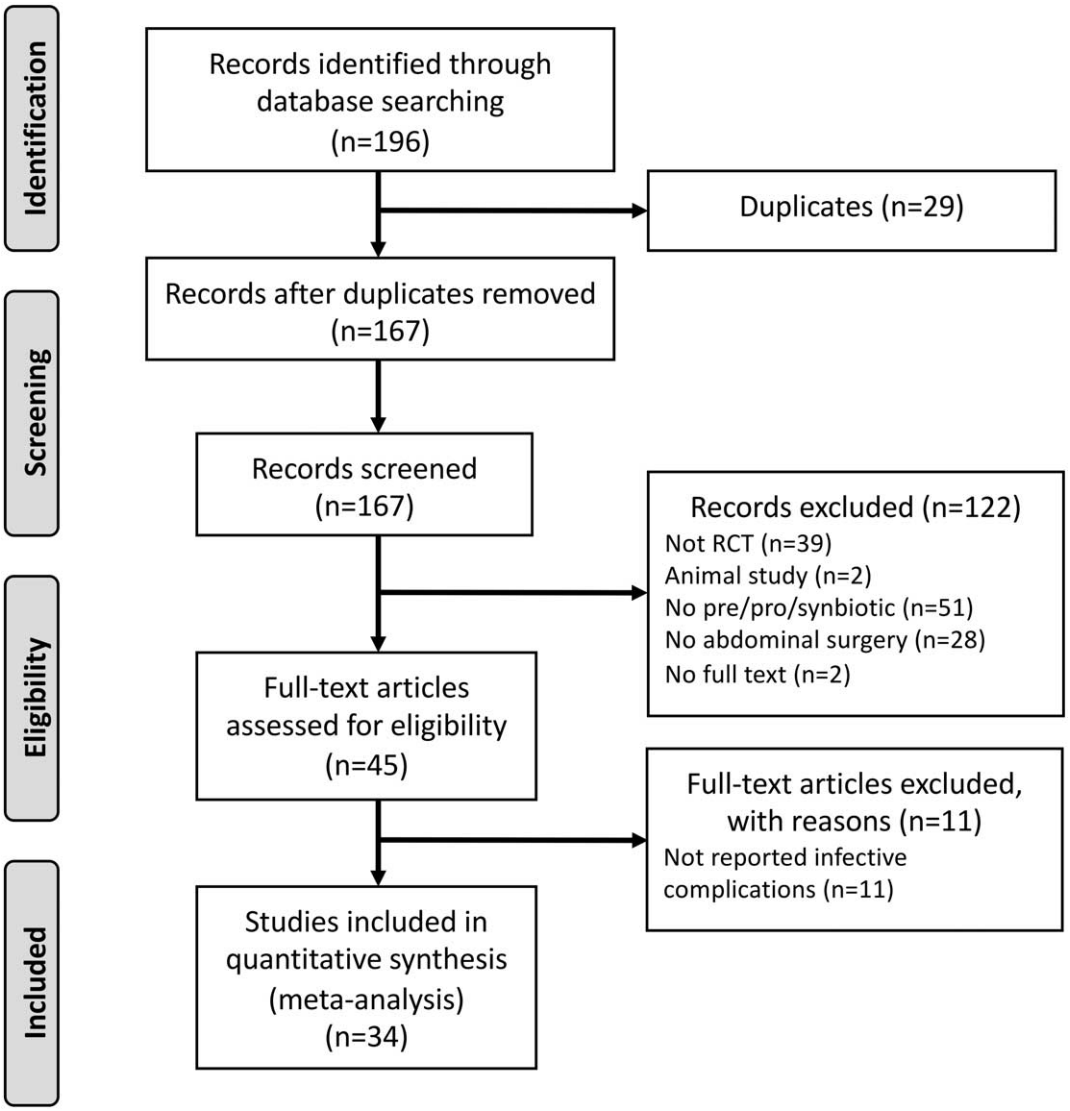


FIGURE 1. PRISMA diagram detailing the study selection and exclusion process.

were randomized to receive either probiotic or synbiotic preparations, whereas 1369 received placebo or standard care.

Participants and Interventions

The mean (standard deviation) age of study participants receiving probiotics or synbiotics was 62.8 (11.4) and 62.4 (10.8) years for those receiving placebo or standard care. A variety of abdominal operations were included: elective colorectal, upper gastrointestinal, transplant, or hepatopancreaticobiliary surgery. Of the studies using probiotics alone, only 3 used a preparation containing a single probiotic species; *Lactobacillus plantarum 299v*[46,47] or *Bifidobacteria*[58] with the remainder using a mixture of probiotics. Similarly, of the studies using synbiotics, only 3 used preparations containing a single probiotic species.[52,54,61] One study compared the use of either synbiotics or prebiotics with heat-deactivated probiotics to standard care.[39] There were insufficient data to include prebiotics alone as a separate subgroup in this meta-analysis. An overview of the studies included[32–65] and their design is summarized in Table 1.

Tolerance and Side Effects of Interventions

There were no serious complications or deaths directly related to the intake of either probiotics or synbiotics. On the whole, intake was well tolerated, and rates of abdominal distension, cramps, and diarrhea were not significantly elevated compared to the placebo or standard care group. Adverse effects are summarized in Table 2.

Postoperative Infectious Complications

Data on postoperative infectious complications were reported in all 34 studies.[32–65] Quantitative pooling of data showed a significant reduction in the incidence of postoperative infectious complications in the intervention group (Fig. 2). The risk of developing a postoperative infectious complication was almost halved (RR 0.56; 95% CI 0.46–0.69; $P < 0.00001$, $I^2 = 42\%$).

In subgroup analysis, there was significant reduction in the incidence of postoperative infectious complications when both intervention types were considered separately. However, the reduction in infectious complications was greater in participants receiving

TABLE 1. Overview of the Studies Included

Study	Type of Surgery	PE (n)	PA (n)	No. Groups	Blinding	Probiotic	Prebiotic	Synbiotic	Placebo or SC	Route	Pre-op DoT	Post-op DoT
Anderson et al, 2004[32]	Elective laparotomy	144	137	2	Yes	–	–	*Lactobacillus acidophilus*, *L bulgaricus*, *Bifidobacterium lactis*, *Streptococcus Thermophilus*, and oligofructose powder	Placebo	Oral or NG/NJ	12	4
Consoli et al, 2016[33]	Colon resection	33	33	2	Not blinded	*Saccharomyces Boulardii*	–	–	SC	Oral	7	0
Diepenhorst et al, 2011[34]	Major pancreatic resection	30	20	3	Not blinded	Ecologic 641	–	–	SC	Oral or NG/NJ	7	7
Eguchi et al, 2011[35]	Liver transplantation	50	50	2	NS	–	–	*B breve*, *Lactobacillus Casei*, and galactooligosaccharides	SC	Oral or NG/NJ	2	14
Flesch et al, 2017[36]	Colorectal cancer	100	91	2	Yes	–	–	*L acidophilus*, *L rhamnosus*, *L paracasei*, *B lactis*, and fructo-oligosaccharides	Placebo	U	5	14
Gianotti et al, 2010[37]	Elective colorectal	49	20	3	Yes	*L johnsonii* and *B longum*	–	–	Placebo	Oral	3	3
Grat et al, 2017[38]	Liver transplantation	55	50	2	Yes	*L lactis*, *L casei*, *L acidophilus*, and *B bifidum*	–	–	Placebo	U	From enrolment	0
Horvat et al, 2010[39]	Elective colorectal	76	40	3	Yes	–	Beta-glucan, inulin, starch, pectin	Mixture of 4 *lactobacilli* and beta-glucan, inulin, starch, pectin	Placebo	Oral	3	0
Kanazawa et al, 2005[40]	Biliary cancer	54	44	2	NS	–	–	*B breve*, *L casei*, and galacto-oligosaccharides (21)	SC (23)	NG	0	14
Komatsu et al, 2016[41]	Laparoscopic colorectal surgery	379	362	2	Not blinded	–	–	*L casei* strain Shirita, *B breve* strain Yakult and galacto-oligosaccharides	SC	Oral	7–11	2–7
Kotzampassi et al, 2015[42]	Colorectal cancer	164	164	2	Yes	*L acidophilus*, *L plantarum*, *B lactis*, and *S boulardii*	–	–	Placebo	Oral	0	14
Liu et al, 2011[44]	Elective colorectal	120	100	2	Yes	*L plantarum*, *L acidophilus*, and *B longum*	–	–	Placebo	Oral or NG/NJ	6	10
Liu et al, 2013[45]	Colorectal cancer	161	150	2	Yes	*L plantarum*, *L acidophilus-1*, and *B longum-88*	–	–	Placebo	Oral	6	10
Liu et al, 2015[43]	Colorectal liver metastases surgery	150	134	2	Yes	*L plantarum*, *L acidophilus-11*, and *B longum-88*	–	–	Placebo	Oral	6	10
Mangell et al, 2012[46]	Elective colorectal	72	64	2	Yes	*L plantarum 299v*	–	–	Placebo	Oral or NG/NJ	8	5
McNaught et al, 2002[47]	Major abdominal surgery	129	129	2	Not blinded	*L plantarum 299v*	–	–	SC	Oral or NG/NJ	9	5
Nomura et al, 2007[48]	Major pancreatic resection	70	64	2	NS	*Enterococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus*	–	–	SC	U	3–15	POD2 till discharge
Okazaki et al, 2013[49]	Upper GI and hepatobiliary pancreatic cancers	53	48	2	Not blinded	–	–	*L casei strain Shirota*, *B breve strain Yakult*, and galacto-oligosaccharides	SC	Oral, NG	7	10
Polakowski et al, 2019[50]	Colorectal cancer	77	73	2	Yes	–	–	*L acidophilus*, *L rhamnosus*, *L casei*, *B lactis*, and fructo-oligosaccharide.	Placebo	Oral	7	0
Rammohan et al, 2015[51]	Frey procedure	79	75	2	Yes	–	–	*S faecalis*, *C butyricum*, *B mesentericus*, *L sporogenes*, and fructo-oligosaccharides	Placebo	Oral	5	10
Rayes et al 2002[52]	Major abdominal surgery	90	60	3	NS	–	–	*L plantarum 299v* and oat fiber	Placebo	NJ	0	5

TABLE 1. (*Continued*)

Study	Type of Surgery	PE (n)	PA (n)	No. Groups	Blinding	Probiotic	Prebiotic	Synbiotic	Placebo or SC	Route	Pre-op DoT	Post-op DoT
Rayes et al, 2002[54]	Liver transplant	105	63	3	NS	–	–	*L plantarum 299v* and oat fiber	Placebo	NJ	0	12
Rayes et al, 2005[56]	Liver transplantation	66	66	2	Yes	–	Beta-glucan, inulin, pectin, and resistant starch	*Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *L paracasei*, *L plantarum*, beta-glucan, inulin, pectin, and resistant starch	–	Oral and NJ	0	14
Rayes et al, 2007[55]	Major pancreatic resection	89	80	2	Yes		Beta-glucan, inulin, pectin, and resistant starch	*P pentosaceus*, *L mesenteroides*, *L plantarum*, *L paracasei*, and beta-glucan, inulin, pectin, resistant starch	–	Oral or NG/ NJ	1	8
Rayes et al, 2012[53]	Liver resection	33	19	2	Yes	–	Beta-glucan, inulin, pectin, and resistant starch	*P pentosaceus*, *L mesenteroides*, *L plantarum*, *L paracasei*, and beta-glucan, inulin, pectin, and resistant starch	–	Oral or NG/ NJ	1	10
Russolillo et al, 2014[57]	Elective extrahepatic bile duct resection	61	40	2	Yes	–	–	*B bifidum*, *S thermophilus*, *S salivarius*, *L acidophilus*, *L casei*, *L bulgaricus*, and galacto-oligosaccharides	SC	U	7	Until discharge
Sadahiro et al, 2014[58]	Colorectal cancer	310	195	3	NS	*Bifidobacteria*	–	–	Placebo	Oral	2–8	5–15
Sommacal et al 2015[59]	Periampullary neoplasm surgery	54	46	2	Yes	–	–	*L acidophilus*, *L rhamnosus*, *L casei*, *B bifidum* and fructo-oligosaccharides	Placebo	U	4	10
Tan et al, 2016[60]	Colorectal cancer	40	40	2	Yes	*L acidophilus*, *L casei*, *L lactis*, *B bifidum*, *B longum*, and *B infantis*	–	–	Placebo	Oral	7	0
Usami et al, 2011[61]	Liver resection	67	61	2	Not blinded	–	–	Yakult B *L. Seichoyaku* and galacto-oligosaccharides	SC	Oral or NG/ NJ	14	12
Woodard et al, 2009[62]	Gastric bypass	44	41	2	Yes	Puritan's Pride *Lactobacillus* species	–	–	SC	Oral	0	186
Yang et al, 2016[63]	Colorectal cancer	92	60	2	Yes	*B longum*, *L acidophilus*, and *E faecalis*	–	–	Placebo	Oral, NG	5	7
Yokoyama et al, 2016[64]	Pancreaticoduodenectomy	50	44	2	Not blinded	–	–	*L casei* strain Shirota, *B breve* strain Yakult, and galacto-oligosaccharides	SC	NJ	7	14
Zhang et al[65]	Colorectal cancer	60	60	2	Yes	*B longum*, *L acidophilus*, and *E faecalis*	–	–	Placebo	Oral	3	0

DoT indicates duration of treatment; GI, gastrointestinal; NG, nasogastric; NJ, nasojejunal; NS, not stated; PA, participants analyzed (groups not relevant to this meta-analysis were excluded); PE, participants enrolled; SC, standard care.

TABLE 2. Summary of Gastrointestinal Adverse Effects Associated With Probiotic and Synbiotic Ingestion in the Randomized Controlled Trials Included

Study	Probiotic	Synbiotic	Placebo or Standard Care	*P*
Anderson et al, 2004[32]	–	Diarrhea: 4/72 Unpalatable: 1/72	Not stated	–
Consoli et al, 2016[33]	Not stated	–	NS	
Diepenhorst et al, 2011[34]	Ileus: 1	–	Ileus: 1	–
Eguchi et al, 2011[35]	–	Poor tolerance: 0/25	Poor tolerance: 0/25	–
Flesch et al, 2017[36]	–	Not stated	Not stated	–
Gianotti et al, 2010[37]	Not stated	–	Not stated	–
Grat et al, 2017[38]	Diarrhea: 4/24 Nausea: 1/24 Constipation: 1/24	–	Diarrhea: 3/26 Nausea: 2/26 Constipation: 1/26	0.99
Horvat et al, 2010[39]	–	Not stated	Not stated	–
Kanazawa et al, 2005[40]	–	Not stated	Not stated	–
Komatsu et al, 2016[41]	–	Not stated	Not stated	–
Kotzampassi et al, 2015[42]	Not stated	–	Not stated	–
Liu et al, 2011[44]	Diarrhea: 11/50 Cramps: 9/50 Distension: 13/50	–	Diarrhea: 11/50 Cramps: 9/50 Distension: 13/50	<0.05
Liu et al, 2013[45]	Diarrhea: 11/75	–	Diarrhea: 22/75	0.03
Liu et al, 2015[43]	Diarrhea: 16/66 Cramps: 15/66 Distension: 22/66	–	Diarrhea: 31/68 Cramps: 33/68 Distension: 35/68	0.012 0.017 0.038
Mangell et al, 2012[46]	Not stated	–	Not stated	–
McNaught et al, 2002[47]	Unpalatable: 9/69 Nausea: 9/69 Ileus: 12/69	–	Not stated	–
Nomura et al, 2007[48]	Delayed gastric emptying: 3/30		Delayed gastric emptying: 7/34	0.1
Okazaki et al, 2013[49]	–	Not stated	Not stated	–
Polakowski et al, 2019[50]	–	Flatulence: 4/36	Flatulence: 3/37	0.34
Rammohan et al, 2015[51]	–	Not stated	Not stated	–
Rayes et al, 2002[52]	Distension, cramps or diarrhea: 6/31	–	Distension, cramps or diarrhea: 11/32	–
Rayes et al, 2002[54]	Distension: 3/30 Cramps: 4/30	–	Distension: 6/30 Cramps: 5/30	–
Rayes et al, 2005[56]	–	Diarrhea: 2/33 Cramps: 5/33	Diarrhea: 3/33 Cramps: 6/33	–
Rayes et al, 2007[55]	–	Diarrhea: 2/40 Cramps: 3/40	Diarrhea: 2/40 Cramps: 6/40	–
Rayes et al, 2012[53]	–	Diarrhea: 3/9 Cramps: 3/9	Diarrhea: 3/10 Cramps: 3/10	–
Russolillo et al, 2014[57]	–	Diarrhea: 3/20 Nausea: 4/20	Not stated	–
Sadahiro et al, 2014[58]	Not stated	–	Not stated	–
Sommacal et al, 2015[59]	–	Not stated	Not stated	–
Tan et al, 2016[60]	Not stated	–	Not stated	
Usami et al, 2011[61]	–	Not stated	Not stated	–
Woodard et al, 2009[62]	Not stated	–	Not stated	–
Yang et al, 2016[63]	Diarrhea: 8/30 Distension: 9/30	–	Diarrhea: 16/30 Distension: 13/30	0.035 0.284
Yokoyama et al, 2016[64]	–	Not stated	Not stated	–
Zhang et al[65]	Not stated	Not stated	Not stated	–

synbiotics (RR: 0.46; 95% CI: 0.33–0.66; $P < 0.0001$, $I^2 = 53\%$) than in those receiving probiotics alone (RR: 0.65; 95% CI: 0.53–0.80; $P < 0.0001$, $I^2 = 18\%$).

Duration of Treatment

Studies were subjected to a weighted linear multiple regression to determine the influence of treatment duration on incidence of postoperative infectious complications. The results of this weighted analysis demonstrated that although there was a trend for a reduction in postoperative infectious complications with increasing treatment duration, this relationship, was not statistically significant ($r^2 = 0.0047$, $P = 0.4554$).

Length of Hospital Stay

A total of 12 studies[40,43,44,51,52,54–57,59,61,63] reported on the outcome of length of primary hospital stay. Analysis of pooled data revealed a statistically significant difference between treatment groups (WMD: −2.59; 95% CI: −4.31 to −0.87, $P = 0.003$, $I^2 = 88\%$) (Fig. 3A). However, in subgroup analysis, the decrease in length of stay was only significant in the synbiotics group (WMD:

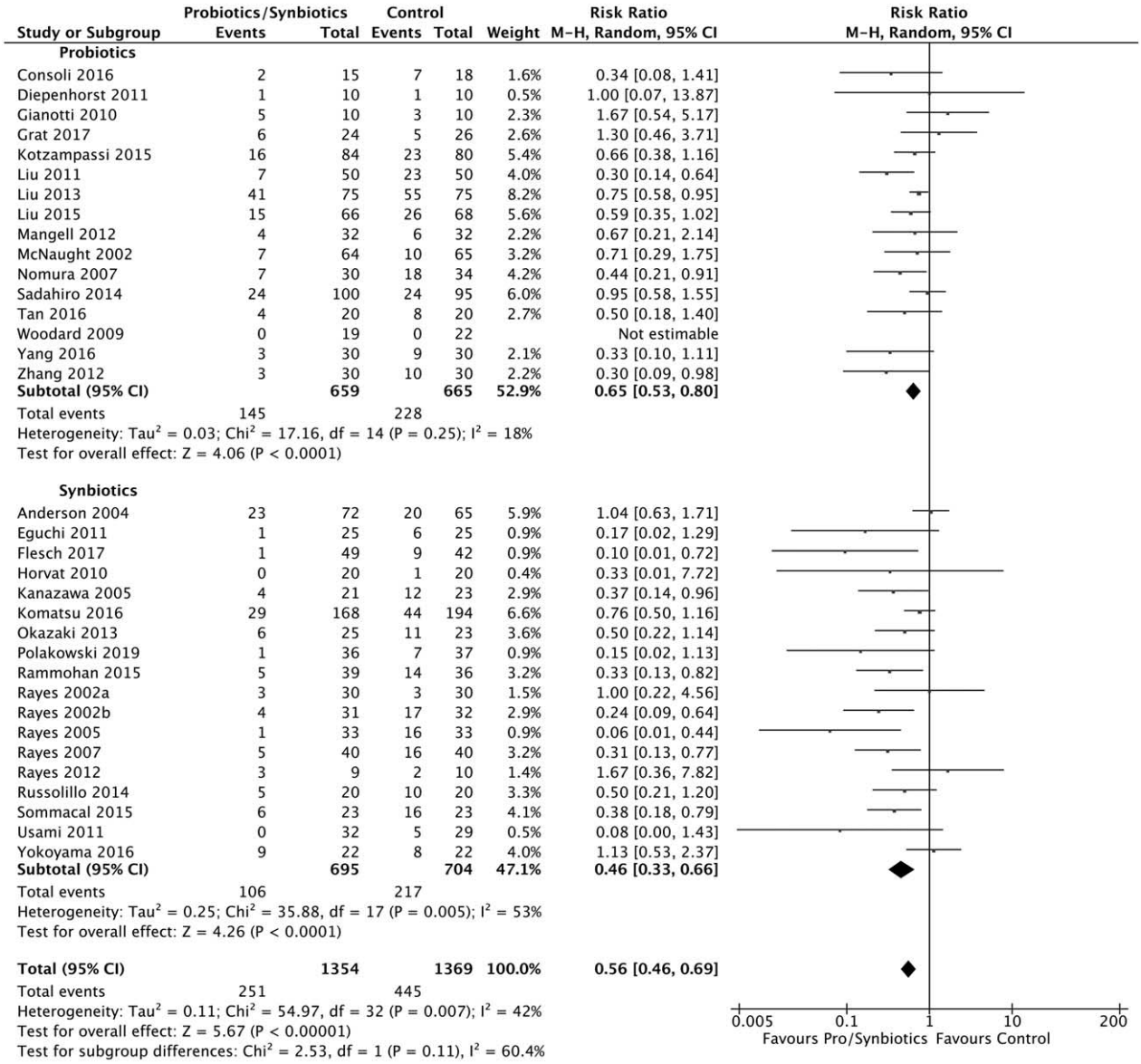


FIGURE 2. Forest plot of pooled data from randomized controlled trials demonstrating the reduction in risk of infectious complications.

−3.89; 95% CI: −6.60 to −1.18; $P = 0.005$, $I^2 = 91\%$) and not significant in the small probiotics only group (WMD: −0.65, CI: −2.03–0.72, $P = 0.35$, $I^2 = 65\%$).

Mortality

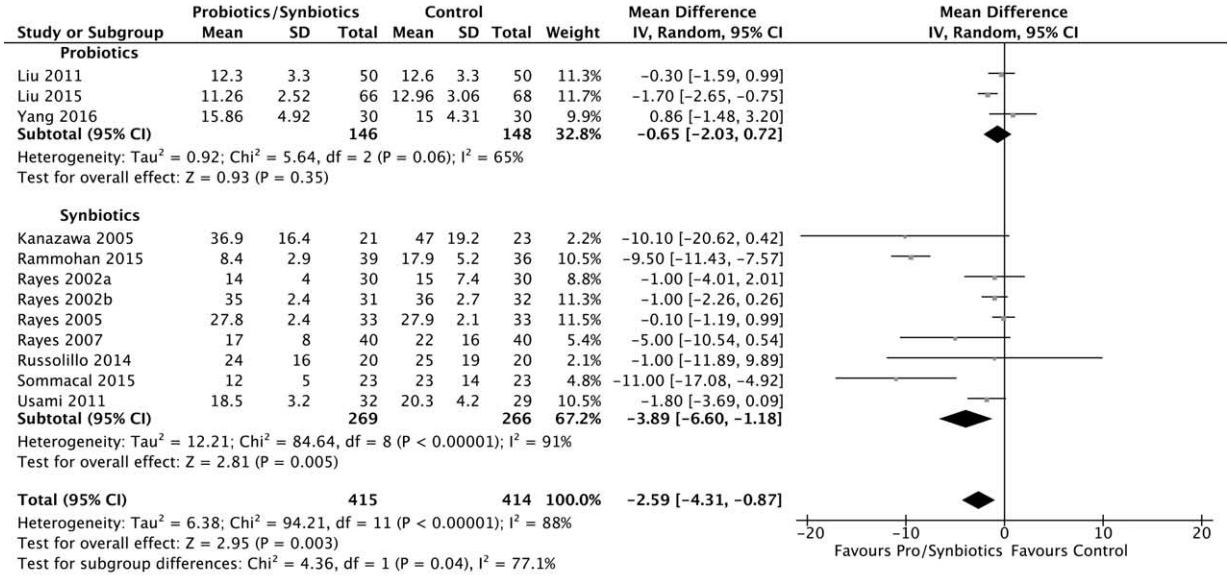
A total of 23 studies[32,33,35,37,39–41,43,44,46–50,53,55–57,59–62,64] reported data on mortality. Twelve studies[33,37,39–41,43,44,49,53,56,61,62] recorded no deaths in either treatment arm. There was no significant difference in mortality between patients receiving probiotics or synbiotics compared with those who received placebo or standard care (RR: 0.98; 95% CI: 0.54–1.80; $P = 0.96$, $I^2 = 0\%$) (Fig. 3B) this was also confirmed on subgroups analysis.

Noninfectious Complications

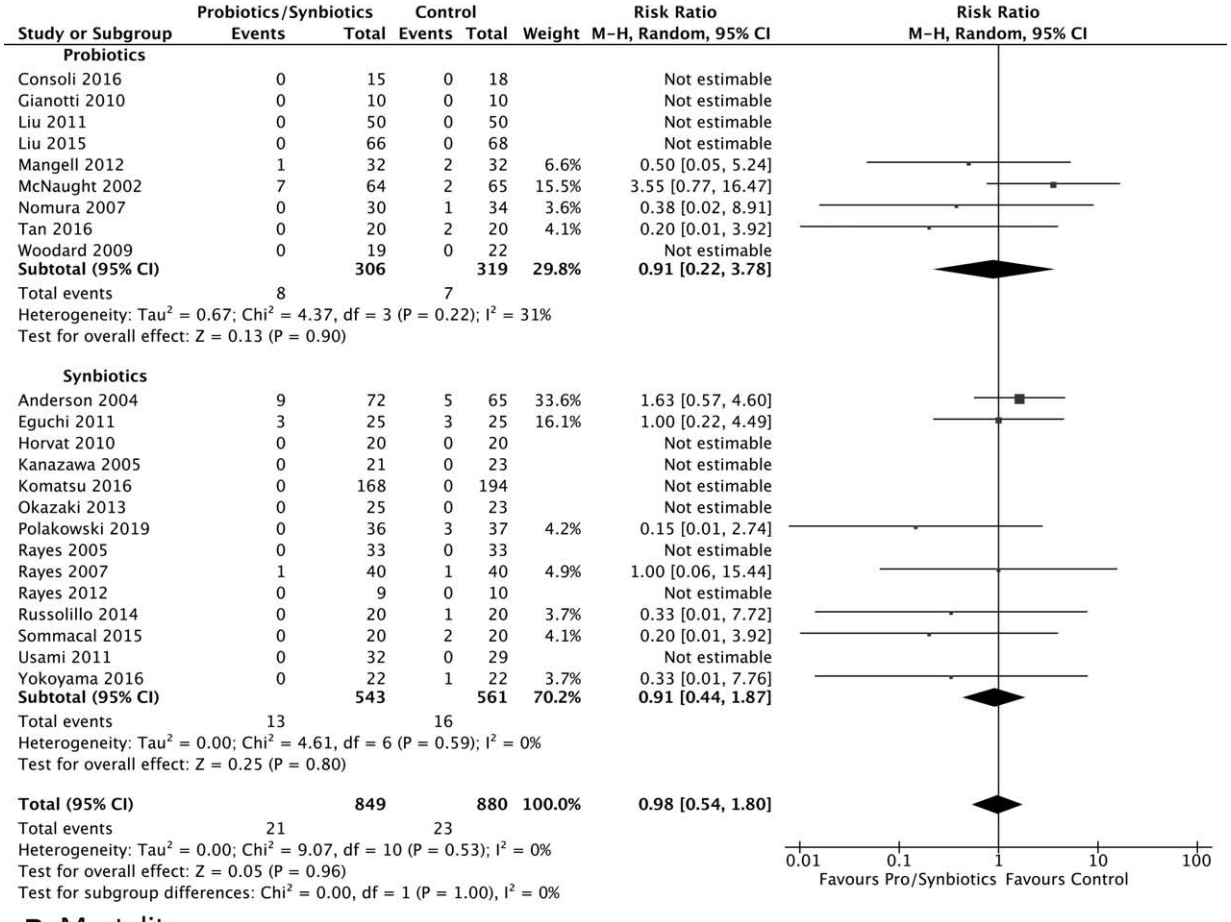
Some studies provided a count of the number of participants with noninfectious complications; others reported the different types of complications but not the number of patients with these complications. In addition, what counted as noninfectious complications differed between individual studies, as such formal pooling of this outcome could not be undertaken. However, where number of patients with noninfectious complications were reported there was no significant difference between the treated and control arms in the individual studies.[34,35,38,39,41,42,46,48–50,52,53,55–57,59–61,63–65]

Impact of Source of Funding

We undertook a separate analysis to assess the impact corporate funding had on the primary outcome. Studies were stratified into "industry sponsored," "undeclared," and "not industry sponsored"—the RR favored probiotics/synbiotics in all cases ["industry sponsored" RR 0.65 (95% CI 0.53–0.81, $P < 0.0001$, $I^2 = 49\%$); "undeclared" RR 0.47 (95% CI 0.31–0.72, $P = 0.0006$, $I^2 = 52\%$) and "not industry sponsored" RR 0.25 (95% CI 0.09–0.69, $P = 0.007$, $I^2 = 17\%$).



A Length of stay



B Mortality

FIGURE 3. Forest plot of (A) pooled weighted mean difference from randomized controlled trials demonstrating the effect on risk ratio for length of hospital stay and (B) mortality with probiotic and synbiotic perioperative treatment.

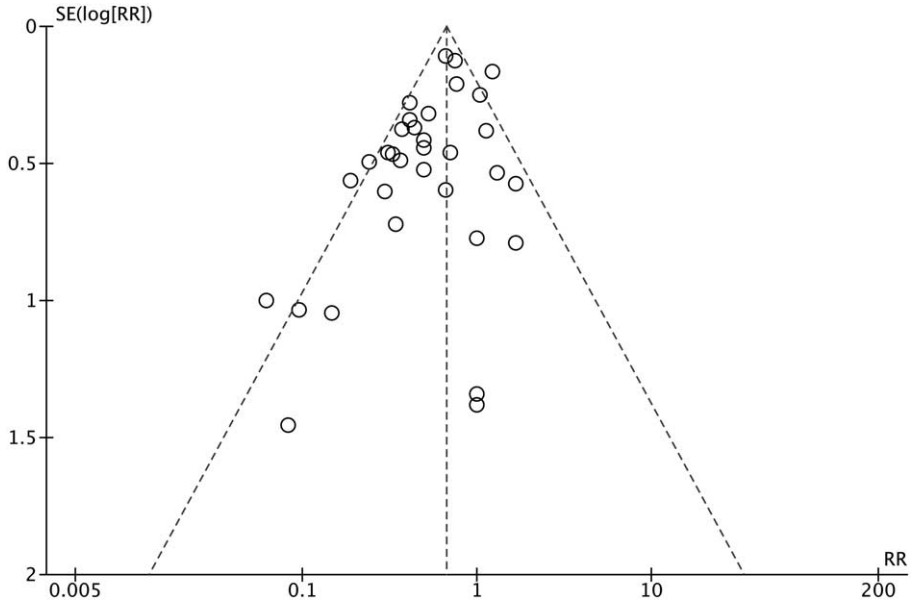


FIGURE 4. Funnel plot of included randomized controlled trials demonstrating the treatment effect relative to study size. SE indicates standard error.

Publication Bias

It is recognized that studies are more likely to be published if positive outcomes are demonstrated. Consequently, published studies may not be truly representative of all valid studies undertaken. The assessment of publication bias based on the primary outcome of infectious complications showed minor asymmetry in favor of positive studies with fewer studies which cross the margin of no effect (Fig. 4).

Risk of Bias Analysis

The risk of bias of the studies included is summarized in Figure 5.

DISCUSSION

What This Study Found

The analysis of pooled data from RCTs demonstrates that the perioperative administration of probiotics and synbiotics significantly reduces the risk of infectious complications following abdominal surgery, with the magnitude of this risk reduction approaching 50%. The reduction in risk of infections was greater with synbiotic preparations than with probiotics alone, confirming that the beneficial effects of probiotics can be enhanced by the addition of prebiotic substrates. In addition, there was a reduction in LOS in the synbiotic group but not the probiotics group. There was no impact on noninfectious complications or mortality.

The studies included in this meta-analysis employed different treatment durations; the majority of the larger studies which provided most of weighting had treatment durations lasting more than 10 days. The reduction in infection risk remained whether treatment was given for less than 10 days or for 10 days or more. Separate weigthed metaregression of treatment duration against RR of infection did not reveal a significant relationship. This might be accounted for by 2 possible explanations, possibly that a minimum treatment duration is sufficient to observe an effect above which no additional effect is seen, or that the analysis lacks studies with a sufficient range of treatment durations thereby diminishing power. It is, therefore, difficult to infer either minimum or optimum duration of treatment from this analysis.

What is Available in the Literature

The reduction in infectious complications demonstrated in this meta-analysis are consistent with the results of other systematic reviews.[66–69] In addition, Kinross et al[67] also found a similarly pronounced benefit of synbiotics over probiotics. A reduction in postoperative infectious complications was also found in studies carried out in patients undergoing nonabdominal surgery.[70]

Importantly, both probiotics and synbiotics were tolerated well and were associated with few gastrointestinal adverse effects, even in participants who had undergone major gastrointestinal reconstructions or liver transplantation, where a significant degree of immunosuppression can occur. The serious complications of probiotic usage observed in nonsurgical patients such as bowel ischemia[26] and *Lactobacillus*-related sepsis[71] were not evident in the setting of elective abdominal surgery. It is noteworthy that the increased risk of bowel ischemia as detected in the PROPATRIA study[26] has not been validated by a second study, thereby making the true clinical relevance of this association uncertain. Furthermore, a meta-analysis of 2972 critically ill patients admitted to the intensive care unit found no differences in rates of mortality between those who received probiotics and those who did not.[72] Hence, the potential detrimental impact of probiotics in the acutely unwell patient has not been substantiated by this meta-analysis.[72] The present meta-analysis also did not demonstrate any significant side effects of probiotics in the setting of elective abdominal surgery.

The studies varied in the types of patients and complexity of surgery carried out, ranging from elective colorectal resections for benign disease to complex hepatopancreaticobiliary resections and reconstructions for malignant disease. It would be expected that patients undergoing more complex surgery would be subject to a greater risk of complications and mortality and longer hospital stay. This was borne out in the data which showed that mortality was generally low in studies on colorectal surgery compared with hepatopancreaticobiliary surgery. On the whole, mortality rates were low, with the highest recorded for the study by Anderson et al[32] with an overall mortality rate of 10.2%. This might be considered slightly high in the setting of elective abdominal surgery. Overall, there were, however, no significant differences in mortality demonstrated between patients who received probiotics or synbiotics (21 of 849

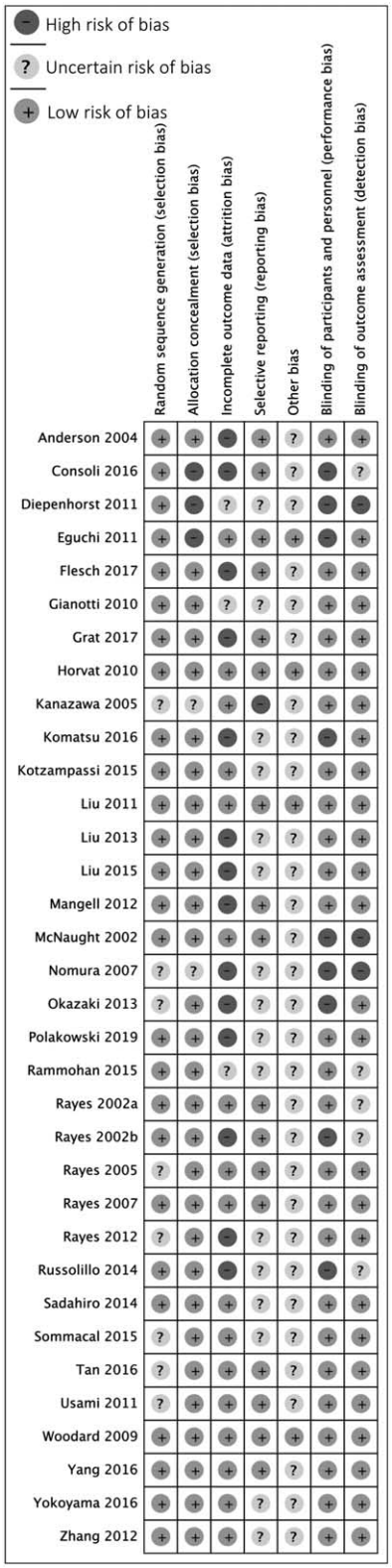


FIGURE 5. Risk of bias analysis for the studies included.

patients, 2.5%) compared with those receiving placebo or standard care (23 of 880 patients, 2.6%). The prior reviews also identified no differences in noninfectious complications or mortality.[66–69]

Perioperative administration of probiotics and synbiotics was seen to decrease length of stay significantly by 2 days in 12 studies that reported length of stay. There was, however, a high degree of statistical heterogeneity in the pooled synthesis. Length of stay is influenced by many confounding factors and not necessarily directly related to the incidence of infection. Length of stay data are also subject to bias if blinding of patients, healthcare staff, and study data analysts to treatment groups is not effective.

Although this meta-analysis does not provide any evidence for mechanism of action, it does indicate a role for the addition of prebiotic compounds to enhance the action of probiotics. Patients undergoing major abdominal surgery would be expected to experience a period of postoperative gut dysfunction which may have several important implications when administering probiotic or synbiotic preparations. For instance, delivery of probiotic bacteria to their proposed site of action may be impaired in the presence of vomiting or paralytic ileus. Any delay in the return to normal gut function may also disrupt local bacterial ecology and prevent the establishment of probiotic niches due to the impaired delivery of probiotic substrates during periods of inadequate enteral nutrition.

Although this meta-analysis has shown a clear reduction in the risk of infectious complications with probiotics and synbiotics, there was no significant effect on noninfectious complications, consistent with the proposed theory of the gut as an origin of sepsis and in agreement with the earlier reviews.[66,67] Noninfectious complications are also likely to be influenced by confounding factors such as patient cohort, complexity of surgery, and access to critical care facilities. The analysis based on the source of funding demonstrated that the impact of probiotics and synbiotics on the primary outcome was preserved regardless of whether the studies were industry funded, undeclared, or unfunded.

It is difficult, from this analysis, to determine which probiotic or synbiotic strains were most effective in reducing infectious complications as the variability in species and genera used in the studies was wide. The majority of the studies used *Lactobacilli* either alone or in combinations with prebiotics. Twenty-one studies[32,35,37,38,40–44,48–51,57–60,63–65] used *Bifidobacteria* species, whereas galacto-oligosaccharides, known to selectively enhance the growth of *Bifidobacteria*,[73,74] were used in 6 of the studies.[35,40,49,57,61,64] At present it is not certain whether some strains of probiotic bacteria are more effective at reducing infection risk than others. This, however, clearly remains an area for further study. In addition, 2 recent studies have suggested that the same probiotic supplement may behave differently in different individuals.[75,76] Probiotics may not colonize the gut of all patients, suggesting that the bacteria may pass through the gastrointestinal tract of some people with no effect.[76] The same group of investigators also showed that compared with spontaneous postantibiotic recovery, probiotics induced a delayed and incomplete return of the native microbiota and that potential postantibiotic benefits of probiotics may be offset by a compromised gut mucosal recovery.[75] It has been proposed that in the not too distant future machine learning algorithms could be used to predict which particular strains of probiotics would be most beneficial on an individual patient basis.[75–77] Although this is promising, it remains only a hypothesis at present.

Strengths and Limitations

This systematic review and meta-analysis comprehensively assessed clinically relevant outcomes in patients undergoing elective gastrointestinal surgery. It included searches of the major online databases as well as the WHO Global Index Medicus, allowing studies

from low- and middle-income countries countries to also be identified. The focus on elective gastrointestinal surgery, helped reduce the within study and between study variability and heterogeneity.

There are however, a number of limitations to this analysis which warrant discussion. Firstly, there has been no standardization of preparation of probiotic, duration of treatment, or route of administration making comparison of the trials challenging. In addition, some studies have used synbiotics or multispecies preparations. Furthermore, control groups in some studies comprised only standard care, whereas other studies employed a placebo. This lack of consistency is likely to introduce significant heterogeneity and whilst we attempted to account for this by employing a random effects meta-analysis, this must be borne in mind when drawing any conclusions. Other sources of heterogeneity include the use of preoperative bowel preparation, pre- and postoperative antibiotic usage, and surgical technique, which were all, in general, reported poorly in all the studies. Large high-quality multicenter studies would be needed to reduce the influence of these factors.

Different probiotics and synbiotic preparations were used in the RCTs included, with some employing a singular strain and others a cocktail or combinations of strains (Table 1). As such subgroup analysis based on strain of probiotics used could not be achieved in any clinically meaningfully way due to the wide spread of strains used in the individual studies. More work is required in exact strain identification and characterization of strain-specific clinical effects. Although perioperative administration of probiotics and synbiotics used in the studies included in this meta-analysis demonstrated a reduction in infectious complications, all probiotic bacterial strains cannot be interpreted as equivalent. As such the clinically beneficial effects of a select number of bacterial strains cannot be simply extrapolated to other strain(s) of probiotics not yet subjected to a rigorous RCT. It must, therefore, be stressed that the findings of this meta-analysis are only applicable to the strains studied in the individual RCTs.

This would ensure future reviews could pursue analysis of benefit based on different probiotic strain preparations to potential identify which species of probiotics or synbiotics harbor the most clinical benefit.

CONCLUSIONS

Probiotics and synbiotics are safe in the setting of elective abdominal surgery and associated with few adverse effects. Both probiotics and synbiotics reduce the risk of postoperative infection but the effect is greater for synbiotics than for probiotics. Further large multicenter studies with standardization of probiotic and synbiotic preparations, participants, type of surgery, and postoperative care are required before the effectiveness of particular preparations and optimum duration of treatment can be established.

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