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REVIEW ARTICLE

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Comparative effectiveness of oral antibiotics, probiotics, prebiotics, and synbiotics in the prevention of postoperative infections in patients undergoing colorectal surgery: A network meta-analysis

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Abstract

Oral antibiotics (OAB), probiotics, prebiotics, and synbiotics are reported to be effective for preventing postoperative infection following colorectal surgery, but the comparative effectiveness between them has not been studied. To compare these interventions through a network meta-analysis. Ovid Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) were searched from inception to January 1, 2022 without any language restriction. Two reviewers independently screened the retrieved articles, assessed risk of bias, and extracted information from the included randomised controlled trials (RCTs). The primary outcome was infection rate, and the secondary outcome was anastomotic leakage rate. 4322 records were retrieved after literature search, and 20 RCTs recruiting 3726 participants were finally included. The analysis showed that usual care (UC) + Synbiotics ranked the most effective treatment (SUCRA = 0.968), UC + OAB ranked the second (SUCRA = 0.797), and UC + IAB ranked the third (SUCRA = 0.678) for preventing postoperative infection rate, but only UC + OAB achieved statistical significance. UC + OAB was the most effective treatment (SUCRA = 0.927) for preventing anastomotic leakage rate. Our study confirmed that preoperative administration of OAB was associated with lower infection rate and anastomotic leakage rate than placebo and UC alone. However, the beneficial effect of probiotics and synbiotics should still be investigated by large-scale randomised controlled trials.

KEYWORDS

oral antibiotics, prebiotics, postoperative infections, colorectal surgery, network meta-analysis

Key Messages

- a network meta-analysis comparing prebiotics, probiotics, synbiotics, and OAB with usual care for reducing SSI rate for colorectal surgery was conducted.

- preoperative administration of OAB was associated with lower infection rate and anastomotic leakage rate than placebo and UC alone.
- the beneficial effect of probiotics and synbiotics should still be investigated by large-scale randomised controlled trials.

1 | INTRODUCTION

Sepsis is still a lethal complication after abdominal surgery, although surgical techniques, and perioperative management have been prominently improved. Surgical site infection (SSI) is the most essential factor leading to sepsis, and SSI is prevalent in elective colorectal surgery, which occurs in 20% of the patients receiving colorectal surgery.[1] Prevention of SSI is therefore a job of the first order in postoperative management.

The use of intravenous antibiotics (IAB) after surgery is proposed for preventing SSI, but it raises concerns about antimicrobial resistance. Consequently, the use of mechanical bowel preparation (MBP) and oral antibiotics (OAB) are recommended before surgery by the American Society for Enhanced Recovery and the Perioperative Quality Initiative to decrease SSI rate. Recent meta-analyses confirm the effectiveness of MBP plus OAB in preventing SSI after surgery.[2-6] Among them, a network meta-analysis comparing MBP plus OAB, OAB alone, MBP alone with no preparation found that MBP plus OAB was the most effective treatment and OAB alone ranked the second.[6] Although the evidence seems solid for using OAB before surgery to prevent SSI, it will undoubtedly increase the chance of antimicrobial resistance.

Prebiotics, probiotics, and synbiotics are reported to be beneficial in the preventive treatment of SSI, which are normally given before surgery. Prebiotics are food ingredients that escape digestion in the upper gastrointestinal tract to stimulate the growth of probiotic bacteria. When prebiotics and probiotics are combined in one preparation, they are known as synbiotics. Recent meta-analyses showed that prebiotics, probiotics, and synbiotics were effective for the prevention of SSI in abdominal surgeries.[7-9]

Based on the above facts, prebiotics, probiotics, synbiotics, and OAB are treatments aiming to suppress harmful bacterial taxa such as *Enterococcus faecalis* and increase beneficial bacterial taxa such as *Lactobacillus*. These treatments might reverse microbiota dysbiosis to prevent SSI. Although they are all effective and promising for preventing SSI, the comparative effectiveness between them has not been studied.

We performed a systematic review and network meta-analysis, aiming to conduct pairwise comparisons between prebiotics, probiotics, synbiotics, and OAB in adjunctive to usual care for reducing SSI rate in patients receiving elective colorectal surgery.

2 | METHODS

We conducted the systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for network meta-analysis. The systematic review and meta-analysis did not include participant-level data, so ethical approval for the study was not required.

2.1 | Study source

Ovid Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) were searched from inception to January 1, 2022 without any language restriction. We searched the databases using comprehensive search strategies and provided the strategies in the supplementary files. Previously published systematic reviews and meta-analyses were also searched in Medline and acquired in full-text copies to examine whether there were missing studies.

2.2 | Selection criteria

The inclusion criteria included: (1) study design of randomised controlled trial (RCT); (2) adult participants who received elective colorectal surgery; (3) participants who received any of the interventions—antibiotics, probiotics, prebiotics, synbiotics, usual care (UC), or placebo; (4) RCTs that assessed any of the outcomes—postoperative infection, or anastomotic leakage. The exclusion criteria included: (1) RCTs with the lack of data for analysis; (2) RCTs that were reported in the form of research letters; (3) RCTs that recruiting participants who were not receiving secondary colorectal surgery (eg, the colorectal surgery was performed because of liver metastasis to the colon).

Two reviewers independently screened the retrieved articles. They first read the title and abstracts of the articles and made the first decision, and they obtained the full-text copies for further evaluation when decisions could not made upon titles and abstracts. Discrepancies between the two reviewers were solved by group discussion and arbitrated by a third reviewer.

2.3 | Data extraction

Pilot standardised forms were developed to extract information from articles. Final forms were assigned to two independent reviewers, who extracted the study data independently. The reviewers extracted trial characteristics, participant characteristics, information of the interventions and controls, and outcome parameters. The trial characteristics included the name of the first author, year of publication, total sample size, and follow-ups. The participants characteristics included mean age, sex, and type of surgery. The types of interventions and controls were described in detail, and the outcome parameters and statistics were summarised for data analysis.

2.4 | Risk of bias assessment

We assessed the risk of bias (RoB) using the second version of the Cochrane risk of bias (RoB 2.0). In RoB 2.0, the RoB assessment had five domains. Each domain requires answers to one or more questions, which leads to judgements of the RoB for a specific study—low, some concerns, or high RoB.[10]

2.5 | Data synthesis

We summarised and described the study data across the included studies, and then we performed a network meta-analysis comparing different interventions in the prevention of infection rate after colorectal surgery. We first calculated the effect size of each intervention in contrast to UC and estimated the standard errors of the effect size, and then we performed pairwise comparisons among different interventions. We secondarily computed the probability of each intervention to be the best treatment by using the Surface Under the Cumulative Ranking (SUCRA) method. The netgraphs and forest plots were presented for each outcome with the effect sizes measured as relative ratios (RRs).

The consistency of this study was examined through a comparison among direct, indirect, and network estimates. We checked the significance of inconsistency by z test. The global heterogeneity of the network meta-analysis was calculated by global I2 statistics and tau-squared value. I2 > 50% or a tau-squared value >0.36 was considered as a sign of large heterogeneity. When a network meta-analysis has large heterogeneity, we further performed design-by-treatment analysis to detect the source of heterogeneity.

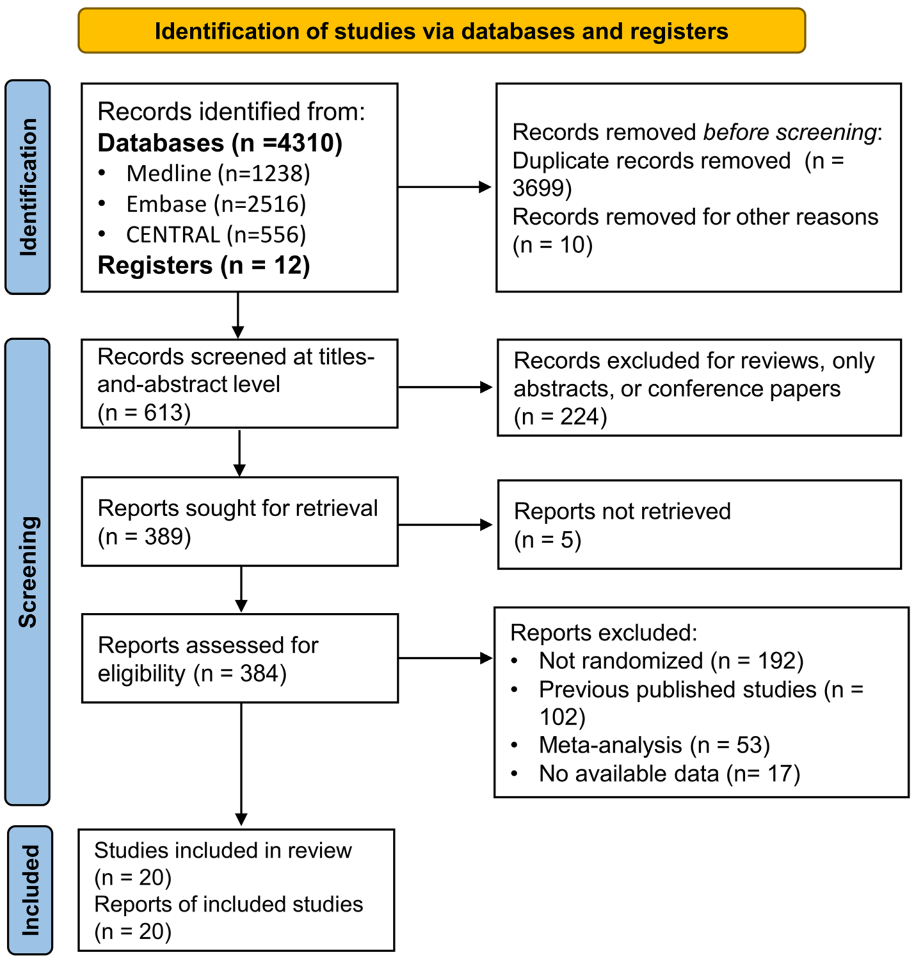

FIGURE 1 Study flowchart. CENTRAL, Cochrane Central Register of Controlled Trials.

TABLE 1 Characteristics of the included trials

Study ID	Total sample size	No. of intervention group	No. of control group	Type of resection (n)	Laparoscopic or open surgery	Intervention	Control	Intravenous antibiotics (Yes/no)	Mechanical bowel preparation (Y/N)
28	83	38	45	Ileocecal resection–5; Right colectomy–14; Left colectomy–3; Transverse colectomy–6; Sigmoidectomy–24; LAR–24; Miles' APR–7	Open	UC + OAB	UC	Yes	Yes
18	143	72	71	Colectomy–76 Anterior resection–47 APR–9 Total proctectomy with J pouch–3 Total pelvic exenteration–4 Other–4	Unclear	UC + OAB	UC	Yes	Yes
19	484	242	242	Colon–241; Rectum–243	Unclear			Yes	Yes
25	162	76	86	Right sided hemicolectomy–42; Left sided hemicolectomy–15; Subtotal transversectomy–4; Colectomy–3; Sigmoid resection–38; LAR–43	Laparoscopic or open surgery	UC + OAB	UC	Yes	Yes
15	579	289	290	Colectomy–376; Anterior resection–183; APR–20	Laparoscopic	UC + OAB	UC	Yes	Yes
17	511	255	256	Colonic surgery–309; Anterior resection–177; APR–25	Laparoscopic	UC + OAB	UC	Yes	Yes
11	455	228	227	Right hemicolectomy–162; Transverse colectomy–17; Left hemicolectomy–41; Sigmoid resection–124; Low anterior resection–103; Other–8	Laparoscopic or open surgery	UC + OAB	UC	Yes	Yes
27	80	40	40	Low anterior resection with TME–80	Unclear	UC + OAB	UC + Placebo	Yes	Yes
26	310	104	104/102	Right colon-99; Transverse colon-38; Left colon-107	Laparoscopic or open surgery	UC + Probiotics	UC + Placebo	Yes	Yes

TABLE 1 (Continued)

Study ID	Total sample size	No. of intervention group	No. of control group	Type of resection (n)	Laparoscopic or open surgery	Intervention	Control	Intravenous antibiotics (Yes/no)	Mechanical bowel preparation (Y/N)
29	40	20	20	Anterior resection-27; hemicolectomy-2; Hartmann's procedure-1; Left hemicolectomy-2; Panproctocolectomy-1; Resection with ileoanal pouch-1; Right hemicolectomy-4; Sigmoid colectomy-1; Total colectomy-1	Unclear	UC + Probiotics	UC + Placebo	Unclear	Unclear
30	60	30	30	Ascending colon and right hemicolectomy-24; Descending colon and left hemicolectomy-15; Sigmoid colon and sigmoid colectomy-8; Rectum and anterior resection-7; Abdominopernieal excision-6	Laparoscopic	UC + Probiotics	UC + Placebo	Yes	Yes
12	33	15	18	Left colectomy-24; Right colectomy-6; Total colectomy-3	Laparoscopic or open surgery	UC + Probiotics	UC + Placebo	Yes	Yes
13	91	49	42	Rectum resection-52; Colon resection-39	Laparoscopic or open surgery	UC + Synbiotics	UC + Placebo	Yes	Yes
14	31	21	10	Left colectomy-15; Right colectomy-7; Rectal resection-9	Unclear	UC + Probiotics	UC + Placebo	Yes	Yes
16	76	48	20	−26; Left hemicolectomy-3; Rectosigmoid resection-29; Low anterior resection-9; Resection of transverse colon Left hemicolectomy-1	Unclear	UC + Synbiotics	UC + Placebo	Yes	Unclear

(Continues)

TABLE 1 (Continued)

Study ID	Total sample size	No. of intervention group	No. of control group	Type of resection (n)	Laparoscopic or open surgery	Intervention	Control	Intravenous antibiotics (Yes/no)	Mechanical bowel preparation (Y/N)
20	168	86	82	Low anterior resection-77; Recto-sigmoidectomy-42; Right hemicolectomy-29; Total colectomy-16	Open	UC + Probiotics	UC + Placebo	No	Unclear
21	114	57	57	Transverse colon resection-15; Descending colon-15; Sigmoid colon-46; Rectum resection-24	Laparoscopic	UC + Probiotics	UC + Placebo	Yes	No
22	161	81	80	Transverse colon resection-27; Descending colon resection-27; Sigmoid colon resection-58; Rectum resection-38	Laparoscopic	UC + Probiotics	UC + Placebo	Yes	No
23	72	36	36	Ileocecal resection-3; Right hemicolectomy-29; Transverse colon resection-3; Left hemicolectomy-4; Sigmoid colon resection-22; Total colectomy −2; No resection-1	Laparoscopic	UC + Probiotics	UC + Placebo	Yes	Yes
24	73	36	37	Rectosigmoidectomy-36; Rectosigmoidectomy with colostomy/ileostomy-32; Right colectomy-5	Unclear	UC + Synbiotics	UC + Placebo	Yes	Yes

We performed a subgroup analysis by including only studies that adopted laparoscopic surgeries. The subgroup analysis had disconnected networks, so we used a component network meta-analysis method.

3 | RESULTS

Detailed results of the screening process were shown in Figure 1. We retrieved 4322 records after literature search and finally included 20 RCTs.[11-30] The majority of the records were excluded for duplicate records in differential databases (n = 3699), and the rest of them were mainly excluded for being reviews or merely abstracts (n = 223), non-randomised studies (n = 192), and previously reported studies (n = 102).

The included 20 RCTs recruited 3726 participants. Six RCTs recruited participants with laparoscopic surgery, two recruited participants with open surgery, five with both types of surgeries, and the rest RCTs were unclear. The most adopted oral antibiotics were the combination of kanamycin plus metronidazole and the combination of polymyxin B, tobramycin, and vancomycin. The most adopted probiotic combination was *L plantarum* plus *L acidophilus*; the most adopted synbiotic combination was *Lactobacillus* plus *Bifidobacterium*; the most adopted prebiotic combination was beta-glucan, inulin, pectin, and resistant starch. Oral antibiotics were normally administrated 3 days before surgery at a frequency of three to four times daily. The probiotics, prebiotics, or synbiotics were normally given 7 days before surgery at a frequency of 2–3 three times daily. Table 1 shows in detail for the types of resections, names of interventions and controls, and whether MBP or IAB was used.

3.1 | Infection rate

Seven treatments were compared, the number of RCTs and participants for each treatment were shown in Figure 2. We performed a network meta-analysis comparing differential treatments in reducing infection rate, which included 20 RCTs and 3726 participants.

The analysis showed that UC + Synbiotics ranked the most effective treatment (SUCRA score = 0.968), UC + OAB ranked the second (SUCRA score = 0.797), and UC + IAB ranked the third (SUCRA score = 0.678). Unimportant heterogeneity was found in the analysis (global I^2 = 13.5%, tau-square = 0.026). Results were consistent between direct and indirect evidence (Supplementary tables). Figure 2 shows the effect sizes of differential treatments

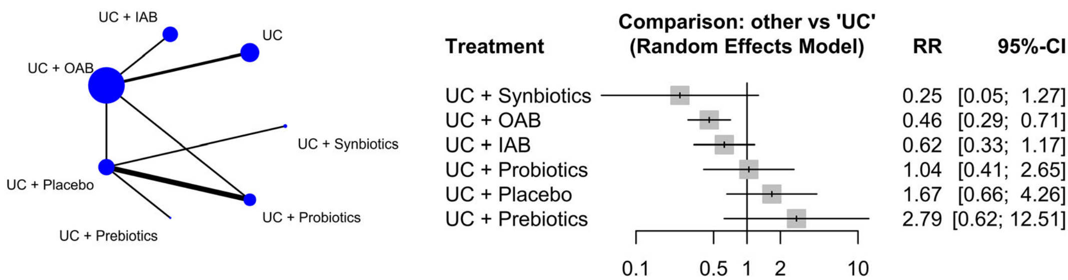

FIGURE 2 Network graph and forest plot for infection rate. RR, relative ratio; UC, usual care; UC + IAB, usual care plus intravenous antibiotics; UC + OAB, usual care plus oral antibiotics. The left side of the figure shows the net graph of the network meta-analysis comparing differential treatments in improving infection rate. The right side shows the forest plots comparing differential treatments against UC, and the treatments were ranked by P-scores—the mean probability of a treatment being the best one. The treatment at the top was the one with the highest P-score.

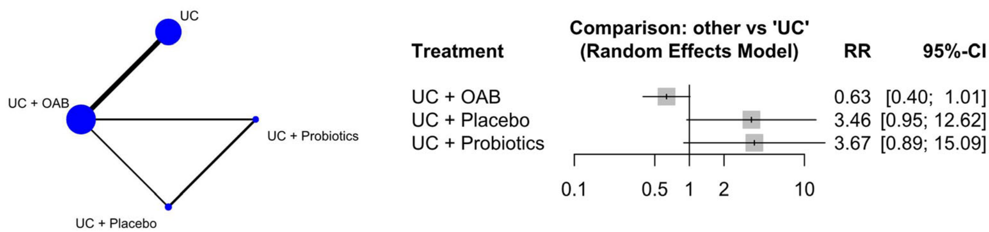

FIGURE 3 Network graph and forest plot for leakage rate. RR, relative ratio; UC, usual care; UC + OAB, usual care plus oral antibiotics. The left side of the figure shows the net graph of the network meta-analysis comparing differential treatments in improving the leakage rate. The right side shows the forest plots comparing differential treatments against UC, and the treatments were ranked by P-scores—the mean probability of a treatment being the best one. The treatment at the top was the one with the highest P-score.

compared with placebo. Table 2 shows pairwise comparisons among the treatments. UC + Synbiotics was associated with lower infection rate when compared with UC + Placebo (RR 0.15, 95% CI 0.04 to 0.57) and UC + Probiotics (RR 0.24, 95% CI 0.06 to 0.94). UC + OAB showed significant better effect than UC + Placebo (RR 0.27, 95% CI 0.12 to 0.62) but not UC + Probiotics (RR 1.84, 95% CI 0.38 to 8.82).

To minimised the impact of the surgery style on the results, we performed subgroup analysis by including studies that adopted only laparoscopic surgery. Because the network was disconnect, we used a component network meta-analysis that use a common component (UC) as a connecter of the network. The results were consistent with the main analysis. We further discovered that OAB (compared with UC, RR 0.86, 95% CI 0.62 to 1.19) and probiotics were the most effective component (compared with UC, RR 0.72, 95% CI 0.55 to 0.93).

3.2 | Anastomotic leakage

The network meta-analysis of anastomotic leakage included 10 RCTs and 2531 participants. Four treatments were compared, and Figure 2 shows the net graph containing the number of participants and RCTs for each treatment.

The results showed that UC + OAB was the most effective treatment (SUCRA score = 0.927); the analysis had no heterogeneity (global I^2 = 0%, tau-square = 0). Results were consistent between direct and indirect evidence (Supplementary tables). Figure 3 shows the effect sizes of differential treatments compared with placebo. Table 3 shows pairwise comparisons among the treatments. The pairwise comparison showed that UC + OAB was associated with significantly lower leakage rate than UC + Placebo (RR 0.18, 95% CI 0.05 to 0.61) and UC + Probiotics (RR 0.17, 95% CI 0.05 to 0.65).

The sensitivity analysis including laparoscopic surgery only constituted a disconnect network, and we performed a component network meta-analysis, which showed consistent results with the main analysis. We discovered that OAB (compared with UC, RR 0.67, 95% CI 0.28 to 1.64) and probiotics were the most effective component (compared with UC, RR 0.5, 95% CI 0.11 to 2.31).

3.3 | Risk of bias assessment

Figure 4 shows the assessment results. Six RCTs were classified with low risk of bias, and the rest 14 RCTs were classified with some concerns. The most rated some-concerns domain was in missing outcome data, which involved 9 RCTs.

TABLE 2 Pairwise comparisons of treatments in infection rate

UC	—	2.19 (1.41 to 3.40)	—	—	—	—
1.60 (0.86 to 3.00)	UC + IAB	1.37 (0.87 to 2.14)	—	—	—	—
2.19 (1.41 to 3.40)	1.37 (0.87 to 2.14)	UC + OAB	0.34 (0.14 to 0.80)	—	0.34 (0.13 to 0.86)	—
0.60 (0.23 to 1.52)	0.37 (0.15 to 0.95)	0.27 (0.12 to 0.62)	UC + Placebo	0.60 (0.19 to 1.94)	1.61 (1.25 to 2.08)	6.74 (1.77 to 25.62)
0.36 (0.08 to 1.61)	0.22 (0.05 to 1.00)	0.16 (0.04 to 0.69)	0.60 (0.19 to 1.94)	UC + Prebiotics	—	—
0.96 (0.38 to 2.46)	0.60 (0.23 to 1.54)	0.44 (0.19 to 1.01)	1.61 (1.25 to 2.07)	2.69 (0.81 to 8.93)	UC + Probiotics	—
4.02 (0.79 to 20.52)	2.51 (0.49 to 12.83)	1.84 (0.38 to 8.82)	6.74 (1.77 to 25.62)	11.23 (1.90 to 66.49)	4.18 (1.07 to 16.27)	UC + Synbiotics

Note: The comparisons between any two treatments should be read from left to right, and the comparison estimate (expressed as relative ratio [RR] and its related 95% CI) is in the cell between the column-defining treatment and the row-defining treatment. The top half of the table presents RRs from direct comparison evidence, while the bottom half of the table presents RRs from network meta-analysis. In top half, RRs < 1 favour row-defining treatments versus column-defining treatments; for example, the value of 0.34 (0.14 to 0.80) favours UC + IAB versus UC + Placebo. In the bottom half, RRs < 1 favour column-defining treatments. Empty cells indicate no direct comparison between two treatments.

Abbreviations: IAB, intravenous antibiotics; OAB, oral antibiotics; UC, usual care.

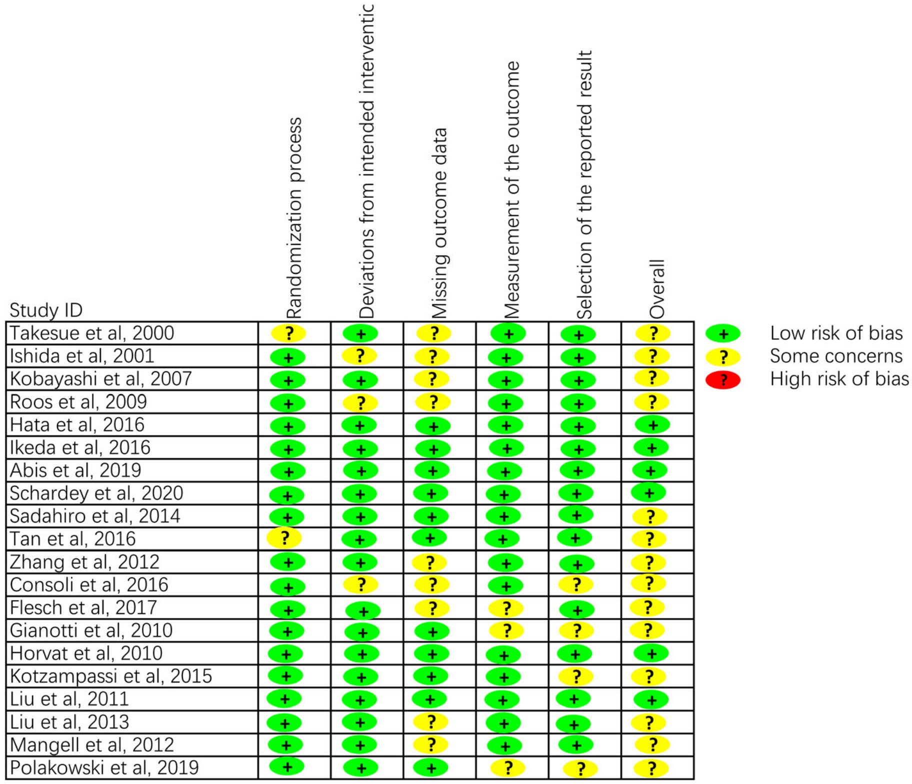

FIGURE 4 Risk of bias assessment. The figure shows the risk of bias assessment for the included studies. Each study was assessed into five domains and summarised into an overall evaluation.

TABLE 3 Pairwise comparison of treatments in anastomotic leakage rate

UC	1.58 (0.99 to 2.53)	—	—
1.58 (0.99 to 2.53)	UC + OAB	0.20 (0.06 to 0.68)	0.08 (0.01 to 0.64)
0.29 (0.08 to 1.05)	0.18 (0.05 to 0.61)	UC + Placebo	1.00 (0.45 to 2.20)
0.27 (0.07 to 1.12)	0.17 (0.05 to 0.65)	0.94 (0.43 to 2.04)	UC + Probiotics

Note: The comparisons between any two treatments should be read from left to right, and the comparison estimate (expressed as relative ratio [RR] and its related 95% CI) is in the cell between the column-defining treatment and the row-defining treatment. The top half of the table presents RRs from direct comparison evidence, while the bottom half of the table presents RRs from network meta-analysis. In top half, RRs < 1 favour row-defining treatments versus column-defining treatments; for example, the value of 0.20 (0.06 to 0.68) favours UC + OAB versus UC + Placebo. In the bottom half, RRs < 1 favour column-defining treatments. Empty cells indicate no direct comparison between two treatments.
Abbreviations: OAB, oral antibiotics; UC, usual care.

4 | DISCUSSION

We performed a network meta-analysis trying to determine which treatment—prebiotics, probiotics, synbiotics, or OAB—was the most effective in reducing infection rate in patients receiving elective colorectal surgery. The results showed that UC + OAB was the most effect in reducing the infection rate and the anastomotic leakage rate. UC + Synbiotics and UC + Probiotics seem to be effective for improving the infection rate, but they were ineffective in improving the anastomotic leakage rate.

Probiotics refer to the products that contain an adequate dose of live microbes that have been documented in target-host studies to confer a health benefit.[31] Prebiotics are a group of nutrients that are degraded by gut microbiota. The prebiotics are short-chain fatty acids that are released into blood circulation, consequently, having beneficial effects on human health.[32] Synbiotics are defined as mixtures of probiotics and prebiotics that confer a health benefit on the host by improving the survival and activity of beneficial microorganisms in the gut.[33] Previous systematic reviews and meta-analyses focused on examine the effectiveness of probiotics and antibiotics separately, and these studies confirmed that probiotics and synbiotics used perioperatively decreased the incidence of SSI,[7-9] and they also confirmed that preoperative administration of OAB was associated with lower incidence of SSI.[1,2,4,6] Our study was the first to compare probiotic treatments with OAB, and the results showed that pretreatment with OAB was a better option for reducing infection rate and anastomotic leakage rate. The anastomotic leakage rate, according our study results, was not decreased by using probiotics and synbiotics, which also supported that OAB was a better option for preventing post-operative complications.

Although theoretically both probiotics and OAB improved infection rate by suppressing pathogenic bacterial taxa, they did not exert the same treatment effect. Studies have shown that the composition of the intestinal flora changed after colorectal surgery, the pathogenic microorganisms increased and had negative effects for the host.[34-36] OAB resisted the pathogenic microorganisms to reduce infection rate, while probiotics and synbiotics might work against them by increasing the other beneficial microorganisms.[9] Based on this assumption, probiotics and synbiotics alone might not be enough for reducing infection rate. They should be used in combination with IAB or OAB according to our study results.

It is worth noted that synbiotics had a large treatment effect in reducing infection rate, although the wide 95% CI made this finding insignificant (the 95% CI contained the null value). This result indicated that the synbiotics arm was underpowered, and trials with a larger sample size are warranted in future trials.

Various formulas of probiotics and synbiotics were adopted in the included trials, and this variety might also cause underestimation of the treatment effects. However, we assume that the variation in formulas would not change our study results. On one hand, most of the studies used probiotic or synbiotic preparations containing *Lactobacillus* and *Bifidobacteria*, which are the main ingredients of currently available probiotic-related products. On the other hand, the network meta-analysis of infection rate had a global I^2 value of 13.5%, which is a small value indicating unimportant heterogeneity.

Several factors might also affect our study results. We performed subgroup analysis by including only laparoscopic surgery, the study results were consistent with the main analysis. The type of resection was heterogenous in the included studies, which might cause bias in the effect estimation. However, owing to the significant difference in the type of resection, we cannot accurately assess the impact of resection type on the study results. Acquiring individual participant level data from all the included studies and performing subgroup analyses might solve the problem. The follow-up periods ranged across different trials; this might be the consequence of the difference in surgical types. Owing to the lack of statistical power in performing subgroup analyses, we did not perform the analyses. We found that antibiotics and probiotics related interventions were used in addition to usual care, so in future studies we might use component network meta-analysis to further assess the exact effect of each component.[37]

Our study had several limitations. First, although we tried to search in databases with comprehensive search strategies, we might not be able to include all trials. The missing information from these trials might affect the study results. Second, less than half of the included studies were classified with low risk of bias, indicating that the effect estimates might not be accurate and might be affected by bias. Third, owing to the lack of studies assessing the effect of synbiotics, we could not conclude whether synbiotics were more effective than other treatments.

In conclusion, our study confirmed that preoperative administration of OAB was associated with lower infection rate and anastomotic leakage rate than placebo and UC alone. However, the beneficial effect of probiotics and synbiotics should still be investigated by large-scale randomised controlled trials.

FUNDING INFORMATION

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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