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Preoperative combined mechanical and oral antibiotic bowel preparation for preventing complications in elective colorectal surgery (Review)

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[Intervention Review]

Preoperative combined mechanical and oral antibiotic bowel preparation for preventing complications in elective colorectal surgery

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ABSTRACT

Background

The success of elective colorectal surgery is mainly influenced by the surgical procedure and postoperative complications. The most serious complications include anastomotic leakages and surgical site infections (SSI)s, which can lead to prolonged recovery with impaired long-term health.
Compared with other abdominal procedures, colorectal resections have an increased risk of adverse events due to the physiological bacterial colonisation of the large bowel. Preoperative bowel preparation is used to remove faeces from the bowel lumen and reduce bacterial colonisation. This bowel preparation can be performed mechanically and/or with oral antibiotics. While mechanical bowel preparation alone is not beneficial, the benefits and harms of combined mechanical and oral antibiotic bowel preparation is still unclear.

Objectives

To assess the evidence for the use of combined mechanical and oral antibiotic bowel preparation for preventing complications in elective colorectal surgery.

Search methods

We searched MEDLINE, Embase, CENTRAL and trial registries on 15 December 2021.
In addition, we searched reference lists and contacted colorectal surgery organisations.

Selection criteria

We included randomised controlled trials (RCTs) of adult participants undergoing elective colorectal surgery comparing combined mechanical and oral antibiotic bowel preparation (MBP+oAB) with either MBP alone, oAB alone, or no bowel preparation (nBP). We excluded studies in which no perioperative intravenous antibiotic prophylaxis was given.

Data collection and analysis

We used standard methodological procedures as recommended by Cochrane. Pooled results were reported as mean difference (MD) or risk ratio (RR) and 95 % confidence intervals (CIs) using the Mantel-Haenszel method. The certainty of the evidence was assessed with GRADE.

Main results

We included 21 RCTs analysing 5264 participants who underwent elective colorectal surgery.

None of the included studies had a high risk of bias, but two-thirds of the included studies raised some concerns. This was mainly due to the lack of a predefined analysis plan or missing information about the randomisation process.

Most included studies investigated both colon and rectal resections due to malignant and benign surgical indications. For MBP as well as oAB, the included studies used different regimens in terms of agent(s), dosage and timing.
Data for all predefined outcomes could be extracted from the included studies. However, only four studies reported on side effects of bowel preparation, and none recorded the occurrence of adverse effects such as dehydration, electrolyte imbalances or the need to discontinue the intervention due to side effects.

Seventeen trials compared MBP+oAB with sole MBP.
The incidence of SSI could be reduced through MBP+oAB by 44% (RR 0.56, 95% CI 0.42 to 0.74; 3917 participants from 16 studies; moderate-certainty evidence) and the risk of anastomotic leakage could be reduced by 40% (RR 0.60, 95% CI 0.36 to 0.99; 2356 participants from 10 studies; moderate-certainty evidence). No difference between the two comparison groups was found with regard to mortality (RR 0.87, 95% CI 0.27 to 2.82; 639 participants from 3 studies; moderate-certainty evidence), the incidence of postoperative ileus (RR 0.89, 95% CI 0.59 to 1.32; 2013 participants from 6 studies, low-certainty of evidence) and length of hospital stay (MD -0.19, 95% CI -1.81 to 1.44; 621 participants from 3 studies; moderate-certainty evidence).

Three trials compared MBP+oAB with sole oAB.
No difference was demonstrated between the two treatment alternatives in terms of SSI (RR 0.87, 95% CI 0.34 to 2.21; 960 participants from 3 studies; very low-certainty evidence), anastomotic leakage (RR 0.84, 95% CI 0.21 to 3.45; 960 participants from 3 studies; low-certainty evidence), mortality (RR 1.02, 95% CI 0.30 to 3.50; 709 participants from 2 studies; low-certainty evidence), incidence of postoperative ileus (RR 1.25, 95% CI 0.68 to 2.33; 709 participants from 2 studies; low-certainty evidence) or length of hospital stay (MD 0.1 respectively 0.2, 95% CI -0.68 to 1.08; data from 2 studies; moderate-certainty evidence).

One trial (396 participants) compared MBP+oAB versus nBP. The evidence is uncertain about the effect of MBP+oAB on the incidence of SSI as well as mortality (RR 0.63, 95% CI 0.33 to 1.23 respectively RR 0.20, 95% CI 0.01 to 4.22; low-certainty evidence), while no effect on the risk of anastomotic leakages (RR 0.89, 95% CI 0.33 to 2.42; low-certainty evidence), the incidence of postoperative ileus (RR 1.18, 95% CI 0.77 to 1.81; low-certainty evidence) or the length of hospital stay (MD 0.1, 95% CI -0.8 to 1; low-certainty evidence) could be demonstrated.

Authors' conclusions

Based on moderate-certainty evidence, our results suggest that MBP+oAB is probably more effective than MBP alone in preventing postoperative complications. In particular, with respect to our primary outcomes, SSI and anastomotic leakage, a lower incidence was demonstrated using MBP+oAB. Whether oAB alone is actually equivalent to MBP+oAB, or leads to a reduction or increase in the risk of postoperative complications, cannot be clarified in light of the low- to very low-certainty evidence. Similarly, it remains unclear whether omitting preoperative bowel preparation leads to an increase in the risk of postoperative complications due to limited evidence.

Additional RCTs, particularly on the comparisons of MBP+oAB versus oAB alone or nBP, are needed to assess the impact of oAB alone or nBP compared with MBP+oAB on postoperative complications and to improve confidence in the estimated effect. In addition, RCTs focusing on subgroups (e.g. in relation to type and location of colon resections) or reporting side effects of the intervention are needed to determine the most effective approach of preoperative bowel preparation.

PLAIN LANGUAGE SUMMARY

Can combined mechanical and oral antibiotic bowel preparation reduce the risk of complications after scheduled colon or rectal resections compared with purely mechanical, purely oral antibiotic or no bowel preparation?

Key messages

- A combined mechanical (using laxatives) and oral antibiotic bowel preparation probably reduces the occurrence of infections of the surgical site (wound infections and infections in the abdominal cavity) as well as the likelihood of anastomotic leakage (leakage of the suture connection of the bowel) compared with mechanical bowel preparation alone.

- Oral antibiotics alone might be as effective as a combined mechanical and oral antibiotic bowel preparation, but this cannot be clearly determined based on the available data.

- Whether no bowel preparation compared with a combined mechanical and oral antibiotic bowel preparation has an influence on the occurrence of postoperative complications could not be determined on the basis of the available data.

What is the purpose of preoperative bowel preparation?
Due to the naturally bacterial colonisation of the large bowel, infections of the surgical site are more frequent after operations in which the large bowel is opened. To prevent these infections, bowel preparation before surgery is intended to reduce faecal contamination of the bowel and minimise bacterial colonisation.

How is the bowel preparation done?

Preoperative bowel preparation can be done mechanically, using laxatives to rinse the bowel, or by taking oral antibiotics that lead to local decontamination. These two methods can be performed either alone or in combination.

What did we want to find out?
We wanted to find out whether combined mechanical and oral antibiotic bowel preparation compared with mechanical or oral antibiotic preparation alone or no bowel preparation has an effect on:

- the occurrence of surgical site infections

- the occurrence of anastomotic leakages

In addition, we wanted to find out whether combined bowel preparation had an effect on mortality, the occurrence of mild or severe postoperative complications, the likelihood of postoperative ileus (bowel motility disorder) or the length of hospital stay. Furthermore, we wanted to investigate whether side effects of the bowel preparation interventions differ between combination therapy and sole mechanical, sole oral antibiotic, or no bowel preparation.

What did we do?
We searched for studies comparing combined mechanical and oral antibiotic bowel preparation with sole mechanical, sole oral antibiotic, or no bowel preparation in patients scheduled for colon or rectal resection.
We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?
We included 21 studies in which patients scheduled for colon or rectal resection were assigned either to a group receiving combined mechanical and oral antibiotic bowel preparation or to a comparison group. The comparison group received mechanical bowel preparation alone in 17 studies, oral antibiotics alone in three studies, and no bowel preparation at all in one study. All participants received intravenous antibiotic prophylaxis during surgery. The studies included a total of 5968 participants, of whom 5264 were analysed.
Most of the studies were conducted in industrialised countries in Europe or Asia. Bowel preparation was conducted over one to three days before surgery and the follow-up period was 30 days in most of the studies. No industrial funding was reported by any of the studies, but only five of the 21 studies provided information on their funding.
Overall, slightly more men (58%) than women (42%) were included. The average age of the study participants varied between 42 and 69 years.

We found moderate-certainty evidence that combined mechanical and oral antibiotic bowel preparation probably reduces the risk of surgical site infections and leakages without affecting mortality, the occurrence of postoperative ileus or length of hospital stay.
When comparing combined bowel preparation with oral antibiotics alone or with no bowel preparation, we found low-certainty evidence that there is little to no difference between the compared approaches.

What are the limitations of the evidence?
There are different reasons why our confidence in the evidence is limited.
We are moderately confident in the evidence regarding the reduction of surgical site infections through combined mechanical and oral antibiotic bowel preparation, because different surgical strategies (in terms of surgical access and type and location of bowel resection) and also different methods of bowel preparation (in terms of agent, dose and timing) were used. We are also only moderately confident in the reduction of anastomotic leakage through combined mechanical and oral antibiotic bowel preparation, because just a few cases occurred across the included studies.
Regarding the comparison of combination therapy with oral antibiotics alone, we have little confidence in the evidence because not enough studies examined this issue to be certain about the results of our outcomes. In addition, there are some concerns about the methods used in the included studies.
As there is only one study, we also have little confidence in the evidence comparing combined bowel preparation with no bowel preparation.

How up to date is this evidence?
This evidence is up-to-date as of December 2021.

Summary of findings 1. Summary of findings table - Combined mechanical and oral antibiotic bowel preparation versus mechanical bowel preparation alone

Combined mechanical and oral antibiotic bowel preparation versus mechanical bowel preparation alone

Patient or population: Patients undergoing elective colorectal surgery
Setting: Any type of hospital offering elective colorectal resections. Both single and multicentre studies are included
Intervention: MBP+oAB
Comparison: MBP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MBP	Risk with MBP +oAB				
SSI follow-up: 30 days	137 per 1000	**77 per 1000** (58 to 101)	**RR 0.56** (0.42 to 0.74)	3917 (16 RCTs)	⊕⊕⊕⊖ Moderate[a]	Combined mechanical and oral antibiotic bowel preparation probably results in a reduction in surgical site infections.
Anastomotic leakage follow-up: 30 days	44 per 1000	**26 per 1000** (16 to 43)	**RR 0.60** (0.36 to 0.99)	2356 (10 RCTs)	⊕⊕⊕⊖ Moderate[b]	Combined mechanical and oral antibiotic bowel preparation may result in a reduction in anastomotic leakage.
Mortality follow-up: 30 days	18 per 1000	**16 per 1000** (5 to 51)	**RR 0.87** (0.27 to 2.82)	639 (3 RCTs)	⊕⊕⊕⊖ Moderate[c]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in mortality.
Incidence of postoperative ileus follow-up: 30 days	49 per 1000	**43 per 1000** (29 to 64)	**RR 0.89** (0.59 to 1.32)	2013 (6 RCTs)	⊕⊕⊖⊖ Low[d,e]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in incidence of postoperative ileus.
Length of hospital stay follow-up: 30 days		MD **0.19 lower** (1.81 lower to 1.44 higher)	-	621 (3 RCTs)	⊕⊕⊕⊖ Moderate[d]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in length of hospital stay.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431253836665717559.

[a] The rating was downgraded by one level due to moderate heterogeneity between studies that could not be explained by the subgroup analyses; I2 =44%.
[b] The rating was downgraded by one level for imprecision. Few events occurred in the included trials (28 in the intervention group and 52 in the control group) and the confidence intervals include both benefits and no effect.
[c] The rating was downgraded by one level for imprecision. Few events occurred in the included studies (5 in the intervention group and 6 in the control group) and the confidence intervals include considerable benefit and harm.
[d] The rating was downgraded by one level due to imprecision, as the confidence interval includes considerable benefit and harm.
[e] The rating was downgraded by one level due to possible puplication bias, as small studies reported statistically significant benefits while larger studies showed a much smaller and statistically non-significant effect.

Summary of findings 2. Summary of findings table - Combined mechanical and oral antibiotic bowel preparation versus oral antibiotics alone

Combined mechanical and oral antibiotic bowel preparation versus oral antibiotics alone

Patient or population: Patients undergoing elective colorectal surgery
Setting: Any type of hospital offering elective colorectal resections. Both single and multicentre studies are included
Intervention: MBP+oAB
Comparison: oAB

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with oAB	Risk with MBP +oAB				
Surgical site infections follow-up: 30 days	68 per 1000	**59 per 1000** (23 to 151)	**RR 0.87** (0.34 to 2.21)	960 (3 RCTs)	⊕⊝⊝⊝ Very low[a,b,c]	Combined mechanical and oral antibiotic bowel preparation may have no effect on surgical site infections, and the evidence is very uncertain.
Anastomotic leakage follow-up: 30 days	25 per 1000	**21 per 1000** (5 to 86)	**RR 0.84** (0.21 to 3.45)	960 (3 RCTs)	⊕⊕⊝⊝ Low[a,c]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in anastomotic leakage.
Mortality follow-up: 30 days	14 per 1000	**14 per 1000** (4 to 49)	**RR 1.02** (0.30 to 3.50)	709 (2 RCTs)	⊕⊕⊝⊝ Low[a,c]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in mortality.

Incidence of post-operative ileus follow-up: 30 days	47 per 1000	**59 per 1000** (32 to 111)	**RR 1.25** (0.68 to 2.33)	709 (2 RCTs)	⊕⊕⊖⊖ Low[a,c]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in the incidence of postoperative ileus.
Length of hospital stay follow-up: 30 days	In two studies, the reported mean difference between groups was 0.1 and 0.2 (95% CI -0.68 to 1.08) days, respectively.			(2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Combined mechanical and oral antibiotic bowel preparation probably results in little to no difference in length of hospital stay.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431253847765418810.

[a] The rating was downgraded by one level because of some concerns about risk of bias, as information on a predefined analysis plan could not be identified for any of the included studies.
[b] The rating was downgraded by one level due to moderate heterogeneity between studies; I2 =69%.
[c] The rating was downgraded by one level due to imprecision, as the confidence interval includes considerable benefit and harm.

Summary of findings 3. Summary of findings table - Combined mechanical and oral antibiotic bowel preparation versus no bowel preparation

Combined mechanical and oral antibiotic bowel preparation versus no bowel preparation

Patient or population: Patients undergoing elective colorectal surgery
Setting: Any type of hospital offering elective colorectal resections. Both single and multicentre studies are included
Intervention: MBP+oAB
Comparison: nBP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with nBP	Risk with MBP +oAB				

Surgical site infections follow-up: 30 days	105 per 1000	**66 per 1000** (35 to 129)	**RR 0.63** (0.33 to 1.23)	396 (1 RCT)	⊕⊕⊖⊖ Low[a]	Combined mechanical and oral antibiotic bowel preparation may result in little to no difference in surgical site infections.
Anastomotic leakage follow-up: 30 days	40 per 1000	**36 per 1000** (13 to 97)	**RR 0.89** (0.33 to 2.42)	396 (1 RCT)	⊕⊕⊖⊖ Low[a]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in anastomotic leakage.
Mortality follow-up: 30 days	10 per 1000	**2 per 1000** (0 to 42)	**RR 0.20** (0.01 to 4.22)	396 (1 RCT)	⊕⊕⊖⊖ Low[a]	Combined mechanical and oral antibiotic bowel preparation may result in little to no difference in mortlaity.
Incidence of postoperative ileus follow-up: 30 days	160 per 1000	**189 per 1000** (123 to 290)	**RR 1.18** (0.77 to 1.81)	396 (1 RCT)	⊕⊕⊖⊖ Low[a]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in incidence of postoperative ileus.
Length of hospital stay follow-up: 30 days		MD **0.1 higher** (0.8 lower to 1 higher)	-	396 (1 RCT)	⊕⊕⊖⊖ Low[a]	Combined mechanical and oral antibiotic bowel preparation may result in no difference in length of hospital stay.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431253860479140670.

[a] The rating was downgraded by two levels due to imprecision because of the small sample size and the wide confidence intervals, which include considerable benefit and harm.

BACKGROUND

Description of the condition

Colorectal operations are amongst the most frequently performed surgical procedures worldwide. In addition to emergency surgery (e.g. bowel perforations, diverticulitis, lower gastrointestinal bleeding), colon resections are performed for treating inflammatory diseases (e.g. ulcerative colitis or Crohn's disease) and colorectal cancer (Kuhry 2008; Spanjersberg 2011).

The treatment outcome is significantly influenced by the surgical procedure itself along with the occurrence of postoperative complications. Amongst the most serious complications are anastomotic leaks and surgical site infections (SSIs), which can lead to a prolonged and severe clinical course with impaired long-term outcomes. In oncological cases, prolonged postoperative recovery can lead to a delayed start of adjuvant oncological treatment and thus to an increased risk of metastasis or local recurrence (Beck 2020; Kulu 2015; Nachiappan 2016; Young 2012). The incidence of complications is, amongst other factors, related to the type of surgery performed. Whilst anastomotic leaks are infrequent for small bowel and elective colon resections (1% to 3%), they occur far more frequently after rectal resections (10% to 23%) (ISOS 2016; Kulu 2015; Toh 2018; Walker 2004; Weidenhagen 2007). Compared with other abdominal operations, colorectal resections present an eight-fold higher risk for the occurrence of adverse events. For instance, the SSI rate in colorectal surgery lies between 9% and 24 %, while in non-colorectal surgery it is only 2% to 9 % (Anjum 2017; Migaly 2019). One reason for the increased complication rate in colorectal surgery is the high bacterial colonisation by the physiological intestinal flora, the so-called microbiome.

Overall, there are numerous recommendations to reduce the risk of surgical complications. These range from specified preoperative preparation of the surgical field (e.g. preoperative whole-body bathing or showering, hair removal, and disinfection methods) to intravenous antibiotic prophylaxis (Ling 2019; Nelson 2014; NICE 2019; WHO 2018). However, there is disagreement about what might be the best strategy for bowel preparation before elective colon and rectal surgery.

Description of the intervention

The underlying idea of preoperative bowel preparation is to clean the bowel from faeces, thereby reducing the bacterial load, which could lead to a lower rate of postoperative complications, especially SSIs and anastomotic leakage. Furthermore, removing the faeces makes it easier to manipulate the bowel in laparoscopic surgeries and lowers the risk of unwanted faecal spillage into the abdominal cavity.

In summary, there are four widespread interventions for bowel preparation before colorectal surgery in everyday clinical practice:

- no bowel preparation;
- mechanical bowel preparation (MBP);
- oral antibiotics (oAB);
- combination of oral antibiotics and mechanical bowel preparation (MBP+oAB).

For MBP, osmotically active solutions are mainly used nowadays (Kumar 2013; WHO 2018). By translocating fluid into the intestine, these lead to the development of diarrhoea and as a result the emptying of the bowel. Given the constant development of the applied solutions in the last decade, complications such as dehydration, electrolyte imbalance, or cardiovascular dysfunction rarely occur (Kumar 2013).

Regarding the antibiotic regimen, a combination of active substances that are effective against both aerobic and anaerobic bacteria are used (Migaly 2019; WHO 2018). Numerous different protocols exist regarding the active substance, dosage, and duration of treatment (WHO 2018). Two meta-analyses from 2018 recommend a combination of an aminoglycoside (kanamycin or neomycin) and metronidazole or erythromycin administered one to three days before surgery (McSorley 2018; Toh 2018).

There is some evidence that luminal faeces may lead to an inactivation of the topically acting antibiotics. Consequently, oAB should be administered after, or at least in combination with MBP (Schardey 2017). However, the evidence for this hypothesis is ambiguous. Recent meta-analyses failed to demonstrate a significant difference in SSI or anastomotic leak rates after combined or sole oral antibiotic bowel preparation, calling into question the need for combination therapy (Nelson 2020; Rollins 2019).

How the intervention might work

It is well known that the intestinal microbiome is important for myriads of physiological processes such as metabolism of drugs and nutrition degradation, biosynthesis of neurotransmitters and hormones, and influences immune maturation, host cell proliferation, and neurological signalling – to name but a few examples. However, the microbiome also plays an important role in disease development, for example autoimmune and gastrointestinal disease, but also neuropsychiatric illnesses (Lynch 2016). There is growing evidence that the intestinal microbiome is also involved in wound-healing processes, especially in the healing of bowel anastomosis or the development of an anastomotic leakage (Schardey 2017). In addition to the surgical technique, bacterial colonisation of the intestinal mucosa of the anastomotic region also influences the occurrence of an insufficiency. Due to the surgical trauma and resulting ischaemia, mucosal bacteria such as *Enterococcus faecalis* or *Pseudomonas aeruginosa* develop the ability to express collagenases and activate matrix metalloproteinase 9 in the patient's intestinal tissue. This mechanism promotes the degradation of synthesised tissue leading to vulnerability of the newly created anastomosis (Anjum 2017; Schardey 2017; Shogan 2015).

In order to prevent these wound-healing disturbances, preoperative preparation of the bowel is intended to create a clean working environment by reducing bacterial contamination of the intestine and respectively of the surgical field.

Why it is important to do this review

In several publications, as well as a Cochrane Review published in 2011, the use of MBP compared with no preparation or rectal enemas did not demonstrate an improved outcome for patients, which led to the recommendation to refrain from preoperative bowel preparation (Güenaga 2011).

In contrast, a current large registry study with more than 8000 patients demonstrated a significantly lower rate of postoperative

SSIs as well as a shorter length of hospital stay with combined therapy of oAB and MBP compared with no bowel preparation or monotherapy with MBP or oAB (Klinger 2019). In addition, the combination therapy group also had the lowest readmission rate. Based on these data, the American Society of Colon and Rectal Surgeons recommended a combined mechanical and oral antibiotic bowel preparation prior to elective colon and rectal resections (Migaly 2019).

Despite the evidence for a beneficial effect of supplementing oAB to MBP, a current survey amongst members of the German Society of General and Visceral Surgery revealed that MBP alone is performed in over 50% of colon and over 75% of rectal operations. Additional oAB was only performed in about 10% of these operations (Buia 2019). A comparable survey amongst members of the European Society of Coloproctology revealed similar results (Devane 2017). Whilst the majority of respondents reported to regularly use MBP, less than 10% prescribe oral antibiotic therapy. In the USA, the rate of usage of combination therapies is much higher, although it has decreased over the last few years. In a survey conducted by the American Society of Colon and Rectal Surgeons in 1990, 88% of the participants reported using a combined bowel preparation (Solla 1990). In a more recent survey from 2010, only 36% of the colorectal surgeons still prescribe oral antibiotic therapy (Markell 2010).

The results of these surveys reveal that there is currently no uniform approach. Although there are already several meta-analyses on this topic, they differ considerably in their conclusions: whilst some meta-analyses report a benefit of combined oral and intravenous antibiotic therapy, with an unclear effect of concurrent mechanical bowel preparation (Nelson 2020; Rollins 2019), other meta-analyses have shown superiority of the combination of oral antibiotic prophylaxis and mechanical bowel preparation (Toh 2018). However, these differences are not due to more recent findings, but rather to differences in the literature search, study selection criteria, and data extraction management. In order to establish an evidence-based therapy, a structured and high-quality meta-analysis of the available evidence is necessary to provide optimal guidance on preoperative bowel preparation aiming to reduce the postoperative complication rate as well as overall mortality.

OBJECTIVES

The aim of this review is to assess the evidence for the use of combined mechanical and oral antibiotic bowel preparation for preventing complications in elective colorectal surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished, and ongoing randomised controlled trials (RCTs) or quasi-RCTs (trials in which randomisation is attempted but potentially predictable, such as allocating participants by day of the week or sequence of entry into trial) comparing preoperative bowel preparation using MBP and oAB prior to elective colon or rectal surgery. We considered all identified studies for inclusion regardless of date, location, or language of publication.

Types of participants

Adult participants (18 years of age and older) undergoing elective colorectal surgery.

There were no exclusion criteria regarding the indication for surgery (both benign and malignant diseases were eligible); the type of colorectal surgery performed ((extended) right/left hemicolectomy, transverse colectomy, sigmoid resection, rectal resections, proctocolectomies or reanastomoses (provided a colorectal anastomosis was performed)); any previous treatment of the patient (e.g. neoadjuvant therapy); patient co-morbidities; or the timing and location of the surgery.

For studies that include both eligible participants and others (e.g. children), we extracted data only from the eligible participants. We requested this information from the study authors if necessary. For one study, it was not possible to extract eligible data separately, and we could not obtain further information from the study author, so this study was classified as awaiting classification.

Types of interventions

We included any combination therapy of preoperative oAB and MBP.

We anticipated that there were different protocols in terms of the timing, duration, and frequency of administration, as well as the dosage of substances used (both in terms of antibiotics and mechanical bowel preparation). Any type of preoperative oral antibiotic prophylaxis, as well as any method of mechanical bowel cleansing, was eligible regardless of the mode of delivery, dose, duration, intensity, and co-interventions. However, combination therapy and parenteral antibiotic prophylaxis (in both the control and intervention group) was mandatory. Regarding the effect of MBP or oAB alone, analyses already exist in further Cochrane Reviews (Güenaga 2011; Nelson 2014). We included studies using standard of care regarding parenteral antibiotic prophylaxis in both participant groups (intervention and control).

We included the following comparisons:

- combination of MBP and oAB versus MBP alone;
- combination of MBP and oAB versus oAB alone;
- combination of MBP and oAB versus no preoperative preparation or placebo control (nBP).

Types of outcome measures

We analysed the occurrence of the predefined primary and secondary outcome parameters listed below within 30 days postoperatively. We assessed only the incidence of complications, and not the time of their occurrence. The outcome parameters listed below can be differentiated into efficacy and safety outcomes, whereby all listed outcome parameters, with the exception of length of hospital stay, refer to patient safety.

Reporting one or more of the listed outcomes was not a study inclusion criterion of the review.

Primary outcomes

If an outcome occurred in a participant at multiple sites (e.g. wound infection) or at different time points during the 30-day

postoperative observation interval, we counted such an outcome measure only once.

We considered the following primary outcomes.

- Number of participants with SSIs (infection of the incision site involving the skin and subcutaneous tissue (superficial), deep soft tissue (deep), or a part of the body deeper than the fascia/muscle layers that was opened or manipulated during the surgical procedure (organ/space) and occurs within 30 days after the surgical procedure);
- Number of participants with anastomotic leakage.

For the above outcome parameters, an absolute risk reduction (RRR) of 5 % was considered clinically relevant. From this RRR value, a risk ratio (RR) of 0.95 can be derived. This means that the RR and the 95% confidence interval (CI) for SSI and anastomotic leakages should be equal to or smaller than 0.95 to be considered a clinically relevant difference.

Secondary outcomes

We recorded the number of participants with the following adverse events (as defined by the primary study author) within 30 days postoperatively.

- Mortality.
- Mild postoperative complications (Clavien-Dindo grade I and II).
- Severe postoperative complications (Clavien-Dindo grade III and IV).
- Incidence of postoperative ileus.
- Length of hospital stay (LOS) [days].
- Side effect of intervention:
  - incidence of adverse effects of MBP such as dehydration, electrolyte imbalance, renal failure, or cardiac dysfunction (as defined by the primary study author);
  - incidence of adverse effects of oAB such as diarrhoea or pseudomembranous enterocolitis (as defined by the primary study author);
  - number of participants for whom the intervention was discontinued due to side effects, as well as the number of participants for whom therapy was initiated to treat the complications.
- *C. difficile*-related diarrhoea

Our prespecified outcome measures were not independent of each other. For example, people with SSIs, anastomotic leakages, or other adverse events were additionally classified according to the severity of the complications that occurred using the Clavien-Dindo classification (Clavien 2009).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases from inception to December 15, 2021:

- Cochrane Central Register of Controlled Trials (CENTRAL via the Cochrane Library; 1998 to 2021);
- MEDLINE (via PubMed; 1946 to 2021);
- Embase (via Ovid; 1988 to 2021).

The search strategies are given in Appendix 1.

Searching other resources

We also searched the trial registries ClinicalTrials.gov (www.clinicaltrials.gov, see Appendix 1) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (trialsearch.who.in, see Appendix 1). Furthermore, we screened the reference lists of all included publications and the included studies of related meta-analyses for additional studies. We contacted organisations (e.g. regional colorectal surgery societies) to ask if they have knowledge of ongoing or completed studies to complement our database searches. We sought both published and unpublished trials. We did not limit the search by language or date.

Data collection and analysis

Selection of studies

Two review authors (MW and TV) screened the title and abstract of each study identified in the electronic search for potential relevance. Each review author independently decided on trial inclusion using the following predetermined eligibility criteria.

- Study design: RCT or quasi-RCT.
- Population: adults undergoing elective colorectal surgery.
- Intervention: preoperative bowel preparation using oAB and MBP.
- Comparison: no preoperative bowel preparation (nBP) or sole treatment with either MBP or oAB.

Any disagreements regarding study eligibility during title and abstract screening were resolved by a third review author or by contacting the study authors for clarification.

Afterwards, two review authors (MW and TV) independently carried out the full-text screening using the same inclusion criteria.

Data extraction and management

Two review authors (MW and SS) independently abstracted the following information from the included studies using a standardised form. The data extraction form was previously piloted on two studies and adjusted where necessary.

- General information
  - Study ID, study title, corresponding author and contact details, publication date, country where the study was conducted, duration of trial and duration of follow-up, aim of study (short description), inclusion and exclusion criteria, baseline imbalances, any conflicts of interest stated by the investigators, source of funding, ethics approval, trial registration, and sample size calculation.
- Number of participants
  - Number randomised, number analysed, number of participants in the intervention/control group.
- Population
  - Age, sex, co-morbidities, surgery indication, type of operation, subgroups reported, and subgroups measured.
- Intervention
  - Description of the intervention, agent and dose used for MBP, agent and dose used for oAB, timing of preparation (MBP),

timing of preparation (oAB), modification of intervention, and concomitant medications.

- Control
  - Description of control, agent and dose used, and timing of preparation.
- Outcomes
  - Incidence of SSI, incidence of incisional (superficial or deep) and organ/space SSI, incidence of anastomotic leakage, spectrum of organisms detected, postoperative complications subdivided according to Clavien-Dindo in mild (I/II) and severe (III/IV) complications as reported by the authors, incidence of postoperative ileus according to the definition of the primary study author, LOS (days), mortality, and side effects of the intervention (e.g. electrolyte imbalances, renal failure, incidence of *Clostridium difficile* infection, or termination of the intervention due to side effects).
  - Outcomes reported in trial but not used in review.

In cases where the majority of the required data was not reported in an identified publication, we searched for the associated study report or attempted to obtain the required data through correspondence with the study author. Trials whose results were published in more than one publication were included as one study. Data extraction was based on the main primary publication, but secondary publications were also considered for additional information. All publications are listed in the references of included studies.

Any disagreements were resolved by discussion or by consultation with a third review author if required.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies using Cochrane's RoB 2 tool (Sterne 2019; Higgins 2021). Two review authors (MW and SS) independently assessed the risk of bias of the results, with any disagreements resolved through discussion with a third review author.

We were interested in the effect of allocation at baseline, regardless of whether the intervention was delivered as intended (i.e. the 'intention-to-treat' effect). Consistent with the RoB 2 tool (Sterne 2019; Higgins 2021), we considered the following five domains in our assessment:

- risk of bias arising from the randomisation process;
- risk of bias due to deviations from the intended interventions (effect of assignment as well as adhering to intervention);
- missing outcome data;
- risk of bias in measurement of the outcome;
- risk of bias in selection of the reported result.

We assessed the risk of bias for the following five outcomes that also contribute to the summary of findings tables of the review, measured at a time point closest to the 30-day postoperative window (see 'Summary of findings and assessment of the certainty of the evidence' section below):

- SSIs;
- anastomotic leakage;
- mortality;
- incidence of postoperative ileus;
- LOS.

We assessed these domains using the 'Excel tool to implement RoB 2' (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2), and followed the recommended algorithm of signalling questions and response options to reach one of the following risk of bias judgements for each of the five domains, and consequently for each of our prespecified outcome measures:

- low risk;
- some concerns;
- high risk.

To assess the overall risk of bias of an outcome, we considered judgements of the five individual domains. To be judged as 'low risk', all domains had to be rated as at low risk of bias. We assessed an outcome as 'some concerns' if risk of bias had been rated as some concerns in at least one domain, and high risk of bias in no domains. We assessed an outcome as 'high risk' if high risk of bias was identified in even one domain. We also classified an outcome as 'high risk' if we judged several domains as 'some concerns', as we consider confidence in such an outcome to be considerably reduced (Higgins 2021).

Measures of treatment effect

For continuous outcomes (e.g. LOS), we extracted the final mean value and standard deviation (SD) of each outcome of interest as well as the number of participants evaluated at the final assessment in each treatment arm. With these data, we calculated the mean difference (MD) and the 95% CI and, if appropriate, a pooled estimate of treatment effects. In cases were MDs and SDs were reported by the primary study authors, those data were used.

For dichotomous outcomes (SSIs, anastomotic leakage, mortality, postoperative complications, incidence of postoperative ileus, treatment-related adverse effects), we extracted the RR including the 95% CI. If the RR was not reported, the number of affected participants were extracted to estimate an RR and its 95% CI.

Unit of analysis issues

We expected neither cross-over studies nor cluster-randomised studies in this clinical area, therefore the protocol did not specify how such studies should have been handled if we had identified one.

Our review includes one intervention group (MBP+oAB) and three comparison groups (comparison 1: MBP alone; comparison 2: oAB alone; comparison 3: no preoperative bowel preparation (nBP)). As there were no restrictions on the methodology of the intervention, no further subdivision of the intervention or comparison groups was intended.

We identified one study with two intervention groups (Espin-Basany 2005), which we combined for statistical analysis in order to assign it to our predefined intervention group.

Dealing with missing data

For relevant data missing from a trial report, we attempted to contact the corresponding author to obtain the missing information. We did not impute missing information.

Assessment of heterogeneity

Clinical heterogeneity may be caused by several factors, such as patient age and co-morbidities, indication, and treatment prior to surgery, as well as the procedures used to decontaminate the bowel. In addition, different surgical procedures, as well as the type of access route (minimally invasive versus open surgery), also contribute to heterogeneity. Methodological heterogeneity may be caused by the different risks of bias between studies. To assess the impact of clinical and methodological heterogeneity, we performed subgroup and sensitivity analyses on these topics. We identified statistical heterogeneity through visualisation of the forest plots as well as the Chi^2 test. We used the I^2 statistic for the quantification of heterogeneity.

We interpreted the I^2 value as follows (Deeks 2021).

- < 30% to 40%: little or no heterogeneity.
- 41% to 74%: moderate heterogeneity.
- 75% to 100%: considerable heterogeneity.

Possible reasons for considerable heterogeneity were investigated and reported.

Assessment of reporting biases

To assess whether selective reporting of outcomes might affect the review findings, we matched the study protocols or registry entries, if available, with the published information on outcomes.

As we identified more than 10 studies reporting on our primary outcomes for the comparison MBP+oAB versus MBP, we created a funnel plots to assess the potential for small-study effects where possible.

Data synthesis

Before conducting the meta-analysis, we checked whether the participants, interventions, comparisons, and outcomes were sufficiently similar to ensure that the result of the analysis were clinically meaningful.

To calculate an overall treatment effect, we combined the data using a random-effects model. As different agents of MBP and a variety of oAB with different administration intervals and combination options were included, a variance between the included trials has been assumed.

We included all eligible studies in the meta-analysis regardless of their risk of bias rating. We performed the statistical analysis with Review Manager 5 software (Review Manager 2020) and RevMan Web (RevMan Web 2020). To combine dichotomous outcome data, we used the method proposed by Mantel-Haenszel (Deeks 2021). If meta-analysis was not appropriate due to an insufficient number of eligible studies or substantial heterogeneity between studies, we provided a narrative description of study characteristics and results.

Subgroup analysis and investigation of heterogeneity

Provided that sufficient studies were identified to justify subgroup analyses or meta-regressions (at least 10 studies per outcome), we investigated the possible causes of heterogeneity by means of subgroup analyses for the primary outcome parameters.

We conducted subgroup analyses for the first comparison (MBP +oAB versus MBP) with regard to the outcome SSI for the following aspects:

- surgery indication;
- type of surgery;
- surgical approach;
- duration of mechanical bowel preparation;
- agent combination of oral antibiotics;
- duration of intravenous prophylaxis.

We assessed differences between subgroups by performing a test for heterogeneity across subgroups (i.e. Cochran's Q) and analysing I^2.

Sensitivity analysis

We conducted sensitivity analysis to examine the robustness of our findings, investigating the influence of studies judged at 'some concerns' on the effect size by removing these studies for each outcome and re-analysing the remaining studies to see if the results were influenced by these factors.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using GRADEpro GDT software (GRADEpro GDT) for each comparison (MBP+oAB versus MBP/oAB/nBP) for the following outcomes, as measured during the 30-day postoperative duration (Schünemann 2021):

- SSIs;
- anastomotic leakage;
- mortality;
- incidence of postoperative ileus;
- LOS.

Two review authors independently assessed the certainty of the evidence based on the five GRADE domains (overall RoB 2 judgement, imprecision, inconsistency, indirectness, and publication bias) (Schünemann 2013). Any disagreements were resolved through discussion or by involving a third review author. The GRADE assessment resulted in one of four degrees of certainty (high, moderate, low, or very low certainty), expressing our confidence in the estimate of impact.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies tables.

We contacted the authors of six studies included in the full-text screening and asked for more information to better assess whether these studies could be included in our review (Abis 2019; Arezzo 2021; Ikeda 2016; Mulder 2020; Tagliaferri 2020; Uchino 2019). Based on this additional information we received, we included Arezzo 2021; Ikeda 2016 and Uchino 2019 in our review and excluded Mulder 2020.
As Abis 2019 includes both eligible and ineligible patients which can not be separated based on the published version of the study, we

classified this study as awaiting classification. Tagliaferri 2020 was classified as an ongoing study as only an abstract with primary results was found and no published report of the final study results.

Results of the search

The process of our literature search is shown in a PRISMA flowchart in Figure 1. We identified 1954 records through the electronic searches of the Cochrane Central Register of Controlled Trials (459 records), MEDLINE (922 records) and Embase (573 records). Additionally, 40 records were identified by searching trial registries (clinicaltrials.gov: 17 records; ICTRP: 23 records). Further, 25 records were identified by contacting colorectal surgical societies, screening reference lists and reviewing included studies in related meta-analyses.

Of the 1488 records after removing 531 duplicates, we excluded 1396 clearly irrelevant records by screening their titles and abstracts. We retrieved the full text of 92 records for further assessment. We excluded 30 studies for the reasons listed in the Characteristics of excluded studies tables.

Figure 1. Figure 1: PRISMA flowchart

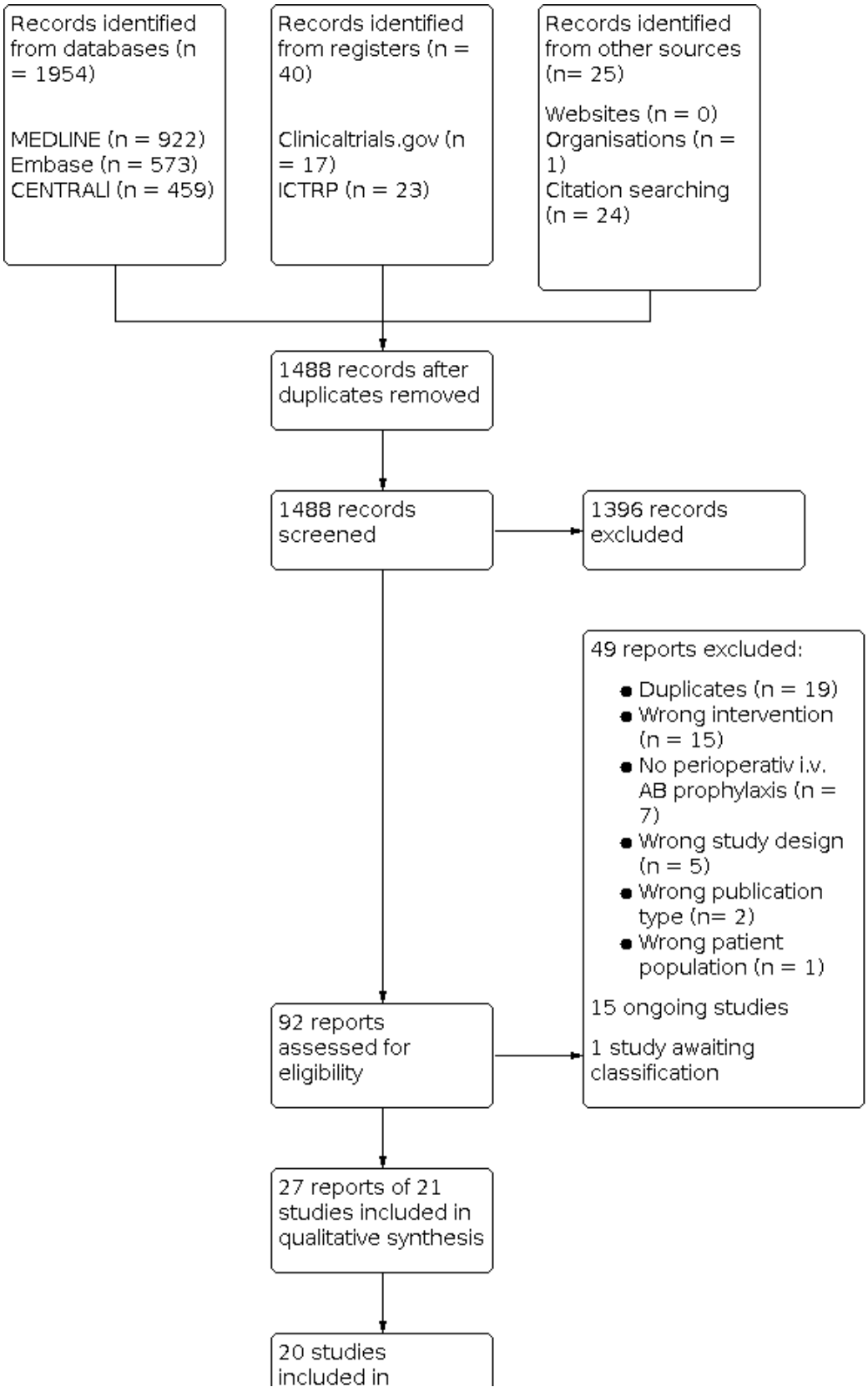
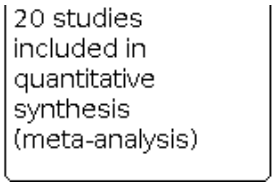


Figure 1. (Continued)



We also identified 15 ongoing studies (see Characteristics of ongoing studies), and found one study investigating the effect of selective bowel decontamination with oral antibiotics(OABs) and oral antimycotics (Abis 2019). Mechanical bowel preparation (MBP) was performed only in left-sided colon, sigmoid and low-anterior resections. To determine if any of the study participants might be eligible for our review, the authors were asked to provide primary data of the study. As we have not received a response yet, the study was rated as awaiting classification (see Studies awaiting classification).

Included studies

We included 21 studies. Seventeen studies compared MBP+oAB with sole MBP (Anjum 2017; Arezzo 2021; Espin-Basany 2005; Hata 2016; Horie 2007; Ikeda 2016; Ishida 2001; Kobayashi 2007; Lau 1988; Lazorthes 1982; Lewis 2002; Oshima 2013; Papp 2021; Rybakov 2021; Sadahiro 2014; Takesue 2000; Uchino 2019). In three studies, MBP+oAB was compared with oAB alone (Ram 2005; Suzuki 2020; Zmora 2003). Only one study compared MBP+oAB with nBP (Koskenvuo 2019).

Participants

In total, 5968 patients were randomised and 5264 participants analysed in the 21 included studies. Whereby only a subgroup of participants from four studies (Arezzo 2021; Ikeda 2016;Lazorthes 1982; Uchino 2019) were eligible for our meta-analysis and the corresponding primary data were provided by the authors if necessary. All study participants underwent elective colorectal surgery.

While most studies had a mixed indication profile, 10 studies only included patients who had surgery for colorectal cancer (Arezzo 2021; Hata 2016; Horie 2007; Ikeda 2016; Kobayashi 2007; Lau 1988; Rybakov 2021; Sadahiro 2014; Suzuki 2020; Takesue 2000). Two other studies were limited to resections for inflammatory bowel disease (Oshima 2013: ulcerative colitis; Uchino 2019: Crohn's disease).
Regarding the surgical approach, 10 studies included both open and minimally invasive procedures. Seven studies included only open surgery (Horie 2007; Lau 1988; Lazorthes 1982; Oshima 2013; Ram 2005; Takesue 2000; Uchino 2019), and four included only minimally invasive surgery (Arezzo 2021; Hata 2016; Ikeda 2016; Koskenvuo 2019).

Interventions

In 16 studies, MBP was performed on the day before surgery (Anjum 2017; Espin-Basany 2005; Hata 2016; Horie 2007; Ikeda 2016; Ishida 2001; Kobayashi 2007; Koskenvuo 2019; Lewis 2002; Oshima 2013; Papp 2021; Ram 2005; Rybakov 2021; Takesue 2000; Uchino 2019; Zmora 2003). However, two studies each reported on a two-day or three-day laxative programme (Lau 1988; Lazorthes 1982; Sadahiro 2014; Suzuki 2020). The substance most commonly used for MBP was polyethylene glycol (PEG) in 10 studies (Arezzo 2021; Horie 2007; Ishida 2001; Kobayashi 2007; Koskenvuo 2019; Rybakov 2021; Sadahiro 2014; Suzuki 2020; Takesue 2000; Zmora 2003). The second most commonly used substance in nine studies was sodium picosulphate (Anjum 2017; Espin-Basany 2005; Hata 2016; Ikeda 2016; Lewis 2002; Ram 2005; Sadahiro 2014; Suzuki 2020; Uchino 2019), and the third most commonly used were magnesium preparations in six studies (Hata 2016; Ikeda 2016; Lau 1988; Lazorthes 1982; Oshima 2013; Uchino 2019). A total of eight studies used a combination of several agents fo rMBP, while 13 studies used monotherapy (mostly with PEG solutions). The additional use of enemas was reported in four studies (Lau 1988; Lazorthes 1982; Papp 2021; Zmora 2003).

Regarding oral antibiotic therapy, there were multiple combinations of different substances and doses. In almost all studies, a combination of two active substances was used (exception: Horie 2007: monotherapy with kanamycin; Ram 2005: no information on agent, dosage and time of intake). The most common agents used were metronidazole in 14 studies (Anjum 2017; Espin-Basany 2005; Hata 2016; Ikeda 2016; Koskenvuo 2019; Lazorthes 1982; Lewis 2002; Oshima 2013; Papp 2021; Rybakov 2021; Sadahiro 2014; Suzuki 2020; Takesue 2000; Uchino 2019), followed by kanamycin in 11 studies (Hata 2016; Horie 2007; Ikeda 2016; Ishida 2001; Kobayashi 2007; Lazorthes 1982; Oshima 2013; Sadahiro 2014; Suzuki 2020; Takesue 2000; Uchino 2019). The combination of these two agents was also the combination therapy most frequently used. Other agents used were neomycin in seven studies (Arezzo 2021; Espin-Basany 2005; Koskenvuo 2019; Lau 1988; Lewis 2002; Papp 2021; Zmora 2003), erythromycin in five studies (Ishida 2001; Kobayashi 2007; Lau 1988; Rybakov 2021; Zmora 2003) ,and levofloxacin and bacitracin in one study each (Anjum 2017, respectively Arezzo 2021). As for dosage, metronidazole and kanamycin were mostly prescribed at a daily dose of 1500 mg each (in eight and six studies, respectively). However, the daily dose of metronidazole varied between 750 mg and 4000 mg in the included studies. Such differences in daily antibiotic dosage were observed throughout the studies.
In terms of timing of administration, in 15 studies oAB was administered after the mechanical preparation of the bowel in two or three single doses on the day before surgery (Anjum 2017; Arezzo 2021; Hata 2016; Ikeda 2016; Kobayashi 2007; Koskenvuo 2019; Lau 1988; Lewis 2002; Oshima 2013; Papp 2021; Rybakov 2021; Sadahiro 2014; Suzuki 2020; Takesue 2000; Uchino 2019). Three studies report a two- or three-day oral antibiotic preparation (Horie 2007; Ishida 2001; Lazorthes 1982). In addition, one three-armed study compared a three-day and a one-day oAB-regimen in addition to MBP with MBP alone (Espin-Basany 2005).
More detailed information on the agent, dosages used and time of intake for the individual studies can be found in the Characteristics of included studies tables.

Outcomes

Regarding the primary outcomes, all but one of the included studies reported the number of participants with surgical site infections (SSIs) (Lazorthes 1982 subdivided wound infections into major and minor, but only data from major wound infections were reported). Twelve studies also reported a subdivision into incisional and organ/space SSIs. Information on the number of participants with anastomotic leakage was reported in 13 studies.
All predefined secondary outcomes were reported in individual included studies. Table 1 provides an overview of which study reported on which outcome.

Regarding the side effects of the intervention, only four of the 21 included studies reported the occurrence of adverse events related to preoperative bowel preparation (Arezzo 2021; Espin-Basany 2005; Oshima 2013; Papp 2021). The reported side effects included nausea/vomiting or abdominal pain, but none of the included studies reported adverse effects of MBP such as dehydration, electrolyte imbalances, renal failure or cardiac dysfunction. The number of participants who discontinued the intervention due to side effects was also not reported in any study.

Excluded studies

A total of 30 of the identified studies were excluded. Fifteen because they investigated the wrong intervention, seven due to the lack of perioperative intravenous antibiotic prophylaxis, and five for an inappropriate study design. Two other articles were excluded because of the wrong publication type (congress poster and invited commentary, respectively), and one study was excluded for an inappropriate patient population (patients with anastomotic leakages were excluded from the analysis); see Characteristics of excluded studies.

Risk of bias in included studies

The risk of bias assessments, including all domain evaluations and support for the assessment, are reported in the Risk of bias (tables) section and displayed along the forest plots of each analysis.

None of the included studies was assessed to be of high risk of bias. However, two-thirds of the studies raised some concerns about the risk of bias. In most cases, these concerns were due to the lack of a predefined analysis plan or the lack of information about the randomisation process.

Detailed data on the risk of bias assessment, such as the Excel file with the consensus responses to the signalling questions, are available on request.

Surgical site infections (SSIs)

Twelve of the 20 studies that reported this outcome raised some concerns about the risk of bias (Anjum 2017; Espin-Basany 2005; Horie 2007; Ishida 2001; Kobayashi 2007; Lau 1988; Lewis 2002; Oshima 2013; Ram 2005; Suzuki 2020; Takesue 2000; Zmora 2003). The concerns were due to the lack of a predefined analysis plan, and in three of these studies, additional inadequate information about the randomisation process (Espin-Basany 2005; Oshima 2013; Takesue 2000).

Anastomotic leakage

Eight of the 14 studies reporting this outcome were at low risk of bias (Arezzo 2021; Hata 2016; Ikeda 2016; Koskenvuo 2019; Papp 2021; Rybakov 2021; Sadahiro 2014; Zmora 2003), six were considered to have some concerns about the risk of bias because no predefined analysis plan could be identified for these studies (Horie 2007; Ishida 2001; Lau 1988; Ram 2005; Suzuki 2020; Takesue 2000). One of the studies also inadequately described the randomisation process, which also raises concerns about risk of bias (Takesue 2000).

Mortality

Half of the six studies had a low risk of bias (Arezzo 2021; Koskenvuo 2019; Papp 2021). The other three studies were rated as having some concerns regarding the selection of the reported outcomes of the individual studies (Lazorthes 1982; Ram 2005; Zmora 2003); additionally, in one of the three studies, the randomisation process was not adequately described, leading to some concerns regarding the risk of bias (Lazorthes 1982).

Incidence of postoperative ileus.

Only three of the nine studies reporting this outcome raised some concerns about the risk of bias (Espin-Basany 2005; Ram 2005; Zmora 2003). Again, these concerns were due to the lack of a predefined analysis plan and additional an unclear randomisation method in one case (Espin-Basany 2005).

Length of hospital stay

Only one of the four studies reporting this outcome raised some concerns about the risk of bias (Lau 1988). The reason for this is again the lack of a predefined analysis plan.

Assessment of publication bias

The assessment of a small study effect using funnel plots was only possible for the comparison MBP+oAB versus MBP for the outcomes SSI and anastomotic leakage, as no other comparison included ten or more studies.
The funnel plots show a nearly symmetrical distribution, indicating that there was no evidence of publication bias (Figure 2; Figure 3). In the funnel plot for the outcome SSI (Figure 2), one study stands out with a much smaller patient population that does not fit the otherwise symmetrical distribution. This study is Arezzo 2021, of which only a subpopulation was included, which explains the smaller sample size resulting in an outlier from symmetry in the funnel plot.

Figure 2. Comparison 1 (MBP+oAB vs. MBP): Funnel plot regarding the incidence of SSI

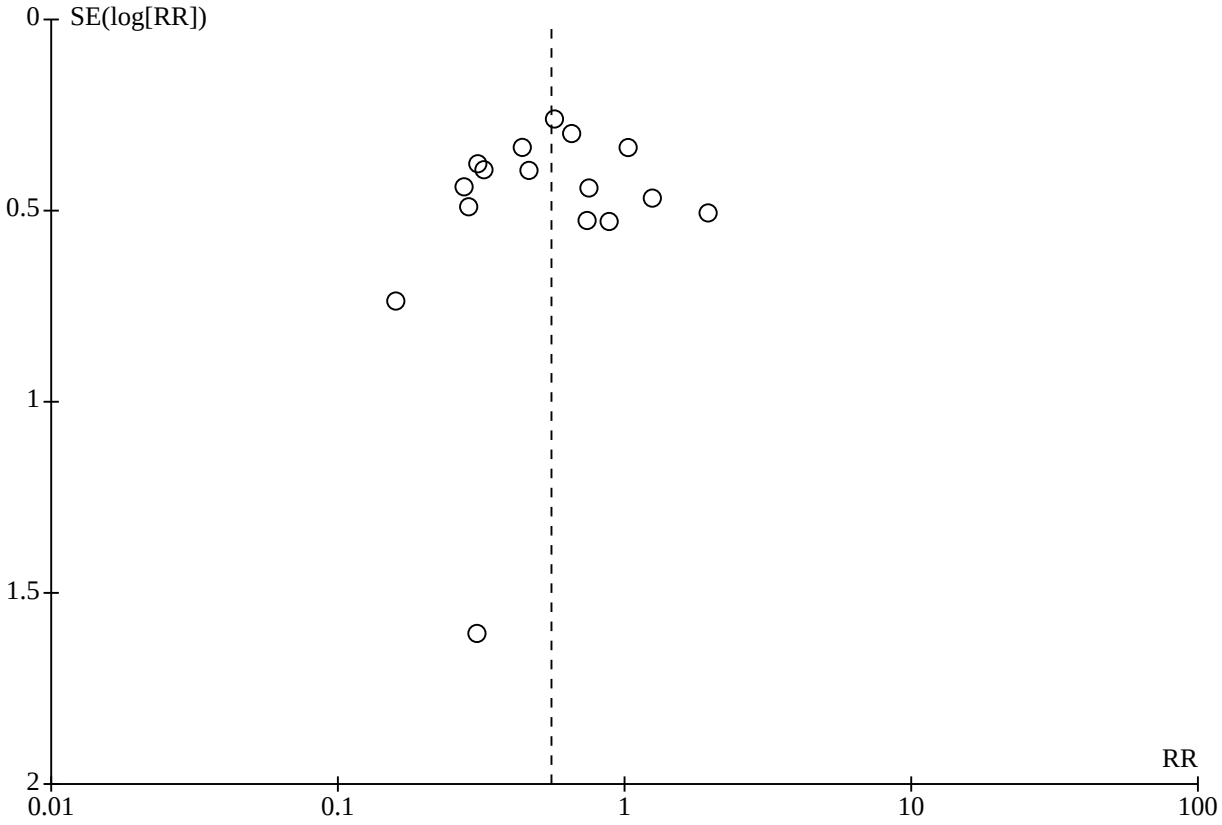
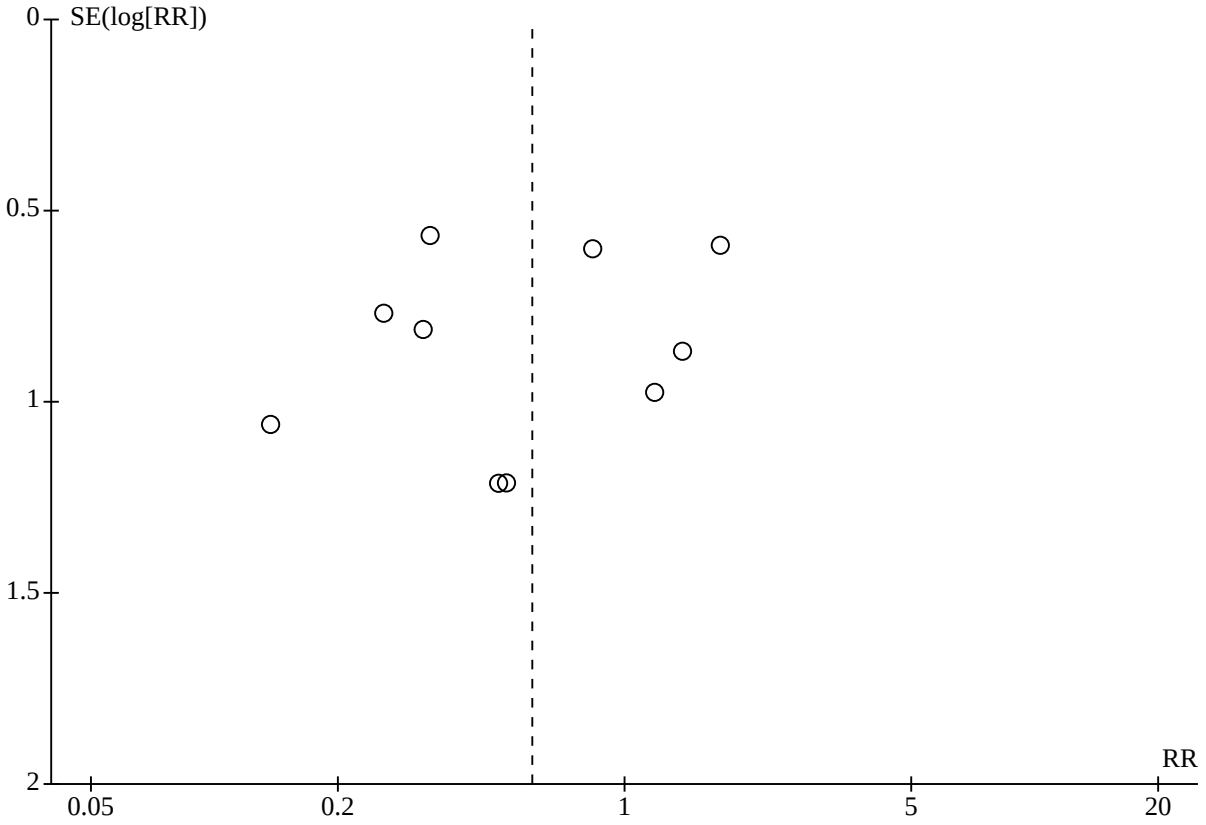


Figure 3. Comparison 1 (MBP+oAB vs. MBP): Funnel plot regarding the incidence of anastomotic leakage



Effects of interventions

See: **Summary of findings 1** Summary of findings table - Combined mechanical and oral antibiotic bowel preparation versus mechanical bowel preparation alone; **Summary of findings 2** Summary of findings table - Combined mechanical and oral antibiotic bowel preparation versus oral antibiotics alone; **Summary of findings 3** Summary of findings table - Combined mechanical and oral antibiotic bowel preparation versus no bowel preparation

See: Summary of findings 1 for combined mechanical and oral antibiotic bowel preparation versus mechanical bowel preparation alone, Summary of findings 2 for combined mechanical and oral antibiotic bowel preparation versus oral antibiotics alone and Summary of findings 3 for combined mechanical and oral antibiotic bowel preparation versus no bowel preparation.

Comparison 1: Combined mechanical and oral antibiotic bowel preparation versus mechanical bowel preparation alone (MBP +oAB versus MBP)

We identified 17 relevant studies for this comparison (Anjum 2017; Arezzo 2021; Espin-Basany 2005; Hata 2016; Horie 2007; Ikeda 2016; Ishida 2001; Kobayashi 2007; Lau 1988; Lazorthes 1982; Lewis 2002; Oshima 2013; Papp 2021; Rybakov 2021; Sadahiro 2014; Takesue 2000; Uchino 2019). As only a subpopulation of participants from Arezzo 2021, Ikeda 2016 and Uchino 2019 were eligible for our meta-analysis, primary data from these studies were requested and received, ensuring that only eligible patients were included in our analysis.

All pre-defined outcomes were addressed in at least three studies, so that meta-analyses could be calculated for all outcomes.

Surgical site infections (SSIs)

A total of 3917 participants from 16 studies were included for this outcome and in corresponding meta-analysis. The results suggested that the intervention (MBP+oAB) reduced the risk of SSI from 137 per 1000 with MBP alone to 77 per 1000 (RR 0.56, 95% CI 0.42 to 0.74; P < 0.0001, I^2 = 44%; Analysis 1.1). This risk reduction is clinically relevant, as we defined an RR and 95% CI of 0.95 or less as a minimally important difference (MID).

The overall certainty of evidence was moderate, downgraded one level for inconsistency due to moderate heterogeneity amongst these studies (Chi^2 = 27.01, df = 15 (P = 0.03); I^2 = 44%). The subgroup analyses performed regarding the indication for surgery (Analysis 1.13), the type of surgery performed (Analysis 1.14) or the surgical approach (Analysis 1.15) as well as concerning the duration of mechanical bowel preparation (Analysis 1.16) or the substances used for oral antibiotic bowel preparation (Analysis 1.17) and with regard to the duration of intravenous antibiotic prophylaxis (Analysis 1.18) could not explain the heterogeneity.

Regarding incisional and organ/space SSIs MBP+oAB also reduced the risk compared with MBP alone (incisional: RR 0.47, 95% CI 0.33 to 0.66; P < 0.0001, I^2 = 37%; 10 studies, 3054 patients; Analysis

1.2; organ/space: RR 0.65, 95% CI 0.44 to 0.98; P = 0.04, I^2 = 0%; 10 studies, 3054 patients; Analysis 1.3).

Anastomotic leakage

A total of 2356 participants from 10 studies were included for this outcome and the respective meta-analysis. The results indicated that the risk of anastomotic leakage could be reduced from 44 per 1000 patients receiving MBP alone to 26 per 1000 patients when MBP+oAB was used (RR 0.60, 95% CI 0.36 to 0.99; P = 0.05, I^2 = 9%; Analysis 1.4).
Whether the risk reduction that can be achieved by MBP+oAB is clinically relevant cannot be ascertained, as the upper limit of the 95% CI slightly exceeds our MID of 0.95.
The overall certainty of the evidence was moderate, downgraded by one level due to the limited number of events in the included studies and a rather wide confidence interval, suggesting imprecision of the results.

Mortality

A total of 639 participants from 3 studies were included in this meta-analysis. The results suggested that there was no difference in mortality between MBP+oAB and MBP alone (RR 0.87, 95% CI 0.27 to 2.82; P = 0.81, I^2 = 0%; Analysis 1.5).
The overall certainty of the evidence was moderate, downgraded by one level due to the limited number of events in the included studies and wide confidence intervals including both, benefit and harm, suggesting imprecision of the results.

Postoperative complications subdivided according to Clavien-Dindo in mild (I/II) and severe (III/IV) complications

A total of 695 participants from 3 studies were included in this meta-analysis. The risk of mild or severe postoperative complications did not differ between MBP+oAB and MBP alone (mild complications: RR 0.76, 95% CI 0.29 to 2.00; P = 0.58, I^2 = 65%; Analysis 1.6. Severe complications RR 1.00, 95% CI 0.59 to 1.70; P = 0.99, I^2 = 0%; Analysis 1.7).

Incidence of postoperative ileus

A total of 2013 participants from 6 studies were included in this meta-analysis. The results indicated that the incidence of postoperative ileus was similar between the MBP+oAB and MBP alone groups (RR 0.89, 95% CI 0.59 to 1.32; P = 0.56, I^2 = 0%; Analysis 1.8).
The overall certainty of the evidence was low, downgraded one level due to suspected publication bias as small studies report a statistically significant benefit while larger studies show a much smaller effect, and downgraded another level due to imprecision because of the limited number of events in the included studies with wide confidence intervals that included both benefits and harms.

Length of hospital stay (LOS)

A total of 621 participants from 3 studies were included in this meta-analysis. LOS seemed to be similar between the MBP+oAB and MBP alone groups as the mean discharge time for patients in the intervention group was only 4.6 hours earlier than for patients in the control group (MD -0.19, 95% CI -1.81 to 1.44; P = 0.82, I^2 = 0%; Analysis 1.9).
The overall certainty of the evidence was moderate, downgraded by one level due to a small sample size and rather wide confidence intervals, suggesting some imprecision of the effect estimate.

Side effect of intervention

A total of 545 participants from 3 studies were included for this outcome. The pooled effect estimate implied that side effects of the intervention, both nausea/vomiting and abdominal pain, occurred more frequently in the MBP+oAB group than in the MBP group (nausea/vomiting: RR 2.22, 95% CI 1.33 to 3.72; P = 0.002, I^2 = 0%; Analysis 1.10). Abdominal pain: RR 1.79, 95% CI 0.67 to 4.82; P = 0.25, I^2 = 0%; Analysis 1.11).

C. difficile-related diarrhoea

Four studies reported on this outcome, but only three were included in the pooled effect estimate. In Arezzo 2021 no patient in this study had *C. difficile*-related diarrhoea (n = 50). The results indicated that with regard to the occurrence of *C. difficile*-related diarrhoea, there seemed to be no difference between the MBP+oAB and MBP groups (RR 0.89, 95% CI 0.24 to 3.34; P = 0.86, I^2 = 9%; 3 studies, 1547 patients; Analysis 1.12).

Sensitivity analysis

A sensitivity analysis including only studies with a low risk of bias revealed that the studies labelled as "some concern" did not have a considerable impact on the overall effect with regard to SSI, mortality, incidence of postoperative ileus and LOS. For the risk of anastomotic leakage on the other hand, excluding the studies with some concern resulted in a stronger effect (RR 0.48, 95% CI 0.25 to 0.95 instead of RR 0.60, 95% CI 0.36 to 0.99; see Appendix 2).

Comparison 2: Combined mechanical and oral antibiotic bowel preparation versus oral antibiotics alone (MBP+oAB versus oAB)

We identified 3 studies for this comparison (Ram 2005; Suzuki 2020; Zmora 2003). The predefined outcomes SSI, anastomotic leakage, mortality and incidence of postoperative ileus were each reported in more than one study so that the data could be pooled in a meta-analysis.

Surgical site infections (SSIs)

A total of 960 participants from 3 studies were included in the meta-analysis for this outcome. The results indicated that there was no difference in the risk of postoperative SSI between the MBP+oAB and the oAB alone group (RR 0.87, 95% CI 0.34 to 2.21; P = 0.76, I^2 = 69%; Analysis 2.1).
The overall certainty of the evidence was very low and was downgraded by three levels in total due to some concerns about the risk of bias, moderate heterogeneity between included studies suggesting inconsistency of results (Chi^2 = 6.41, df = 2 (P = 0.04); I^2 = 69%), and a small sample size with wide confidence intervals, indicating imprecision.

Anastomotic leakage

A total of 960 participants from 3 studies were included in this meta-analysis. The result implicated that the incidence of anastomotic leakage was equal in the MBP+oAB and oAB alone groups (RR 0.84, 95% CI 0.21 to 3.45; P = 0.81, I^2 = 39%; Analysis 2.2).

The overall certainty of the evidence was low, downgraded by two levels due to some concerns the risk of bias in the included studies and a small sample size, limited number of events, and wide confidence intervals, indicating imprecision.

Mortality

A total of 709 participants from 2 studies were included in this meta-analysis. The results indicated that mortality was equal in the MBP +oAB and oAB alone group (RR 1.02, 95% CI 0.30 to 3.50; P = 0.97, I^2 = 0%; Analysis 2.3).
The overall certainty of the evidence was low, downgraded by two levels due to some concerns about the risk of bias in the included studies and a small sample size, limited number of events, and wide confidence intervals, indicating imprecision.

Postoperative complications subdivided according to Clavien-Dindo in mild (I/II) and severe (III/IV) complications

None of the three identified studies collected data on the occurrence of postoperative complications according to the Clavien-Dindo classification.

Incidence of postoperative ileus

A total of 709 participants from 2 studies were included in this meta-analysis. The results indicated that the incidence of postoperative ileus was equal in the MBP+oAB and the oAB alone group (RR 1.25, 95% CI 0.68 to 2.33; P = 0.47, I^2 = 0%; Analysis 2.4).
The overall certainty of the evidence was low, downgraded by two levels due to some concerns about the risk of bias in the included studies and a small sample size, limited number of events, and rather wide confidence intervals, indicating possible imprecision.

Length of hospital stay (LOS)

Both Zmora 2003 and Ram 2005 found no significant differences in the length of hospital stay between the MBP+oAB and the oAB groups. The mean difference between the groups was 0.1 respectively 0.2 (95% CI -0.68 to 1.08) days.

Side effects of the Intervention

None of the three identified studies provided data on the occurrence of side effects of the intervention.

C. difficile-related diarrhoea

The detection rate of *C. difficile* toxin was collected both pre- and postoperatively by Suzuki 2020. It was demonstrated that the number of *C. difficile* detections tended to increase after surgery in all groups, although the absolute number was quite low. *C. difficile*-related diarrhoea was not observed in any group.

Sensitivity analysis

No sensitivity analyses were performed for this comparison as all studies were judged as "some concerns".

Comparison 3: Combined mechanical and oral antibiotic bowel preparation versus no bowel preparation (MBP+oAB versus nBP)

For this comparison, we identified a single relevant study (Koskenvuo 2019) that addressed all of our pre-defined outcomes.

Surgical site infections (SSIs)

The study results suggested that the intervention (MBP+oAB) may result in little to no difference in surgical site infections. (RR 0.63, 95% CI 0.33 to 1.23; P = 0.17; 396 participants). While SSI occurred in 105 per 1000 patients with MBP alone, it only occurred in 66 per 1000 patients in the MBP+oAB group. However, as only one study with a limited number of participants was identified for this comparison and the 95% CI includes both, benefit and harm, the confidence in the evidence was downgraded by two levels due to imprecision.
The possible positive effect of MBP+oAB was confirmed for incisional wound infections (RR 0.45, 95% CI 0.14 to 1.45; P = 0.18; 396 participants), but no important difference was demonstrated for organ/space infections (RR 0.77, 95% CI 0.33 to 1.78; P = 0.53; 396 participants).

Anastomotic leakage

The risk of an anastomotic leakage was equal in the MBP+oAB and nBP group (RR 0.89, 95% CI 0.33 to 2.42; P = 0.82; 396 participants).
The certainty of evidence was however low, as only one study with a limited number of participants was identified, which led to a downgrading of the certainty of evidence by two levels due to imprecision.

Mortality

The study results suggested that MBP+oAB may result in little to no difference in mortality (RR 0.20, 95% CI 0.01 to 4.22; P = 0.30; 396 participants). However, due to the small number of events (MPB +oAB 0/196; nBP 2/200), the validity of the data was limited. The overall certainty of the evidence was low, downgraded by two levels due to imprecision.

Postoperative complications subdivided according to Clavien-Dindo in mild (I/II) and severe (III/IV)

The risk of mild postoperative complications was equal in the MBP +oAB and nBP group (RR 1.15, 95% CI 0.93 to 1.41; P = 0.20; 396 participants). The risk of severe postoperative complications on the other hand seemed to be increased by the Intervention (RR 1.47, 95% CI 0.80 to 2.69; P = 0.22; 396 participants).

Incidence of postoperative ileus

The risk of postoperative ileus was equal in the MBP+oAB and nBP group (RR 1.18, 95% CI 0.77 to 1.81; P = 0.45; 396 participants).
The certainty of evidence was however low, as only one study with a limited number of participants was identified, which led to a downgrading of the certainty of evidence by two levels due to imprecision.

Length of hospital stay (LOS)

The length of the hospital stay did not differ between the MBP +oAB and nBP group (MD 0.10, 95% CI -0.80 to 1.00; P = 0.83; 396 participants). The certainty of evidence was however low, as only one study with a limited number of participants was identified, which led to a downgrading of the certainty of evidence by two levels due to imprecision.

Side effect of Intervention

The incidence of side effects of the intervention was the same in the MBP+oAB and nBP group (RR 0.94, 95% CI 0.44 to 2.01; P = 0.88; 396 participants)

C. difficile-related diarrhoea

The study results suggested that MBP+oAB reduce the risk of *C. difficile*-related diarrhoea compared with nBP (RR 0.34, 95% CI 0.01 to 8.30; P = 0.51; 396 participants). However, due to the small number of events (MPB+oAB 0/196; nBP 1/200), the validity of the data is limited.

Sensitivity analysis

No sensitivity analyses were performed for this comparison as only one study with a low risk of bias was identified.

DISCUSSION

Summary of main results

We identified 21 studies (with 5264 participants analysed) that were eligible for this review.

For the first comparison (mechanical bowel preparation plus oral antibiotics (MBP+oAB versus MBP)), 17 studies (with 3908 participants) were included in our meta-analyses. Based on moderate certainty of evidence, our review shows that MBP+oAB probably reduces the risk of postoperative wound infections and anastomotic leakage, while having no effect on mortality, incidence of postoperative ileus or length of hospital stay compared with MBP alone. More specifically, combined bowel preparation can reduce the risk of SSI from 137 per 1000 patients with MBP alone to 77 per 1000 patients. The risk of anastomotic leakage also decreases from 44 per 1000 with MBP alone to 26 per 1000 with combination therapy (see Summary of findings 1). However, nausea/vomiting as a side effect of the intervention occurred more frequently in the MBP+oAB group than in the MBP alone group.
It should be noted that there was moderate statistical heterogeneity between studies regarding the incidence of SSI, which could not be explained by any subgroup analyses.
Although the risk of bias for the SSI outcome was predominantly rated as "some concerns", while the risk of bias for the other outcomes was evenly split between "low risk of bias" and "some concerns", the sensitivity analyses conducted showed no substantial impact of the risk of bias rating on the overall effect of all outcomes.

For the second comparison (MBP+oAB versus oAB), 3 studies (with 960 participants) were identified. Due to some concerns about the risk of bias in the included studies and the small sample size, we have only a low to very low certainty of the evidence. As far as we can conclude, MBP+oAB may result in little to no difference of SSI rates, anastomotic leakage, mortality or postoperative ileus compared with oAB alone.

For the third comparison (MBP+oAB versus nBP), a single study (with 396 participants) was identified. This suggests that MBP +oAB may reduce SSIs and mortality, while resulting in little to no difference for anastomotic leakage, postoperative ileus, length of hospital stay or the occurrence of side effects of the intervention compared with nBP. However, certainty of evidence is low.

Overall completeness and applicability of evidence

The question of superiority of combined mechanical and oral antibiotic bowel preparation to prevent postoperative complications can only be answered incompletely by this review.

A major limitation is the lack of evidence for the second (MBP+oAB versus oAB) and third (MBP+oAB versus nBP) comparison. While 17 studies were identified for our first comparison (MBP+oAB versus MBP), data for the second and third comparison come from three and one studies, respectively.

However, a further indication of the possible superiority of combination therapy over nBP (third comparison) can be derived from a comparison with the Cochrane review on mechanical bowel preparation by Güenaga 2011. In this meta-analysis, MBP alone was found to be equivalent to nBP, particularly in terms of wound infections and anastomotic leakage. Considering that our review found superiority of combination therapy over MBP alone with respect to these outcomes, one might conclude that combination therapy may be advantageous over nBP. Unfortunately, there is no evidence to support this conclusion.

Another limitation regarding the applicability of our results is that most studies included both colon and rectal resections. There was only one study that included only colon respectively only rectal resections. Furthermore, a differentiation between resection of the right colon versus resection of the left colon was not carried out in the trials. A review of the effect depending on the type and location of the surgery performed, in particular a further subdivision of colon resections, was not possible based on the available data. The same applies to the other performed subgroup analyses, so that further investigation of the effect depending on the indication for surgery, the surgical approach or the agents used for the intervention as well as the duration of the intervention was only conclusive to a limited extent.

In addition, insufficient information about the side effects of the intervention, especially regarding dreaded effects of MBP such as dehydration, electrolyte imbalances, and even cardiac problems, limit the applicability of our results.

We included both small and large studies published over a long period from 1992 to the present. We also identified 15 ongoing studies, indicating that interest in this area remains high. Especially for the second and third comparisons, it is very likely that further research will have an important impact on the findings and our confidence in the estimated effect.

Quality of the evidence

There is moderate to low certainty-evidence comparing MBP+oAB versus MBP for the outcomes assessed in Summary of findings 1. For SSIs, there was moderate heterogeneity between the included studies that could not be explained by the subgroup analyses conducted, so confidence in the evidence was downgraded by one level. However, the subgroup analyses are not reliable since they could not be carried out as planned on the basis of the available data. For example, our subgroup analysis on the type of surgery performed is not very conclusive, as only one study reported results for rectal resections only. The other studies all reported on a mixed

population, and based on the reported data it was not possible to subdivide the results according to the type and location of surgery performed. The same applies to the subgroup analysis regarding the indication for surgery (benign versus malignant) and the surgical approach (open versus laparoscopic). Similarly, the subgroup analysis regarding the agents used for oral antibiotic bowel preparation is of limited value, as different dosages were used within the subgroups, which in turn may contribute to heterogeneity.
Due to the limited number of events and wide confidence intervals of the included studies, the certainty of the estimated effect of anastomotic leakage, mortality, incidence of postoperative ileus and LOS was also downgraded by one level.
Additionally, certainty of the estimated effect on postoperative ileus was downgraded another level because small studies reported statistically significant benefits, while larger studies showed a much smaller effect, indicating possible publication bias.

Only low to very low certainty of the effect estimate was found for the MBP+oAB versus oAB comparison (Summary of findings 2). This is primarily due to the small overall sample size of only three identified studies and "some concerns" about the risk of bias in all included studies, as no predefined analysis plan could be identified for any of these studies.

There is also only low confidence in the evidence for the MBP +oAB versus nBP comparison (Summary of findings 3). Due to the very small sample size with wide confidence intervals in only one identified study, the confidence in the effect estimate was downgraded by two levels due to imprecision.

Potential biases in the review process

A broad search strategy was used to identify studies in this area, searching both electronic databases and study registries without making any restrictions, e.g. based on language. Unfortunately, first order problems in the conceptualisation of the search strategy may have resulted in missed eligible studies, which is a considerable limitation of this review.
Several national and international colorectal surgery organisations were contacted and asked whether they were aware of any ongoing or completed studies on this topic. In addition, all included studies of similar meta-analyses were screened for eligibility.
We believe that, even though our review is limited by conceptualisation issues of the search strategies, it is unlikely that previously conducted and published studies were overlooked; however, unpublished studies or ongoing studies not registered in study registries may be missing. If such studies are identified, we will include them in future updates of the review. Furthermore, our search strategies will be redesigned for future updates.

We attempted to reduce bias as much as possible by having at least two authors work independently on study selection, data extraction, and risk of bias as well as GRADE assessment.

We were only able to examine the potential for publication bias using funnel plots for the two primary outcomes of the first comparison, as there were no other outcomes of interest with 10 or more studies included in any meta-analyses (Figure 2; Figure 3).

Agreements and disagreements with other studies or reviews

There are already numerous reviews and meta-analyses on various aspects of the topic of preoperative bowel preparation, but they all come to different conclusions.
Comparing three high-quality meta-analyses published in the last four years, we find that Toh 2018 associated MBP+oAB with the lowest risk of SSI in a network meta-analysis. Oral antibiotics alone were ranked as second best, but available data on this approach were limited.
In contrast, Rollins 2019 found that MBP+oAB was largely equivalent to oAB alone, and Nelson 2020 proclaimed the superiority of oAB alone over MBP+oAB.
While our results overlap with those of Toh 2018 and Rollins 2019, we were unable to show superiority of oAB alone over combination therapy, as Nelson 2020 did.
An examination of the included studies shows that the different conclusions are mainly not due to more recent publications that were not yet included in the older reviews, but to different inclusion and exclusion criteria or variations in the literature search.
A major difference between our review and the earlier ones is that only studies in which all patients received perioperative intravenous antibiotic prophylaxis were included. Perioperative intravenous antibiotic prophylaxis has a significant impact especially on the likelihood of the occurrence of SSI and should be standard of care (Nelson 2014; WHO 2018). Therefore, studies without perioperative intravenous antibiotic prophylaxis would confound the results of the meta-analysis and were excluded from our review.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of benefit from MBP alone has already been demonstrated in the past leading to the recommendation in several guidelines to avoid MBP (Gustafsson 2019; Güenaga 2011; NICE 2019; WHO 2018). Based on the data from study registries, the "American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Use of Bowel Preparation in Elective Colon and Rectal Surgery" (Migaly 2019) recommends combined mechanical and oral antibiotic bowel preparation.

Our results support the hypothesis that combination therapy is likely superior to MBP alone for reducing the incidence of SSI and anastomotic leakage. Our evidence indicates that MBP only has the desired effect on postoperative complications in combination with oAB.
The efficacy of oAB alone compared with combination therapy has not yet been clearly demonstrated and needs to be investigated in further RCTs before valid conclusions can be drawn. The same applies to the comparison of combination therapy and nBP.

Implications for research

Based on the available evidence, conclusions can only be drawn for one of the three comparisons in our review.
The comparisons of MBP+oAB with oAB alone or nBP are insufficiently studied. Of the ongoing studies identified, the majority continues to investigate the comparison of MBP+oAB versus MBP. Only four trials focus on the comparison MBP+oAB versus oAB (NCT03042091; NCT04931173; ORALEV2; Tagliaferri

2020) and only two investigate the comparison of MBP+oAB versus nBP (MECCLANT –C and –R Trials; Panaiotti 2020).
In order to be able to make an evidence-based assessment of the most effective preoperative bowel preparation, further RCTs, especially on the last two comparisons are required.

In addition, future studies should also examine the different options of bowel preparation in terms of timing, active ingredient, and dosage in more detail. Although our review was able to support the assumption that MBP+oAB has an advantage over MBP alone, there is no clear recommendation regarding the antibiotic regimen to be used. Combination therapies of metronidazole and an aminoglycoside (neomycin or kanamycin) or erythromycin and an aminoglycoside (neomycin or kanamycin) appear to be the most commonly used therapies and do not differ in efficacy (Analysis 1.17). But even within these combination therapies, the dosage used varies across all included studies, necessitating further investigation. The same applies to the substance and duration of mechanical bowel preparation.

Another aspect that should be investigated in future studies are the side effects of the intervention, so that in addition to the benefits, the potential harms of the intervention can also be considered in treatment decisions.

Furthermore, the differences in the effect of MBP+oAB depending on the type of surgery performed, not only colon versus rectum, but also regarding the site of colon surgery, should be further investigated. Since the right colon is physiologically filled with fewer faeces than the left, there are surgeons who prescribe MBP only before resections of the left colon or rectum, but not before resections of the right colon. Studies analysing the different effect of preoperative bowel preparation depending on the localisation of the colon resection have not been identified, so that a corresponding subgroup analysis was not possible in our review.
The benefit of oAB alone might also differ due to the physiologically lower contamination of the right colon compared with the left colon and rectum, so that depending on the location of the planned resection, a different type of bowel preparation might be most effective.

Another aspect that should be further investigated would be a separate evaluation of the benefits and harms of preoperative bowel preparation in minimally invasive and open procedures. Pooled data from studies including both laparoscopic and open procedures demonstrate a clear advantage of combination therapy over MBP alone in terms of SSI rates. However, separate analysis of studies that included only laparoscopic or only open approaches shows a much smaller effect with wide 95% CIs that include both benefit and harm (Analysis 1.15). Therefore, further studies are needed here to better assess the differential effects depending on the surgical approach.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anjum 2017

Study characteristics	
Methods	**Study design:** parallel-group randomised trials **Duration of trial:** July 2014 to January 2016 **Duration of follow-up:** "All outcomes were evaluated daily during the hospital stay, and postoperative follow-up was conducted on postoperative days 30 and 90" **Country of origin:** China
Participants	**Baseline characteristics** Number randomised: 190 participants Number analysed: 184 participants **Intervention:** MBP+oAB • Number of participants [n]: 91 • Age [years; mean (SD)]: 46.3 (14.4) • Gender [male/female; n]: 61/34

Anjum 2017 *(Continued)*

Control: MBP

- Number of participants [n]: 93
- Age [years, mean (SD)]: 45.2 (15.6)
- Gender [male/female; n]: 59/36

Inclusion criteria
18 years of age or older and scheduled for elective colorectal surgery

Exclusion criteria
Patients were excluded if they had any preoperative infection or bowel obstruction, if they were undergoing emergency laparotomy, if they used antibiotics 2 weeks preoperatively, or were being treated with steroids or immunosuppressants preoperatively

Baseline imbalances
None

Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): sodium phosphate • Dose per administration: 133 mL • Time(s) of intake: twice a day on the day before the surgery • Route: oral • Concomitant medications: - **oAB** • Agent(s): metronidazole and levofloxacin • Dose per administration: 400 mg and 200 mg • Time(s) of intake: at 3:00 PM, 7:00 PM, and 11:00 PM on the day before the surgery • Route: poral. • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): second-generation cephalosporin and metronidazole • Dose per administration: - • Time(s) of intake: 30 to 60 minutes before the surgery and repeated every 3 hours during surgery; the antibiotics were continued for 24 hours following surgery. **Adherence to regimen:** Two patients were excluded due protocol violations
Outcomes	**Outcomes sought in review and reported in trial** • SSI (incisional, deep and organ/space) • Incidence of postoperative ileus **Outcomes sought but not reported in trial**

Anjum 2017 *(Continued)*

- Anastomotic leakage
- Mortality
- Length of hospital stay
- Postoperative complications (mild D/C I + II or severe D/C III + IV)
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review

- Extra-abdominal complications
- Readmission rates

Notes

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Conflicts of interest: -

Ethics approval: The study was approved by the ethical committee of the Jinling Hospital

Informed consent: All participants gave their informed consent before randomisation

Clinical trials registration: -

Sample size calculation: "To reach a power of 80%, it was estimated that 90 patients would be required in each group to detect the difference of SSI between 18% and 6% with a type I error of 0.05. A total sample size of 95 patients was established for each arm."

Arezzo 2021

Study characteristics

Methods

Study design: parallel-group randomised trials

Duration of trial: July 2019 to June 2020

Duration of follow-up: patients were followed for at least 30 days after surgery

Country of origin: Italy

Participants

Baseline characteristics
Number randomised: 204 participants
Number analysed: 204 participants
Number eligible and included in this review: 50

Only study patients who underwent preoperative mechanical bowel preparation were included in the meta-analysis.

Intervention: MBP+oAB

- Number of participants [n]: 26
- Age [years; mean (SD)]: 69 (10)
- Gender [male/female; n]: 18/8

Control: MBP

- Number of participants [n]: 24
- Age [years, mean (SD)]: 68 (13)
- Gender [male/female; n]: 15/9

Arezzo 2021 *(Continued)*

	Inclusion criteria Quote: "Patients who were scheduled for colorectal resection in participating centers for any indication (cancer, chronic diverticulitis, inflammatory bowel disease), > 18 years old and in general health condition permitting general anesthesia (ASA, American Society for Anaesthesiology classification I–III) were eligible for inclusion Open, laparoscopic, laparoscopic-assisted, or laparoscopic converted to open were all suitable techniques, as well as any mechanical bowel preparation as indicated by each centre." **Exclusion criteria** Quote: "Emergency surgery; appendectomy; primarily urological/gynaecological or vascular procedure; diagnostic laparotomy/laparoscopy without intestinal resection; surgery involving multi-visceral surgery (e.g. pelvic exenteration); contraindication for MBP; allergy to used drugs; patients who refuse to participate in the study; patients with intra-abdominal sepsis before surgery (abscess); patients who received antibiotics for any reason within two weeks prior to surgery; patients who do not comply strictly with the assigned prophylaxis regimen; patients who cannot be followed at least four weeks after surgery." **Baseline imbalances** -
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): polyethylene glycol • Dose per administration: 4000 mL • Time(s) of intake: - • Route: oral • Concomitant medications: - **oAB** • Agent(s): neomycin and bacitracin • Dose per administration: 25000 UI and 2500 UI • Time(s) of intake: 24, 16 and 8 h before induction of anaesthesia • Route:oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): amoxicillin/clavulanic acid or, in the event of an allergy to penicillin, clindamycin + gentamycin • Dose per administration: 2000/200 mg or, in the event of an allergy to penicillin, 600 mg + 2 mg/kg. • Time(s) of intake: at the time of induction of anaesthesia, redosing with prolonged surgery **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial**

Arezzo 2021 *(Continued)*

- SSI
- Anastomotic leakage
- Mortality
- Postoperative complications (mild D/C I + II or severe D/C III+IV)
- Incidence of postoperative ileus
- Length of hospital stay
- Side effects of Intervention(s)

Outcomes sought but not reported in trial

-

Outcomes reported in trial but not used in review

-

Notes	**Source of funding:** Quote: "Open access funding provided by Università degli Studi di Torino within the CRUI-CARE Agreement. Authors have nothing to disclose. This study was supported by Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) under the programme 'Dipartimenti di Eccellenza ex L.232/2016' to the Department of Surgical Sciences, University of Torino" **Conflicts of interest:** quote: "No confict of interest or financial ties to disclose" **Ethics approval:** The study was approved by the local ethics committee **Informed consent:** Written informed consent was obtained from all patients **Clinical trials registration:** NCT04438655 **Sample size calculation:** "Statistical analysis showed that considering the closest limits of the two CI intervals (13.2 and 8.4%), with a β-error of 0.20 and a one-sided α-error of 0.05, 656 patients were needed per group."

Espin-Basany 2005

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: - **Duration of follow-up**: 30 days **Country of origin:** Spain
Participants	**Baseline characteristics** Number randomised: 306 participants Number analysed: 300 participants **Intervention 1:** MBP+oAB • Number of participants [n]: 100 • Age [years; mean]: 66.6 • Gender [male/female; n]: 63/37 **Intervention 2:** MBP+oAB • Number of participants [n]: 100

Espin-Basany 2005 *(Continued)*

- Age [years; mean]: 67
- Gender [male/female; n]: 67/33

Control: nBP

- Number of participants [n]: 100
- Age [years, mean]: 69
- Gender [male/female; n]: 62/38

Inclusion criteria
Quote: "Patients with elective colorectal resections"

Exclusion criteria
Quote: Pregnancy, penicillin allergy (cross reactions with cephalosporins) and contra-in dications for a sodium phosphate (NaP) preparation (renal impairment with serum creatinine over 200 µg/l, massive ascites or severe heart failure)"

Baseline imbalances
"Treatment groups were similar, regarding age, sex, medical history of diabetes mellitus, hyper-tension or chronic obstructive pulmonary disease (COPD), preoperative serum albumin level and haematocrit, preoperative final diagnosis and operations performed"

Interventions

Comparison

- Intervention 1: MBP+oAB (3x)
- Intervention 2: MBP+oAB (1x)
- Control: MBP

MBP

- Agent(s): NaP oral solution (fosfosoda)
- Dose per administration: 45 mL in 90 mL water
- Time(s) of intake: before 11:00 AM and 5:00 PM on the day before surgery
- Route:oral
- Concomitant medications: -

oAB (3x)

- Agent(s): neomycin and metronidazole
- Dose per administration: 1 g each
- Time(s) of intake: at 3:00 PM, 7:00 PM and 11:00 PM
- Route: oral
- Concomitant medications: -

oAB (1x)

- Agent(s): neomycin and metronidazole
- Dose per administration: 1 g each
- Time(s) of intake: at 3:00 PM
- Route: oral
- Concomitant medications: -

Espin-Basany 2005 *(Continued)*

	Perioperative intravenous antibiotic prophylaxis • Agent(s): cefoxitin • Dose per administration: 1 g • Time(s) of intake: before skin incision and two postoperative doses at 8 and 16 h postoperatively **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Incidence of postoperative ileus • Side effects of Intervention(s) **Outcomes sought but not reported in trial** • Anastomotic leakage • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Length of hospital stay **Outcomes reported in trial but not used in review** -
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** - **Informed consent:** Quote: "Threehundred consecutive patients with elective colorectal resections who consented to participate in the study were included." **Clinical trials registration:** - **Sample size calculation:** -

Hata 2016

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: November 2007 to December 2012 **Duration of follow-up**: 30 days **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 584 participants Number analysed: 579 participants **Intervention:** MBP+oAB

Hata 2016 *(Continued)*

- Number of participants [n]: 289
- Age [years; mean (range)]: 67 (60.5 - 75.0)
- Gender [male/female; n]: 153/136

Control: MBP

- Number of participants [n]: 290
- Age [years, mean (range)]: 67.5 (60.0 - 75.0)
- Gender [male/female; n]: 175/115

Inclusion criteria
Quote:"Patients undergoing elective laparoscopic colorectal surgery for colorectal cancer or adenoma; aged 20 years or older, having good oral intake, and having adequate organ function."

Exclusion criteria
Quote:"Bowel obstruction, preoperative infections, antibiotic use within 2 weeks before the surgery; preoperative steroid use, neoadjuvant radiation and/or chemo therapy, uncontrolled diabetes mellitus, pregnant or lactating woman, and severe allergy"

Baseline imbalances
Quote:"The 2 groups were well balanced at the baseline."

Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): sodium picosulfate and magnesium citrate and water • Dose per administration: 75 mg and 34 g and 180 mL • Time(s) of intake: The day before the surgery • Route: oral • Concomitant medications: - **oAB** • Agent(s): kanamycin and metronidazole • Dose per administration: 1 g and 750 mg • Time(s) of intake: at 13 hours and 9 hours before the surgery • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): cefmetazole • Dose per administration: 1 g • Time(s) of intake: 30 min before surgery, additional dose every 3 hours during surgery **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI (superficial, deep and organ/space) • Anastomotic leakage • Incidence of postoperative ileus **Outcomes sought but not reported in trial** • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV)

Hata 2016 *(Continued)*

- Length of hospital stay
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review

- Other infectious complication
- Postoperative noninfectious complication
- Bowel obstruction

Notes	**Source of funding:** Quote: "This study was funded by JMTO, a general incorporated association established in 1999 to support clinical trials, especially multicenter or multinational randomised controlled trials, for the diagnosis, treatment, and prevention of the diseases. The sponsor had no involvement in the design or conduct of the study." **Conflicts of interest:** Quote: "The authors have no conflicts of interest to declare." **Ethics approval:** "This study was approved by the JMTO Ethics Committee in February 2007 and also by the institutional review boards of all of the participating hospitals." **Informed consent:** Quote:"All patients provided written informed consent before randomization." **Clinical trials registration:** NCT00508690 **Sample size calculation:** Quote:"It was planned to enroll 566 patients during the trial design. This sample size would provide an 80% power with a 2-sided significance level of 0.05 to demonstrate the superiority of the Oral-IV group in the reduction of SSI rate."

Horie 2007

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: April 2002 to December 2006 **Duration of follow-up**: - **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 91 participants Number analysed: 91 participants **Intervention:** MBP+oAB • Number of participants [n]: 46 • Age [years; mean (range)]: 69 (16-85) • Gender [male/female; n]: 25/21 **Control:** MBP • Number of participants [n]: 45 • Age [years, mean (range)]: 64.7 (39-86) • Gender [male/female; n]: 29/16 **Inclusion criteria** Elective surgery for colorectal cancer **Exclusion criteria**

Horie 2007 *(Continued)*

	Quote: "Any patient with a colonic obstriction, experience of abdominal operation and resection of other organs synchronously were excluded" **Baseline imbalances** none
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): polyethylene glycol lavage solution • Dose per administration: 2000 mL • Time(s) of intake: 16 hours before surgery • Route: oral • Concomitant medications: - **oAB** • Agent(s): kanamycin • Dose per administration: 1500 mg/day • Time(s) of intake: daily for 3 consecutive days before operation • Route:oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): cefotiam • Dose per administration: 1 g • Time(s) of intake: Quote: ""after induction of anaesthesia and again two times a day for 3 consecutive days after operation" **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage **Outcomes sought but not reported in trial** • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus • Length of hospital stay • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Bacteria cultured from preoperative stool, intraoperative mucosal swabs and from the peritoneal fluid
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** - **Informed consent:** "Informed consent was obtained from all patients"

Horie 2007 *(Continued)*

Clinical trials registration: -

Sample size calculation: -

Ikeda 2016

Study characteristics

Methods

Study design: Parallel-group randomised trials

Duration of trial: June 2013 to April 2014

Duration of follow-up: 30 days

Country of origin: Japan

Participants

Baseline characteristics
Number randomised: 515 participants
Number analysed: 511 participants
Number eligible and in this review included participants: 439

Only study patients who underwent preoperative mechanical bowel preparation were included in the meta-analysis.

Intervention: MBP+oAB

- Number of participants [n]: 223
- Age [years; mean (SD)]: 62.7 (12.6)
- Gender [male/female; n]: 122/101

Control: MBP

- Number of participants [n]: 216
- Age [years, mean (SD)]: 60.1 (11.8)
- Gender [male/female; n]: 122/94

Inclusion criteria
Quote: ""All consecutive patients with colorectal cancer undergoing elective laparoscopic colorectal resection"

Exclusion criteria
Quote: ""Age less than 20 years; patients with bowel obstruction and who could not tolerate liquid intake; pregnancy; history of allergy to the drugs in the protocol; administration of antibiotics in the 2 weeks before surgery; severe dysfunction of liver, kidney, heart or lung; and synchronous resection of other major organs such as the stomach, liver or uterus"

Baseline imbalances
Quote: ""The patient characteristics of the two groups were well balanced at baseline"

Interventions

Comparison

- Intervention: MBP+oAB
- Control: MBP

MBP

- Agent(s): magnesium citrate (1) and sodium picosulfate (2)
- Dose per administration: -
- Time(s) of intake: at 08.00 hours (1) and at 11.00 hours (2) on the day before surgery

Ikeda 2016 *(Continued)*

- Route: oral
- Concomitant medications: -

oAB

- Agent(s): metronidazole and kanamycin
- Dose per administration: 750 mg and 1000 mg
- Time(s) of intake: at 15.00 and 21.00 hours on the day before the surgery
- Route: oral
- Concomitant medications: -

Perioperative intravenous antibiotic prophylaxis

- Agent(s): cefmetazole
- Dose per administration: 1000 mg
- Time(s) of intake: Quote: ""At least 30 min before skin incision, then every 3 h during surgery until skin closure. After completion of surgery, two additional doses of intravenous prophylaxis were given within 24 h."

Adherence to regimen:Quote: " "All patients except for two received the planned antimicrobial doses."

Outcomes	**Outcomes sought in review and reported in trial** • SSI (superficional, deep and organ/space) • Anastomotic leakage • Incidence of postoperative ileus • Length of hospital stay **Outcomes sought but not reported in trial** • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Intra-abdominal abscess • Urinary tract disorder • Anastomotic haemorrhage • Readmission within 30 days
Notes	**Source of funding:** - **Conflicts of interest:** None **Ethics approval:** Quote:**"** "The study was conducted with the approval of the ethics committee of the Cancer InstituteHospital of the Japanese Foundation for Cancer Research, Tokyo, Japan" **Informed consent:** Written informed consent was obtained from all participants **Clinical trials registration:** Quote: ""This trial is registered with the UMIN Clinical Trials Registry (UMIN000019339)." **Sample size calculation:** Quote: ""Assuming a one-sided α of 0·05, a power of 80 per cent and a 5 per cent incidence of overall SSI in both groups, 235 patients per group were needed (Dunnett–Gent test)7. Assuming an 8 per cent drop-out rate, the planned required sample size was 253 patients."

Ishida 2001

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: April 1998 to August 2000 **Duration of follow-up**: Quote: ""The wounds were inspected daily until the patients were discharged from the hospital." **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 146 participants Number analysed: 143 participants **Intervention:** MBP+oAB • Number of participants [n]: 72 • Age [years; mean (range)]: 62 (37-87) • Gender [male/female; n]: 47/25 **Control:** MBP • Number of participants [n]: 71 • Age [years, mean (range)]: 65 (21-89) • Gender [male/female; n]: 42/29 **Inclusion criteria** Quote: ""Patients with colorectal diseases, surgically treated" **Exclusion criteria** Quote: ""The patients in both groups were excluded if a full mechanical bowel preparation was not feasible or if they had taken any antibiotics within 14 days before surgery" **Baseline imbalances** none
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): polyethylene glycol lavage • Dose per administration: 2000 mL • Time(s) of intake: on the day prior to surgery (15:00–19:00 h) • Route: oral • Concomitant medications: - **oAB** • Agent(s): kanamycin and erythromycin • Dose per administration: 500 mg and 400 mg • Time(s) of intake: four doses per day for 2 days before surgery • Route:oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis**

Ishida 2001 *(Continued)*

- Agent(s): cefotiam
- Dose per administration: 1 g
- Time(s) of intake: Quote: ""after the induction of anesthesia, and then again within 1 h after completing surgery. An additional four doses were given twice a day for 2 consecutive days. Patients with renal dysfunction were not given additional doses of cefotiam when appropriate."

Adherence to regimen: -

Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage **Outcomes sought but not reported in trial** • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus • Length of hospital stay • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • MRSA infection
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** - **Informed consent:** - **Clinical trials registration:** - **Sample size calculation:** -

Kobayashi 2007

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: May 2001 to December 2004 **Duration of follow-up**: 6 weeks **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 491 participants Number analysed: 484participants **Intervention:** MBP+oAB • Number of participants [n]: 242 • Age [years; mean (range)]: 67.9 (31-92) • Gender [male/female; n]: 154/88 **Control:** MBP

Kobayashi 2007 *(Continued)*

- Number of participants [n]: 242
- Age [years, mean (range)]: 69.1 (46-95)
- Gender [male/female; n]: 137/105

Inclusion criteria
"At least 20 years of age and referred for elective surgery for colorectal cancer"

Exclusion criteria
Quote: ""Contraindication to mechanical bowel preparation, known allergy to a penicillin or cephalosporin, treatment with any antibiotic within the past 2 weeks, pregnancy, and evidence of an infection at the time of surgery moderate or severe liver disease (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, or total bilirubin more than five times the upper limit of normal), or severe renal impairment (serum creatinine >220 µmol/l)"

Baseline imbalances
none

Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): polyethylene glycol • Dose per administration: 2000 mL • Time(s) of intake: at 10:00, completed by 14:00, on the day before surgery • Route: oral • Concomitant medications: - **oAB** • Agent(s): kanamycin and erythromycin • Dose per administration: 1000 mg and 400 mg • Time(s) of intake: at 14:00, 15:00, and 23:00 h on the day before surgery • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): cefmetazole • Dose per administration: 1 g • Time(s) of intake:Quote: " "after the induction of anesthesia, and an additional dose if the operation was prolonged beyond 3 h, and cefmetazole was administered again twice daily for 3 consecutive days after the operation" **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI (superficial and organ/space) **Outcomes sought but not reported in trial** • Anastomotic leakage • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus • Length of hospital stay • Side effects of Intervention(s)

Kobayashi 2007 *(Continued)*

Outcomes reported in trial but not used in review

- SSI according to the surgical procedure (colon vs. rectum)

Notes

Source of funding: -

Conflicts of interest: -

Ethics approval: "The study was approved by the ethics boards of the participating centers."

Informed consent: "Written informed consent was required"

Clinical trials registration: -

Sample size calculation: "On the basis of an SSI rate of 11% at the last evaluable follow-up assessment for both treatment groups, a power of 0.80, and the requirement to show that intravenous antimicrobial prophylaxis was noninferior to oral and intravenous antimicrobial prophylaxis with a δ of 8%, a total sample size of 482 patients (241 assigned to intravenous anti microbial prophylaxis, and 241 assigned to oral and intravenous antimicrobial prophylaxis) satisfying the criteria for the intention-to-treat population was calculated to be required. Taking into account an estimated ineligibility rate before the start of the study of 5%, a total of about 500 patients was thus considered to be needed."

Koskenvuo 2019

Study characteristics

Methods

Study design: Parallel-group randomised trials

Duration of trial: March 2016 to August 2018

Duration of follow-up: Quote: ""During the hospital stay and at 1-month clinical follow-up visit at the outpatient clinic"

Country of origin: Finland

Participants

Baseline characteristics
Number randomised: 417 participants
Number analysed: 396 participants

Intervention: MBP+oAB

- Number of participants [n]: 196
- Age [years; mean (range)]: 69.9 (61.1-75.2)
- Gender [male/female; n]: 105/91

Control: nBP

- Number of participants [n]: 200
- Age [years, mean (range)]: 70.3 (61-76)
- Gender [male/female; n]: 96/104

Inclusion criteria
Quote: ""Patients scheduled for colon resection in participating centres. Both benign and malignant indications were eligible, as were both laparoscopic and open procedures."

Exclusion criteria
Quote: ""Need for emergency surgery; bowel obstruction; colonoscopy planned to be undertaken during surgery; other indications for mechanical preparation or contraindications; allergy to drugs

Koskenvuo 2019 *(Continued)*

	used in the trial (polyethylene glycol, neomycin, metronidazole); and age younger than 18 years or older than 95 years." **Baseline imbalances** Quote: ""Patient baseline characteristics were similar between the two groups"
Interventions	**Comparison** • Intervention: MBP+oAB • Control: nBP **MBP** • Agent(s): polyethylene glycol • Dose per administration: 2000 mL • Time(s) of intake: before 6 PM on day before surgery • Route: oral • Concomitant medications: - **oAB** • Agent(s): neomycin and metronidazole • Dose per administration: 2 g each • Time(s) of intake: Neomycin at 7 PM and metronidazole at 11 PM • Route:oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): cefuroxime and metronidazole • Dose per administration: 1500 mg and 500 mg • Time(s) of intake:Quote: ""At the start of anaesthesia before skin incision. The prophylactic intravenous antibiotics were re-administered if the surgery lasted longer than 3 h from the first antibiotic dose, or if blood loss exceeded 1,5 L" **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage • Mortality • Length of hospital stay • Side effects of oAB **Outcomes sought but not reported in trial** • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus • Side effects of MBP **Outcomes reported in trial but not used in review** • Comprehensive Complication Index • Prevalence of adjuvant therapy • 5-year overall survival
Notes	**Source of funding:** Quote: " "Vatsatautien Tutkimussäätiö Foundation, Mary and Georg Ehrnrooth's Foundation, and Helsinki University Hospital research funds"

Koskenvuo 2019 *(Continued)*

Conflicts of interest: "VS reports grants from Vatsatautien Tutkimussäätiö Foundation, Mary and Georg Ehrnrooth's Foundation, and Helsinki University Hospital research funds, during the conduct of the study; grants from Finnish Surgical Society, Finska Läkaresällskapet, and Finnish Gastroenterological Society; personal fees from City of Vantaa, Finnish Gastroenterological Society, Novartis, and University of Helsinki; and non-financial support from Astellas, outside of the submitted work. TS reports personal fees from Johnson & Johnson's laparoscopic colorectal surgery advisory board, outside of the submitted work. All other authors declare no competing interests"

Ethics approval: Quote: ""The research plan was approved by the Finnish National Committee on Medical Research Ethics and Finnish Medicines Agency. The research plan was further approved by the local ethics committee of Helsinki University Hospital and by each participating centre's institutional review board (Helsinki University Hospital, Oulu University Hospital, Central Finland Central Hospital, and Seinäjoki Central Hospital)"

Informed consent: Patients provided written informed consent

Clinical trials registration: ClinicalTrials.gov (NCT02652637) and EudraCT (2015–004559–38)

Sample size calculation: Quote: " "With a power of 80% and significance at 5%, 396 patients would be needed to show this difference. The sample size was adjusted for a possible 5% loss, yielding a final sample size of 415 patients"

Lau 1988

Study characteristics

Methods

Study design: Parallel-group randomised trials

Duration of trial: May 1981 to June 1987

Duration of follow-up: 3 months

Country of origin: Hong Kong

Participants

Baseline characteristics
Number randomised: 140 participants
Number analysed: 132 participants

Intervention: MBP+oAB

- Number of participants [n]: 65
- Age [years; mean (SD)]: 62.3 (15.7)
- Gender [male/female; n]: 37/28

Control: MBP

- Number of participants [n]: 67
- Age [years, mean (SD)]: 63.5 (14.9)
- Gender [male/female; n]: 137/105

Inclusion criteria
"Elective colorectal surgery for carcinoma"

Exclusion criteria
Quote: "Inflammatory bowel disease, an existing colostomy, an active infection, a history of sensitivity to any of the antibiotics used, a history of renal insufficiency or eighth nerve dysfunction, an obstructing colonic lesion, or a history of receiving antibiotics within the 2 weeks before operation."

Baseline imbalances

Lau 1988 *(Continued)*

	Quote:"The randomised groups were well matched with respect to patient characteristics and surgical procedures"
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): bisacodyl, magnesium sulphate and saline enema • Dose per administration: - • Time(s) of intake: 3-day preparation • Route: oral/rectal • Concomitant medications: - **oAB** • Agent(s): neomycin and erythromycin • Dose per administration: 1000 mg each • Time(s) of intake: at 1 PM, 2 PM and 11 PM during the day before operation • Route:oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): metronidazole and gentamicin • Dose per administration: 500 mg/kg/KG and 2 mg/kg/KG • Time(s) of intake: over half an hour just before surgery **Adherence to regimen**: Quote:"3 patients were excluded due to violation of the study protocol"
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage • Length of hospital stay **Outcomes sought but not reported in trial** • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Fever of unknown origin
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** Quote: "The study was approved by the ethics boards of the participating centers" **Informed consent:** Quote: "After informed consent was obtained, patients were stratified into three categories" **Clinical trials registration:** -

Lau 1988 *(Continued)*

	Sample size calculation: Quote: "The initial study was projected to require 200 patients to show a statistical difference. We analysed our results statistically after inclusion of the first 202 patients"

Lazorthes 1982

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: January 1979 to March 1980 **Duration of follow-up**: 2 months **Country of origin:** France
Participants	**Baseline characteristics** Number randomised: 90 participants Number analysed: 90 participants Number eligible and included in this review: 60 **Only a subset of the study patients was included in the meta-analysis. Patients in study group O did not receive perioperative intravenous antibiotic prophylaxis and were therefore excluded from the meta-analysis.** **Intervention:** MBP+oAB • Number of participants [n]: 30 • Age [years; mean (SD)]: 64.8 (11.94) • Gender [male/female; n]: 20/10 **Control:** MBP • Number of participants [n]: 30 • Age [years, mean (SD)]: 65.4 (10.21) • Gender [male/female; n]: 14/16 **Inclusion criteria** Elective colorectal surgery **Exclusion criteria** Quote:"Patients requiring colostomy alone* or having to undergo surgery for hemorrhagic rectocolitis, as well as patients who had received antibiotics for seven days prior to surgery, were excluded from the study." **Baseline imbalances** None
Interventions	**Comparison** • Intervention: MBP+oAB + antibiotic administered intramuscularly (Group O + S´) • Control: MBP (Group S) **MBP** • Agent(s): magnesium sulfate and procedures such as enemas and low-residue diet • Dose per administration: - • Time(s) of intake: over three days preoperatively • Route: oral/rectal • Concomitant medications: -

Lazorthes 1982 *(Continued)*

	oAB • Agent(s): kanamycin and metronidazole • Dose per administration: 1000 mg and 250 mg • Time(s) of intake: Quote:"During the three days prior to surgery in four equally divided doses" • Route: oral • Concomitant medications: 2 mg/kg/KG gentamicin i.m. at the time of premedication **Perioperative intravenous antibiotic prophylaxis** • Agent(s): cephradine • Dose per administration: 2 g • Time(s) of intake: During induction of surgery **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • Mortality • Length of hospital stay **Outcomes sought but not reported in trial** • SSI • Anastomotic leakage • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Wound abscesses • Septicaemia • Fistula • Abdominal abscesses • Septic deaths
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** - **Informed consent:** - **Clinical trials registration:** - **Sample size calculation:** -

Lewis 2002

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: 1992 - 1995

Lewis 2002 *(Continued)*

Duration of follow-up: Quote: "The patients were followed up by the infection control nurse on postoperative days 3, 5 to 7, 10 to 14, and at 1 month for diagnosis of surgical site infection, using the modified CDC criteria."

Country of origin: Canada

Participants	**Baseline characteristics** Number randomised: 215 participants Number analysed: 213 participants **Intervention:** MBP+oAB • Number of participants [n]: 108 • Age [years; mean (SD)]: 68.8 (13.5) • Gender [male/female; n]: 53/56 **Control:** MBP • Number of participants [n]: 105 • Age [years, mean (SD)]: 71.4 (12.9) • Gender [male/female; n]: 43/63 **Inclusion criteria** Quote: "All patients who underwent elective surgery of the colon at the Queen Elizabeth Hospital in Montreal were eligible to enter the study" **Exclusion criteria** Quote: "Patients who were allergic to the study antibiotics or who had received antibiotics within the 2 weeks before operation, pregnant patients and those who refused informed consent were excluded." **Baseline imbalances** Quote: "The treatment groups were evenly matched with respect to age, gender, body mass index and preoperative serum albumin level and blood lymphocyte count. There were no significant differences between the groups with respect to the preoperative final diagnoses and operations performed."
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): sodium phosphate (and saline enemas) • Dose per administration: - • Time(s) of intake: Quote: "on the day before surgery until the rectal effluent was clear. If not, saline enemas were given at 1800 on the day before operation until they were clear" • Route: oral/rectal • Concomitant medications: - **oAB** • Agent(s): neomycin and metronidazole • Dose per administration: 2 g each • Time(s) of intake: at 19.00, and 23.00 hours on the day before surgery • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis**

Lewis 2002 *(Continued)*

	• Agent(s): amikacin and metronidazole • Dose per administration: 1 g each • Time(s) of intake: Quote: "On the way to the operating room" **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage **Outcomes sought but not reported in trial** • Mortality • Incidence of postoperative ileus • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Length of hospital stay • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Organisms found in wound
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** - **Informed consent:** Quote: "All patients gave informed consent to participate in the study" **Clinical trials registration:** - **Sample size calculation:Quote:** "The sample size was calculated assuming an infection rate at the surgical site of 10% to 15%, and a treatment difference of 10% (α risk 0.05, β risk 0.20)"

Oshima 2013

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: July 2006 to April 2009 **Duration of follow-up**:Quote: "during the hospital stay, and at 4-weeek and 3-month postoperative" **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 200 participants Number analysed: 195 participants **Intervention:** MBP+oAB • Number of participants [n]: 97 • Age [years; mean (SD)]: 41.8 (14.8) • Gender [male/female; n]: 55/42 **Control:** MBP

Oshima 2013 *(Continued)*

- Number of participants [n]: 98
- Age [years, mean (SD)]: 40.6 (14.8)
- Gender [male/female; n]: 57/41

Inclusion criteria
Quote: "Patients with ulcerative colitis scheduled to undergo restorative proctocolectomy with IPAA with an open approach"

Exclusion criteria
Quote:"Patients were excluded if they had received antibiotics within 2 weeks before randomization, were allergic to any of the drugs used, were aged less than 18 years, had abdominal sepsis within 6 months before randomization, were pregnant or breast feeding, were being treated with steroids or had any form of chronic immunosuppression, or had obstructive symptoms. Patients were excluded after randomization if they did not receive the study drugs according to the study protocol or if they did not have ananastomosis created during surgery for any reason."

Baseline imbalances
none

Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): magnesium citrate solution • Dose per administration: 1800 mL • Time(s) of intake: at 11:00 AM • Route:oral • Concomitant medications: - **oAB** • Agent(s): kanamycin and metronidazole • Dose per administration: 500 mg each • Time(s) of intake: at 2:00 PM, 3:00 PM, and 9:00 PM on the day before surgery • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): second-generation cephalosporin (flomoxef) • Dose per administration: - • Time(s) of intake: Quote: "30 minutes before the surgery and repeated every 3 hours during surgery; the same antibiotics were continued for 24 hours following surgery" **Adherence to regimen**: Protocol violations were detected in 6 patients in group A (MBP+oAB) and 7 patients in group B (MBP without oAB)
Outcomes	**Outcomes sought in review and reported in trial** • SSI (superficial, deep and organ/space) • Side effects of oAB **Outcomes sought but not reported in trial** • Anastomotic leakage • Mortality • Length of hospital stay

Oshima 2013 *(Continued)*

- Postoperative complications (mild D/C I + II or severe D/C III+IV)
- Incidence of postoperative ileus
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review

- Organisms found in SSI

Notes

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The protocol was approved by institutional review board"

Informed consent:Quote: "Informed consent was required from all participants"

Clinical trials registration: -

Sample size calculation:Quote: "When the power was 80%, it was assumed that 90 patients would be required in each group to detect a difference between 18% and 6% SSI rate (favoring oral antibiotics) with a probability of a type 1 error less than 0.05. Allowing for a loss of evaluable patients, a total sample size of 100 patients in each arm was chosen."

Papp 2021

Study characteristics

Methods

Study design: Parallel-group randomised trials

Duration of trial: November 2016 to June 2018

Duration of follow-up: 30 days

Country of origin: Hungary

Participants

Baseline characteristics
Number randomised: 600 participants
Number analysed: 529 participants

Intervention: MBP+oAB

- Number of participants [n]: 253
- Age [years; mean (SD)]: 66.1 (12.1)
- Gender [male/female; n]: 152/101

Control: MBP

- Number of participants [n]: 276
- Age [years, mean (SD)]: 66.5 (12.3)
- Gender [male/female; n]: 130/146

Inclusion criteria
Quote: "All indications for colorectal anastomosis were considered eligible, including Hartmann's reversal, with the exception of loop colostomy closure."

Exclusion criteria
Quote: "Patients requiring colostomy alone or having to undergo surgery for hemorrhagic rectocolitis, as well as patients who had received antibiotics for seven days prior to surgery, were excluded from the study."

Papp 2021 *(Continued)*

	Baseline imbalances none
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): castor oil and paraffin and enema(s) • Dose per administration: 40 mL and 20 mL • Time(s) of intake: on the day before surgery; enema was given in the evening before surgery and again on the morning of surgery • Route: oral/rectal • Concomitant medications: - **oAB** • Agent(s): metronidazole neomycin sulphate • Dose per administration: 500 mg and 1000 mg • Time(s) of intake: at 13.00, 15.00, and 19.00 hours on the day before surgery • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): ceftriaxone and metronidazole • Dose per administration: 2 g and 500 mg • Time(s) of intake:Quote: "Within 60 min of the incision. This was repeated if operating time exceeded 4 h and/or blood loss exceeded 1500 ml" **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus **Outcomes sought but not reported in trial** • Length of hospital stay • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Readmission
Notes	**Source of funding:** Quote: "The SOAP study non-commercial" **Conflicts of interest:Quote:** "The authors declare no conflict of interest" **Ethics approval:** Quote: "Ethical approval was granted by both the Hungarian National Institute of Pharmacy and Nutrition and the Hungarian Medical Research Council." **Informed consent:** All patients gave informed consent **Clinical trials registration:** EudraCT 2015-005614-30

Papp 2021 *(Continued)*

Sample size calculation: Quote: "The study power calculation was based on the international literature, with an estimated 11 per cent incidence of SSI in the OABP– group and 5 per cent in the OABPþ group. Postoperative ileus was estimated to occur in 6 percent of patients in the OABP– group and 3 percent in the OABP+ group. Using d ¼ 3 and an adjusted study power of 80 percent with a 95 percent confidence interval, it was calculated that 282 patients were required for the SSI primary endpoint and 374 for the postoperative ileus endpoint. This was rounded up to 400 patients and, after adjusting for a possible 12.5 percent loss, the final sample size was estimated to be 450 patients."

Ram 2005

Study characteristics

Methods

Study design: Parallel-group randomised trials

Duration of trial: April 1999 to March 2002

Duration of follow-up: Quote: "Complications were registered daily after surgery, and patients were re-examined at the outpatient clinic 1, 3, and 6 weeks following surgery"

Country of origin: Israel

Participants

Baseline characteristics
Number randomised: 329 participants
Number analysed: 329 participants

Intervention: MBP+oAB

- Number of participants [n]: 164
- Age [years; mean (SD)]: 68.17 (11.5)
- Gender [male/female; n]: 99/65

Control: oAB

- Number of participants [n]: 165
- Age [years, mean (SD)]: 68.11 (9.5)
- Gender [male/female; n]: 102/63

Inclusion criteria
Quote: "Elective colorectal procedures for nonobstructive large bowel pathologic features"

Exclusion criteria
Quote: "Patients in both groups were excluded if they had taken antibiotics for the last 10 days before surgery or if there was evidence of infection. Patients undergoing emergency operations were not included. Patients randomised to group 2 were excluded if they had bowel preparation for colonoscopy within 6 days prior to surgery. Patients undergoing proctectomy with low rectal anastomosis or surgery for polypoid lesion were also excluded."

Baseline imbalances
none

Interventions

Comparison

- Intervention: MBP+oAB
- Control: oAB

MBP

- Agent(s): soffodex (monobasic sodium phosphate and dibasic sodium phosphate)

Ram 2005 *(Continued)*

- Dose per administration: 2.4/0.9 g
- Time(s) of intake: On the day before surgery
- Route: oral
- Concomitant medications: -

oAB

- Agent(s): -
- Dose per administration: -
- Time(s) of intake: -
- Route: oral
- Concomitant medications: -

Perioperative intravenous antibiotic prophylaxis

- Agent(s): ceftriaxone and metronidazole
- Dose per administration: 1 g and 500 mg
- Time(s) of intake: 1 hour before induction. The same antibiotic prophylaxis was continued for 48 hours following the operation

Adherence to regimen: -

Outcomes

Outcomes sought in review and reported in trial

- SSI
- Anastomotic leakage
- Mortality
- Incidence of postoperative ileus

Outcomes sought but not reported in trial

- Postoperative complications (mild D/C I + II or severe D/C III+IV)
- Length of hospital stay
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review

- Anastomotic bleeding
- Abdominal/pelvic collection
- Urinary tract infection
- Pulmonary complications
- Thrombophlebitis
- Relaparotomy

Notes

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote:"The study was approved by the hospital ethics committee."

Informed consent: All patients gave informed consent

Clinical trials registration: -

Sample size calculation: -

Rybakov 2021

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: November 2017 to October 2018 **Duration of follow-up**: 30 days **Country of origin:** Russia
Participants	**Baseline characteristics** Number randomised: 150 participants Number analysed: 116 participants **Intervention:** MBP+oAB • Number of participants [n]: 57 • Age [years; median (quartile)]: 65 (59; 66) • Gender [male/female; n]: 24/33 **Control:** MBP • Number of participants [n]: 59 • Age [years, median (quartile)]: 64 (59; 70) • Gender [male/female; n]: 31/28 **Inclusion criteria** Quote: "All the patients with rectal cancer scheduled for elective rectal resection" **Exclusion criteria** "The presence of inflammatory process at the preoperative stage, intestinal obstruction, which contraindicate preoperative mechanical preparation, antibacterial drugs intake for 30 days before surgery, planned simultaneous operation on liver or other major organs, severe renal and/or liver failure, allergy to used antibacterial drugs" **Baseline imbalances** Quote: "Both groups were well matched in terms of demography and laboratory parameters, the presence of diabetes mellitus, ASA score, adjuvant chemoradiation, and surgery."
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): polyethylene glycol solution • Dose per administration: - • Time(s) of intake: Starting at 16:00 on the day before surgery • Route: oral • Concomitant medications: - **oAB** • Agent(s): erythromycin and metronidazole • Dose per administration: 500 mg each • Time(s) of intake: After initiation of MBP at 17:00, 20:00, and 23:00 o'clock. • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis**

Rybakov 2021 *(Continued)*

	• Agent(s): cephalosporin III generation (ceftriaxone) • Dose per administration: 1 g • Time(s) of intake: 30–90 min before the skin incision **Adherence to regimen**: 33 patients excluded due to violation of the protocol (18 in MBP+oAB group an 15 in oAB group)
Outcomes	**Outcomes sought in review and reported in trial** • SSI (superficial, deep and organ/space) • Anastomotic leakage • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Incidence of postoperative ileus **Outcomes sought but not reported in trial** • Mortality • Length of hospital stay • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Bacteria isolated from the pelvic cavity at the end of surgery
Notes	**Source of funding:** - **Conflicts of interest:** None **Ethics approval:** Quote:"The study protocol was approved by the local Ethics Committee" **Informed consent:** Informed consent was obtained from all the participants **Clinical trials registration:** NCT03436719 **Sample size calculation: Quote:** "To reach a power of 80%, it was estimated, that 176 patients would be required in each group to detect significant differences between them."

Sadahiro 2014

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial:** May 2008 to October 2011 **Duration of follow-up:** Four weeks **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 206 participants Number analysed: 194 participants **Intervention:** MBP+oAB • Number of participants [n]: 99 • Age [years; mean (SD)]: 67 (11) • Gender [male/female; n]: 56/43

Sadahiro 2014 *(Continued)*

Control: nBP

- Number of participants [n]: 95
- Age [years, mean (SD)]: 66 (12)
- Gender [male/female; n]: 51/44

Inclusion criteria
Quote: "Patients scheduled to undergo elective colon cancer operations in whom curative resection of tumor(s) was considered feasible. The eligibility criteria were as follows: 20-80 years of age; preoperative performance status of 0 or 1; and no serious coexisting medical conditions."

Exclusion criteria
Quote: "Patients with a history of intestinal resection, patients with a stoma, patients with intestinal stenosis or obstruction that would preclude routine preoperative mechanical bowel preparation, and patients with stage IV disease on preoperative diagnosis were excluded from this study."

Baseline imbalances
None

Interventions	**Comparison** • Intervention: MBP+oAB (Group B) • Control: MBP (Group C) • Group A (MBP + probiotics) was not included in the meta-analysis **MBP** • Agent(s): sodium picosulfate (1) and polyethylene glycol–electrolyte sodium (2) • Dose per administration: 10 mL (1) and 2000 mL (2) • Time(s) of intake: 2 days before surgery (1) and in the morning of the day before the operation (2) • Route: oral • Concomitant medications: - **oAB** • Agent(s): kanamycin sulfate and metronidazole • Dose per administration: 0.5 g each • Time(s) of intake: at 1:00 PM, 2:00 PM, and 11:00 PM the day before the procedure • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): fomoxef • Dose per administration: 1 g • Time(s) of intake: Quote:"1 hour before making an incision. When the operation time exceeded 3 hours, another 1 g dose of flomoxef was administered." **Adherence to regimen**: -
Outcomes	**Outcomes sought in review and reported in trial** • SSI (incisional and organ/speace) • Anastomotic leakage **Outcomes sought but not reported in trial** • Mortality • Length of hospital stay • Postoperative complications (mild D/C I + II or severe D/C III+IV)

Sadahiro 2014 *(Continued)*

- Incidence of postoperative ileus
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review

- Analysis of faecal flora

Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** Quote:"This study was approved by the Ethics Committee of Tokai University" **Informed consent:** Quote: "Patients provided written informed consent" **Clinical trials registration:** Quote:"The trial registration number is University Hospital Medical Information Network (UMIN) Clinical Trials Registry 000003435" **Sample size calculation:** Quote: "Assuming an SSI rate of 9% each in the oral antibiotics group and the probiotics group and an SSI rate of 30% in the control group, we calculated the number needed to treat that would have 90% power to detect differences between the oral antibiotics group and the control group and between the probiotics group and the control group by the Fisher exact test at an overall level of significance of 0.05 (two-sided). We then calculated the number needed to treat per group at a two-sided significance level of 0.0253 for each comparison, adjusting for multiplicity associated with multiple tests by the Dunn-Sidak method. The number needed to treat was thus calculated to be 92 per group. To allow for possible dropouts, a sample size of 300 patients (100 patients per group) was established for this study."

Suzuki 2020

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: August 2014 to April 2017 **Duration of follow-up**: 30 days **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 254 participants Number analysed: 251 participants **Intervention:** MBP+oAB • Number of participants [n]: 125 • Age [years; mean (SD)]: 69 (12) • Gender [male/female; n]: 66/61 **Control:** nBP • Number of participants [n]: 126 • Age [years, mean (SD)]: 70 (9) • Gender [male/female; n]: 68/59 **Inclusion criteria** Quote: "Diagnosis of primary colon cancer, age of 20 to 85 years, and Eastern Cooperative Oncology Group performance status of 0 or 1."

Suzuki 2020 *(Continued)*

Exclusion criteria
Quote: "Patients with a stoma, patients in whom conventional preoperative MBP could not be performed because of stenosis or obstruction, patients with a preoperative diagnosis of stage 4 disease, patients with an American Society of Anesthesi ologists score of ≥4, and patients who were scheduled to simultaneously undergo resection of other organs were excluded from the study"

Baseline imbalances
Quote: "There was no significant difference between the groups in age, sex, or hemoglobin or albumin levels in peripheral blood before surgery, the presence or absence of diabetes mel litus, American Society of Anesthesiologists score, tumor location, or histological stage. There was also no significant difference between the groups in operation time, bleeding volume, or the presence or absence of blood transfusion."

Interventions

Comparison

- Intervention: MBP+oAB
- Control: nBP

MBP

- Agent(s): 1) sodium picosulfate and 2) polyethylene glycol-electrolyte sodium
- Dose per administration: 1) 10 ml; 2) 2000 ml
- Time(s) of intake: 1) 2 days before the surgery: 2) on the morning of the day before surgery
- Route: oral
- Concomitant medications: -

oAB

- Agent(s): kanamycin sulfate and metronidazole
- Dose per administration: 500 mg each
- Time(s) of intake: both at 1:00, 2:00, and 11:00 PM on the day before surgery
- Route: oral
- Concomitant medications: -

Perioperative intravenous antibiotic prophylaxis

- Agent(s): flomoxef
- Dose per administration: 1000 mg
- Time(s) of intake: "Given as a continuous intravenous infusion starting 1 h before surgery. If the operation time exceeded 3 h, 1 g of flomoxef was additionally given"

Adherence to regimen: -

Outcomes

Outcomes sought in review and reported in trial

- SSI (superficial and organ/space)
- Anastomotic leakage
- Length of hospital stay

Outcomes sought but not reported in trial

- Deep SSI
- Mortality
- Postoperative complications (mild D/C I + II or severe D/C III + IV)
- Length of hospital stay
- Incidence of postoperative ileus
- Side effects of Interventions

Outcomes reported in trial but not used in review

Suzuki 2020 *(Continued)*

- Other infectious complications
- Small bowel obstruction

Notes	**Source of funding:** - **Conflicts of interest:Quote:** "The authors declare that they have no conflicts of interest to disclose" **Ethics approval:Quote:** "Ethical approval of Institutional Review Board of Tokai Uni versity was obtained" **Informed consent:** All patients provided written informed consent **Clinical trials registration:** - **Sample size calculation:** Quote: "The required number of patients in each group was estimated to be 115. Given a dropout rate of 10%, the target number of patients per group was set at 127, and the total number of patients in both groups combined was set at 254"

Takesue 2000

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: April 1997 to November 1997 **Duration of follow-up**: Quote: "until discharged from the hospital" **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 100 participants Number analysed: 83 participants **Intervention:** MBP+oAB • Number of participants [n]: 38 • Age [years; median (range)]: 65 (29-85) • Gender [male/female; n]: 25/13 **Control:** MBP • Number of participants [n]: 45 • Age [years, median (range)]: 68 (34-81) • Gender [male/female; n]: 29/16 **Inclusion criteria** Quote: "Elective colorectal surgery" **Exclusion criteria** Quote:"MBP not possible; antibiotics within least 15 days; emergency colonic obstruction" **Baseline imbalances** None
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP

Takesue 2000 *(Continued)*

MBP

- Agent(s): PEG lavage
- Dose per administration: -
- Time(s) of intake: 10 AM to 2 PM on the day before surgery
- Route: oral
- Concomitant medications: -

oAB

- Agent(s): kanamycin and metronidazole
- Dose per administration: 500 mg each
- Time(s) of intake: at 2 PM, 3 PM and 11 PM (when surgery was scheduled for 9 AM)
- Route: oral
- Concomitant medications: -

Perioperative intravenous antibiotic prophylaxis

- Agent(s): cefmetazole
- Dose per administration: 1 g
- Time(s) of intake:Quote: "after induction of anesthesia; and three times daylie for 3 consecutive days after the operation"

Adherence to regimen: 17 excluded after randomisation (12 in MBP+oAB group an 5 in oAB group)

Outcomes

Outcomes sought in review and reported in trial

- SSI
- Anastomotic leakage

Outcomes sought but not reported in trial

- Mortality
- Incidence of postoperative ileus
- Postoperative complications (mild D/C I + II or severe D/C III+IV)
- Length of hospital stay
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review

- Anastomotic bleeding
- Abdominal/pelvic collection
- Urinary tract infection
- Pulmonary complications
- Thrombophlebitis
- Relaparotomy

Notes

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: All patients gave informed consent

Clinical trials registration: -

Sample size calculation: -

Uchino 2019

Study characteristics	
Methods	**Study design:** Parallel-group randomised trials **Duration of trial**: March 2014 to February 2017 **Duration of follow-up**: Quote: "The wounds were inspected daily by a nurse, once a week by the surveillance member, and an attending physician during the hospital stay, and at the 4-week and 3-month postoperative follow-up visits." **Country of origin:** Japan
Participants	**Baseline characteristics** Number randomised: 325 participants Number analysed: 321 participants Number eligible and included in this review: 185 **Only a subset of the study patients was included in the meta-analysis. All patients who underwent colon or rectal surgery with intestinal anastomosis were eligible.** **Intervention:** MBP+oAB • Number of participants [n]: 91 • Age: - • Gender [male/female; n]: 69/22 **Control:** nBP • Number of participants [n]: 94 • Age: - • Gender [male/female; n]: 77/17 **Inclusion criteria** "Patients undergoing surgery for Crohn disease." **Exclusion criteria** Quote: "Patients with emergent surgery, allergy to antibiotics, and antibiotic use within the 2 weeks before surgery were excluded. Moreover, patients treated with a long-tube insertion due to bowel obstruction or surgery for an anal lesion alone were also excluded." **Baseline imbalances** None
Interventions	**Comparison** • Intervention: MBP+oAB • Control: MBP **MBP** • Agent(s): 0.75 % sodium picosulfate hydrate magnesium citrate solution • Dose per administration: 20 mL • Time(s) of intake at 11:00 AM on the day before surgery • Route:oral • Concomitant medications: - **oAB** • Agent(s): kanamycin and metronidazole

Uchino 2019 *(Continued)*

- Dose per administration: 500 mg each
- Time(s) of intake: at 2:00 PM, 3:00 PM, and 9:00 PM on the day before surgery
- Route:oral
- Concomitant medications: -

Perioperative intravenous antibiotic prophylaxis

- Agent(s): fomoxef sodium
- Dose per administration: -
- Time(s) of intake: 30 minutes before the surgery and repeatedly for every 3 hours during the surgery

Adherence to regimen
Quote: "Protocol violations were detected in 2 patients in group A and 3 patients in group B, and the remaining 320 patients were included in the PP analysis."

Outcomes

Outcomes sought in review and reported in trial

- SSI (incisional and organ/speace)

Outcomes sought but not reported in trial

- Anastomotic leakage
- Mortality
- Length of hospital stay
- Postoperative complications (mild D/C I + II or severe D/C III+IV)
- Incidence of postoperative ileus
- Side effects of Intervention(s)

Outcomes reported in trial but not used in review
-

Notes

Source of funding: -

Conflicts of interest: Quote: "The authors report no conflicts of interest."

Ethics approval: Quote:"All study protocols were approved by the Institutional Review Board of the Hyogo College of Medicine (No. 1679)."

Informed consent: Quote: "Informed consent was required from all participants"

Clinical trials registration: Quote: "The study protocols were registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR 000013369)."

Sample size calculation: Quote: **"**It was previously reported that the incidence of SSI in CD surgery without oral antibiotic prophylaxis was approximately 25%. When the power was set to 80%, it was assumed that 149 patients would be required in each group to detect a difference between an SSI rate of 12.5% and 25% (favoring oral antibiotic prophylaxis) with a probability of a type 1 error <0.05. To allow for the potential loss of evaluable patients, a total sample size of 160 patients in each arm was chosen."

Zmora 2003

Study characteristics

Methods

Study design: Parallel-group randomised trials

Duration of trial: July 1997 to July 2000

Zmora 2003 *(Continued)*

	Duration of follow-up: 30 days **Country of origin:** Israel
Participants	**Baseline characteristics** Number randomised: 415 participants Number analysed: 380 participants **Intervention:** MBP+oAB • Number of participants [n]: 187 • Age [years; mean (range)]: 68 (22–89) • Gender [male/female; n]: 103/84 **Control:** oAB • Number of participants [n]: 193 • Age [years, mean (range)]: 68 (23–92) • Gender [male/female; n]: 94/99 **Inclusion criteria** Quote: "Patients undergoing elective colon and rectal surgery with primary anastomosis" **Exclusion criteria** Quote: "Patients with tumors smaller than 2 cm were excluded from the study, as palpation of small tumors may be difficult in an unprepared bowel, and these patients may require intraoperative colonoscopy to identify these lesions. Patients who required a diverting stoma proximal to the anastomosis and those who were found to have an abdominal abscess at the time of surgery were also excluded from the data analysis." **Baseline imbalances** Quote:"Demographic characteristics, indications for surgery, and type of surgery did not significantly differ between the two groups."
Interventions	**Comparison** • Intervention: MBP+oAB • Control: oAB **MBP** • Agent(s): polyethylene glycol (additional enema before rectal surgery) • Dose per administration: one gallon • Time(s) of intake: 12 to 16 hours before surgery (on the day of surgery) • Route: oral,rectal • Concomitant medications: - **oAB** • Agent(s): neomycin and erythromycin • Dose per administration: - • Time(s) of intake: "three doses before surgery" • Route: oral • Concomitant medications: - **Perioperative intravenous antibiotic prophylaxis** • Agent(s): Quote: "Perioperative broad-spectrum intravenous antibiotics" • Dose per administration: -

Zmora 2003 *(Continued)*

	• Time(s) of intake:Quote: "perioperative; continued for at least 24 hours postoperatively. Surgeons were allowed to continue the prophylactic intravenous antibiotics for more then 1 day, and the length of prophylactic treatment was recorded." **Adherence to regimen**: 193 Patient excluded since they did not have MBP
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage • Incidence of postoperative ileus **Outcomes sought but not reported in trial** • Mortality • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Length of hospital stay • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Non-surgical Infections • GI bleeding • Bowel cleansing assessment
Notes	**Source of funding:** - **Conflicts of interest:** - **Ethics approval:** Quote:"The study was approved by the Institutional Review Board (Helsinki committee)" **Informed consent:** Quote:Patients gave their informed consent before randomization." **Clinical trials registration:** - **Sample size calculation:** -

D/C: Clavien-Dindo classification; IV: intravenous; **MBP:** mechanical bowel preparation; **MBP+oAB:** combined mechanical and oral antibiotic bowel preparation; **nMB:** no bowel preparation; **oAB:** oral antibiotics as bowel preparation; **PEG:** polyethylene glycol; **SD:** standard deviation; **SSI:** surgical site infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alverdy 2019	Wrong study design
Anthony 2011	Wrong intervention
Barker 1971	No perioperative intravenous antibiotic prophylaxis
Champault 1981	No perioperative intravenous antibiotic prophylaxis
Clarke 1977	No perioperative intravenous antibiotic prophylaxis
COLONPREP	Wrong study design

Study	Reason for exclusion
Condon 1979	Wrong intervention
Contant 2007	No perioperative intravenous antibiotic prophylaxis
Coppa 1983	Wrong intervention
Eisenberg 1981	Wrong intervention
Emir 2012	Wrong intervention
Flückiger 1980	Wrong intervention
Güenaga 2011	Wrong study design
Hjalmarsson 2015	Wrong intervention
Ishibashi 2009	Wrong intervention
Jagelman 1985	Wrong intervention
Kolovrat 2012	Wrong intervention
Mehdorn 2021	Wrong study design
Mendes Da Costa 1977	No perioperative intravenous antibiotic prophylaxis
Mulder 2020	Wrong intervention
Playforth 1988	Wrong intervention
Reddy 2007	No perioperative intravenous antibiotic prophylaxis
Schardey 2020	Wrong intervention
Tajima 2016	Wrong intervention
Takesue 2009	Wrong publication type (congress poster)
Taylor 1994	Wrong patient population
Thalheimer 2008	Wrong publication type (invited commentary)
Vadhwana 2020	Wrong study design
Wolff 1988	No perioperative intravenous antibiotic prophylaxis
Yabata 1997	Wrong intervention

Characteristics of studies awaiting classification *[ordered by study ID]*

Abis 2019

Methods	**Study design:** randomised clinical trial

Abis 2019 *(Continued)*

	Duration of trial: May 2013 to March 2017 **Duration of follow-up**: follow-up was done at least twice a year in the first 2 years after surgery and then yearly according the Dutch guidelines on colorectal cancer **Country of origin:** the Netherlands
Participants	**Baseline characteristics** Number randomised: 485 Number analysed: 565 Number of eligible participants that could be included in our meta-analysis: 316 **Only study patients who underwent preoperative mechanical bowel preparation (left-sided colonic, sigmoid and low anterior resections) can be included in our meta-analysis. A request to the study authors to provide us with the primary data for the inclusion of eligible patients from the study has not yet been fulfilled.**
Interventions	**Comparison** • Intervention: SDD • Control: no oral antibiotics **Mechanical bowel preparation** Was given for left-sided colectomies, sigmoid and anterior resections. **Oral antibiotics** Oral colistin, tobramycin and amphotericin B were administered to patients in the SDD group to decontaminate the digestive tract. **Perioperative intravenous antibiotic prophylaxis** Both treatment and control group received intravenous cefazolin and metronidazole for perioperative prophylaxis.
Outcomes	**Outcomes sought in review and reported in trial** • SSI • Anastomotic leakage • Mortality • Incidence of postoperative ileus • Length of hospital stay **Outcomes sought but not reported in trial** • Postoperative complications (mild D/C I + II or severe D/C III+IV) • Side effects of Intervention(s) **Outcomes reported in trial but not used in review** • Reoperation • Urinary tract infection • Pulmonary complications • Pulmonary embolism • Cardiac • Fascial dehiscence
Notes	**Source of funding:** this study was funded by the DutchDigestive Foundation, Spaarne Gasthuis Academy Fund. The funder had no role in study design, data collection, data analysis, data interpretation or writing of the report. **Conflicts of interest:** the authors declare no conflict of interest

Abis 2019 *(Continued)*

Ethics approval: the ethics board at the VU University Medical Centre and the institutional review board at each participating centre approved the study.

Informed consent: all patients provided written informed consent.

Clinical trials registration: the trial was registered with ClinicalTrials.gov (number NCT01740947).

Sample size calculation: considering a 9 per cent anastomotic leakage rate in the control group, based on numbers of the Dutch Surgical Colorectal Audit at onset of the trial, and an estimated 4 percent in the intervention group, 381 patients needed to be included per treatment arm (total of 762 patients).

SDD: selective decontamination of the digestive tract; **SSI:** surgical site infections

Characteristics of ongoing studies *[ordered by study ID]*

COMBINE

Study name	Intravenous Versus Combined Oral and Intravenous Antimicrobial Prophylaxis for the Prevention of Surgical Site Infection in Elective Colorectal Surgery
Methods	**Study type:** interventional **Study design** • Allocation: randomised • Intervention model: parallel assignment • Masking: double (participant, investigator) • Primary purpose: prevention
Participants	**Condition or disease:** elective colorectal surgery **Inclusion criteria** • Age > 18 • Laparoscopic or non-laparoscopic elective colorectal surgery **Exclusion criteria** • Non elective colorectal surgery (emergent surgery and/or re-intervention or revision of a previous colorectal procedure) • Significant concomitant surgical procedure (e.g. liver resection for metastasis) • Bacterial infection at the time of surgery or antimicrobial therapy up to 2 weeks before surgery • Inflammatory bowel disease • Severe obesity (defined as a BMI >35 kg/m2) • Known history of hypersensitivity to β-lactams and imidazoles • Preoperative severe impairment in renal function (creatinine clearance (MDRD) < 30 ml/min) • Patients with known colonisation with multidrug-resistant digestive bacteria, especially multidrug-resistant gram-negative bacteria (requiring specific infection control measures) • Allergy to lactose, galactose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption (rare metabolic disease) • Pregnant women, breastfeeding women, women of childbearing age without effective contraceptive- Refusal to participate or inability to provide informed consent **Target sample size:** - **Actual Enrolment:** 920
Interventions	**Treatment arms**

COMBINE *(Continued)*

	• Combined oral and intravenous antimicrobial prophylaxis (intervention group): patients will receive a single oral dose of 1g ornidazole at 12hours before surgery in combination with intravenous dose of 2g cefoxitin at least 30min before surgical incision • Intravenous antimicrobial prophylaxis (control group): patients will receive a single oral dose of placebo at 12hours before surgery in combination with intravenous dose of 2g cefoxitin at least 30 minutes before surgical incision • In each group, an additional dose of 1g cefoxitin will be given every 2hours during surgery. After surgery, no additional antibiotic doses will be given to either of the groups. • Patients will be able to receive oral laxative (1 or 2 packages of X-PREP powder diluted in a glass of water) and retrograde rectal enema the day before surgery, as used previously.
Outcomes	**Primary outcome:** • Occurrence of any SSI within 30 days after surgery. [Time Frame: 30 days after surgery] **Secondary outcome:** • Incidence of individual types of SSI according to the group of treatment • Number of treatment-related adverse events with the combined oral and intravenous antimicrobial prophylaxis • Number of postoperative complications • Number of surgical re-intervention • Number of duration of hospital stay • Number of postoperative mortality related to SSI • Time to introduction of adjuvant chemotherapy related to SSI
Starting date	**Date of registration:** November 5, 2015 **Study Start Date:** May 25, 2016 **Actual Study Completion Date**: June 30, 2020 **Recruitment Status:** Completed
Contact information	**Contact person:** Professor Emmanuel Futier **Affiliation**: University Hospital, Clermont-Ferrand **Country of origin:** France
Notes	**Ethics approval:** COMBINE trial has been approved by an independent ethics committee for all study centres **Source of funding:** COMBINE trial is supported by funding from French Ministry of Health (Programme Hospitalier de Recherché Clinique (PHRC) National 2014) and from the University Hospital of Clermont-Ferrand

CTRI/2018/07/014938

Study name	Role of combined oral antibiotic and mechanical bowel preparation in reducing incidence of surgical site infections in comparison to only mechanical bowel preparation in patients undergoing elective resection for rectal cancer at a tertiary care centre in India: A Randomized Control Trial
Methods	**Study type:** interventional **Study design** • Randomised, parallel group trial

CTRI/2018/07/014938 *(Continued)*

Participants	**Condition or disease:** patients with rectal cancer **Inclusion criteria** • Age 18-80 years • All patients with rectal/rectosigmoid cancer (based on MRI imaging), planned for surgical resection **Exclusion criteria** Patients with rectal cancer who are not eligible for mechanical bowel preparation/ where bowel preparation is contraindicated such as Crohn's disease, obstructed bowel and renal or cardiac impairment.Also patients with known drug allergy to the medications used in the trial. **Target sample size:** 118
Interventions	**Treatment arms** • Comparator Agent (Mechanical bowel preparation): 2 bottles of 45 mL of Exelyte bowel preparation solution (monobasic sodium phosphate dihydrate 24.417 g, disodium hydrogen orthophosphate dihydrate 5.439 g) to be consumed at 8 am and 4 pm on the day prior to surgery. • Intervention (oral antibiotic bowel preparation): all the patients in this arm in addition to the bowel preparation solution (45 mL of Exelyte bowel preparation solution (monobasic sodium phosphate dihydrate 24.417 g, disodium hydrogen orthophosphate dihydrate 5.439 g) to be consumed at 8 am and 4 pm), will also receive 3 tablets each of, 1 g of Erythromycin Estolate and 400 mg of Metronidazole in the package, to be taken at 1pm, 2pm and 11 pm, on the day prior to surgery
Outcomes	**Primary outcome** • To evaluate and assess the superiority of oral antibiotic bowel preparation in reducing incidence of surgical site infections in patients undergoing elective resection for rectal cancer in comparison to only mechanical bowel preparation at a tertiary care centre in India (within 30 days from the day of surgery) **Secondary outcomes** • To assess the impact of antibiotic bowel preparation on post-operative length of hospital stay (within 30 days from the day of surgery) • To assess the impact of antibiotic bowel preparation on post-operative morbidity (within 30 days from the day of surgery)
Starting date	**Date of registration:** 18/07/2018 **Study Start Date:** 25/04/2018 **Study Completion Date**: - **Recruitment Status:** open to recruitment
Contact information	**Contact person:** Mark Ranjan Jesudason **Affiliation**: Christian Medical College, Vellore **Country of origin:** India
Notes	**Ethics approval:** Silver, Research and Ethics Committee, Christian Medical College, Vellore **Source of funding:** Fluid RFesearch Grant, Christian Medical College, Vellore

EUCTR2019-002002-43-ES

Study name	Phase IV, unicentric, randomized and open study to confirm the decrease of the incidence of the surgical site infection after elective right hemicolectomy with anterographic mechanical preparation associated with oral and intravenous antibiotic therapy versus oral and intravenous antibiotic and versus only intravenous antibiotic
Methods	**Study type:** interventional clinical trial of medicinal product **Study design** • Controlled: yes • Randomised: yes • Open: yes • Single blind: no • Double-blind: no • If controlled, specify comparator, Other Medicinal Product: yes • Placebo: no • Number of treatment arms in the trial: 3
Participants	**Condition or disease:** patients undergoing right hemicolectomy **Inclusion criteria** • Patients older than 18 years with surgical indication of right hemicolectomy who do not present any exclusion criteria. **Exclusion criteria** • Patients under 18 years • Urgent colorectal resections. • Patients presenting an occlusive or sub-occlusive condition at the time of surgery. • Patient who does not meet the inclusion criteria in the intensified recovery program based on the RICA route (Intensified Recovery in Abdominal Surgery) • Patients undergoing colonic resection that involve a location other than the right colon. • Patients affected by intra-abdominal or distant infection prior to surgery. • Patients who have been given antibiotics for any other indication during the two weeks prior to the intervention. • Patient with inflammatory bowel disease. • Pregnant or breastfeeding patient. • Patients with immunity disorders or receiving immunosuppressive treatment or with synchronous neoplasms of other organs at the time of surgery. • Previous history of allergy to erythromycin, neomycin or derivatives, as well as Citrafleet®. **Target sample size:** 108
Interventions	**Treatment arms** • CitraFleet • Eritromicina • Neomicina
Outcomes	**Primary outcomes** • Temperature • Appearance of surgical wound • Abdominal examination • C-reactive protein • Surgical wound culture

EUCTR2019-002002-43-ES *(Continued)*

	Secondary outcomes • Anastomotic dehiscence rate • Duration of the post-surgical hospital stay • Global Complication Rate **Time point(s) of evaluation the end point(s):** for 30 days after surgery
Starting date	**Date of registration:** 21/10/2019 **Study Start Date:** 16/12/2019 **Study Completion Date**: - **Recruitment Status:** authorised-recruitment may be ongoing or finished
Contact information	**Contact person:** P. Millan (Unidad de Investigación Clínica) **Affiliation**: Fundación Instituto de Investigación Sanitaria Aragón **Country of origin:** Spain
Notes	**Ethics approval:** Favourable Ethics Committee Opinion of the trial application (2019-12-12) **Source of funding:** Fundación Instituto de Investigación Sanitaria Aragón

KCT0004822

Study name	Infectious surgical site Complications after Oral antibiotic Bowel preparation for minimally-invasive Rectal cAncer surgery (COBRA) – multicenter prospective randomized controlled trial
Methods	**Study type:** interventional study **Study design** • Primary purpose: prevention • Intervention model: factorial • Blinding/masking: open • Allocation: RCT
Participants	**Condition or disease:** neoplasms **Inclusion criteria** • Age 20 - 75 years • Pathologically-confirmed rectal adenocarcinoma of which lower margin is located within 15 cm from anal verge • Radiologicall- confirmed non-metastatic rectal cancer (cTanyNantM0) • ECOG performance status 0-2 • ASA = 3 • A patient who understands this clinical trial and agrees to be enroled **Exclusion criteria** • Anticipated other organ resection • Metastatic disease • One who have been treated for infections or have taken antibiotics within 2 weeks before surgery • Severe major organ dysfunction (heart, lung, liver, kidney)

KCT0004822 *(Continued)*

- A patient who is taking steroid or immunosuppressants
- Inflammatory bowel disease
- A patient who has undergone chemotherapy within 1 month due to malignant disease of other organ
- Decrease in white blood cell for various reasons
- Pregnant or lactating women
- Local resection of rectal cancer

Target sample size: 438

Interventions	**Treatment arms** • Experimental group (A): mechanical bowel preparation (PEG) + IV antibiotics • Control group (B): mechanical bowel preparation (PEG) + IV antibiotics + oral antibiotics (rifaximin + metronidazole) **Mechanical bowel preparation** • PEG preferred • Water only permitted on the day before operation **Oral antibiotics** • 400 mg rifaximin + 500 mg metronidazole • 14, 16, 22 hours the day before surgery **Perioperative intravenous antibiotic prophylaxis** • 2nd generation cephalosporin • Venous injection within 30 minutes before surgery • Additional dose is at the discretion of the operators
Outcomes	**Primary outcome** • Surgical site infection rate during first 30 days **Secondary outcomes** • Adverse event • Anastomotic leakage rate • *C. difficile* colitis • Incisional SSI • Organ/space SSI • Overall complication
Starting date	**Date of registration:** 12.03.2020 **Estimated Study Start Date:** - **Estimated Study Completion Date:** - **Recruitment status:** recruiting
Contact information	**Contact person:** Ji Woong Bae **Affiliation**: Korea University Ansan Hospital **Country of origin:** Korea
Notes	**Ethics approval:** Approval date: 05/03/2020

KCT0004822 *(Continued)*

	Source of funding: Korea University

MECCLANT –C and –R Trials

Study name	Preparation with Mechanical Bowel Cleansing or/and Oral Antibiotics or Nothing for Elective Colorectal Surgery: Two-Two-Arm Multicentre Randomised Controlled Studies (MECCLANT –C and –R Trials)
Methods	**Study type:** interventional **Study design** • Two phase III prospective, randomised, two-arm, comparative, multicentre studies
Participants	**Condition or disease** • MECCLAND -C Trial: patients to undergo surgery for colon cancer, patients to undergo surgery for colonic benign polyps (solitary, multiple), patients to undergo surgery for diverticular disease • MECCLAND –R Trial: patients to undergo surgery for rectal cancer with or without protective stoma, patients to undergo surgery for rectal benign polyps (solitary, multiple) **Inclusion criteria** • Scheduled colorectal surgery **Exclusion criteria** • Patients younger than 18 Years of age or older than 85 years of age • Patients With preoperative hospital stay >2 days • Patients to undergo non-elective (emergency) operation • Patients with contraindication for mechanical bowel preparation • Patients physically unstable requiring intensive preoperative resuscitation sepsis, septic shock, Systemic Inflammatory Response Syndrome (SIRS), acute respiratory failure requiring mechanical ventilation, acute renal failure • American Society of Anesthesiologists (ASA) Physical Status Classification of 4 or 5 • Patients With infection at the site of abdominal incision • Patients with a history of Colo-ectal surgery • Patients to undergo defunctioning Ssoma only • Patients incapable to communicate and provide informed consent • Patients undergoing surgery for IBD • Patients undergoing panproctocolectomy for Familial Adenomatous Polyposis (FAP) **Target sample size:** 356
Interventions	**Treatment arms** • Arm A: no bowel preparation (NBP) • Arm B: mechanical bowel preparation plus oral antibiotics (MBP +OA) **Mechanical bowel preparation** • MECCLAND –C trial: Consume per os 3-4 L of either Klean Prep (Norgine Ltd, Uxbridge, UK) or Fortrans (Beaufour IPSEN Industry, Dreux, France) as MBP. MBP starts at 14:00 and ends by 18:00 on the day prior to surgery. • MECCLAND –R trial: Patients of both Arms consume per os 3-4 L of either Klean Prep (Norgine Ltd, Uxbridge, UK) or Fortrans (Beaufour IPSEN Industry, Dreux, France) as MBP. MBP starts at 14:00 and ends by 18:00 on the day prior to surgery.

MECCLANT –C and –R Trials *(Continued)*

	Oral antibiotic prophylaxis • 2 g of neomycin at 19:00 the day prior to surgery and 1.5 g of metronidazole at 21:00 the day prior to surgery. **Perioperative intravenous antibiotic prophylaxis** • 1.5 g cefuroxime and 1g metronidazole one hour prior to first abdominal incision
Outcomes	**Primary outcome** • Surgical site infection (SSI), including superficLal wound infection, deep wound infection, and intraabdominal infection (contaminated fluLd or pus collection) **Secondary outcomes** • Anastomotic leakage • 30-day mortality • 30-day morbidity • Paralytic ileus • Length of hospital stay • Readmission rate
Starting date	**Date of registration:** - **Study Start Date:** - **Estimated Primary Completion Date:** - **Recruitment Status:** Open/recruiting
Contact information	**Contact person:** Nikolaos Gouvas **Affiliation**: Acute Hospitals, Worcester, UK **Country of origin:** Greece
Notes	**Ethics approval:** - **Source of funding:** -

MOBILE2

Study name	Mechanical Bowel Preparation and Oral Antibiotics Versus Mechanical Bowel Preparation Only Prior Rectal Surgery (MOBILE2)
Methods	**Study type:** interventional (Clinical Trial) **Study design** • Allocation: randomised • Intervention Model: parallel assignment • Masking: quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Primary Purpose: Prevention
Participants	**Condition or disease:** Rectal Adenocarcinoma, Rectum Neoplasm, Rectum Carcinoma, Colorectal Cancer, Colorectal Neoplasms, Colorectal Carcinoma, Surgical Site Infection, Surgery--Complications

MOBILE2 *(Continued)*

	Inclusion criteria • Patients scheduled for anterior rectal resection with primary anastomosis • **Exclusion Criteria** • Emergency operation • Bowel obstruction • Existing stoma • Other reason preventing mechanical bowel preparation • Allergy to neomycin or metronidazole • Age < 18 years • Lack of co-operation **Exclusion criteria** • Patient did not undergo surgery • Anterior resection was not performed • Colonic anastomosis was not performed **Target sample size:** 604
Interventions	**Treatment arms** • MOABP group: bowel preparation using MBP and oral antibiotics • MBP group: Bowel preparation using MBP and placebo. **Mechanical bowel preparation** • The patients drink 2 L of PEG and 1 L of clear fluids of the patient's choice. The MBP can be started 2 days before the surgery at 15:00 and must be completed by 15:00 on a day prior to the surgery. **Oral antibiotic prophylaxis** • The patients take 1 g of neomycin or placebo orally at 15:00 and 23:00 and 1 g of metronidazole or placebo orally at 15:00 and 23:00. **Perioperative intravenous antibiotic prophylaxis** • Cefuroxime 1.5 g and metronidazole 500 mg approximately 1 hour before surgery. The intravenous antibiotics are repeated if surgery is still ongoing 3 hours after the first intravenous dose.
Outcomes	**Primary outcome** • Comprehensive Complication Index (CCI) within 30 days after surgery **Secondary outcomes** • SSI within 30 days after surgery (according to the Centers for Disease and Control and Prevention criteria),including superficial incisional infection, deep incisional infection and organ/space infection • The number and classification of anastomosis dehiscence within 30 days of procedure • The length of hospital stay • Mortality within 90 days after surgery (any cause) • The number of patients who received adjuvant treatment divided by the number of patients that needed it within 6 months of the procedure. **Tertiary outcomes (long-term follow-up)** • 5-year overall survival • 5-year disease-specific survival • 5-year recurrence-free survival

MOBILE2 *(Continued)*

	• Difference in quality-of-life
Starting date	**Date of registration:** February 24, 2020 **Actual Study Start Date:** March 18, 2020 **Estimated Primary Completion Date:** March 2022 **Recruitment Status:** Recruiting (Last Update Posted: June 3, 2021)
Contact information	**Contact person:** Laura Koskenvuo **Affiliation**: Helsinki University Hospital **Country of origin:** Finland
Notes	**Ethics approval:** The research plan has been evaluated by the Finnish National Committee on Medical Research Ethics (TUKIJA) and Finnish Medicines Agency (FIMEA) has been notified. The EUDRA CT number for the clinical drug trials has been applied (No 2018-004355-20). The research plan was further approved by the local ethics committee of Helsinki University Hospital and in each participating centres' institutional review board (Helsinki University Hospital, Tampere University Hospital and Turku University Hospital) **Source of funding:** Cancer Society of Finland

NCT03042091

Study name	Neomycin and Metronidazole Hydrochloride With or Without Polyethylene Glycol in Reducing Infection in Patients Undergoing Elective Colorectal Surgery
Methods	**Study type:** interventional **Study design** • Allocation: randomised • Intervention model: parallel assignment • Masking:none (Open Label) • Primary purpose: Supportive Care
Participants	**Condition or disease:** Colorectal Neoplasms, Diverticulitis, Inflammatory Bowel Diseases, Surgical Site Infection **Inclusion criteria** 1. Patients undergoing ileocolic resections, partial and total colectomies, and rectal resections for neoplasm, inflammatory bowel disease, or diverticulitis 2. Participants with the mental capacity to give informed consent 3. 19 Years and older 4. All sexes eligible for study **Exclusion criteria** 1. Patients undergoing emergent colorectal resections 2. Patients who are decisionally-impaired and lack the mental capacity to give informed consent **Target sample size: 224**
Interventions	**Treatment arms**

NCT03042091 *(Continued)*

	• Arm I (mechanical bowel prep, oral antibiotics) patients receive polyethylene glycol orally (PO), neomycin PO, and metronidazole hydrochloride PO on day -1.Patients undergo colorectal resection on day 0. • Arm II (oral antibiotics)Patients receive neomycin PO and metronidazole hydrochloride PO on day -1.Patients undergo colorectal resection on day 0.
Outcomes	**Primary outcome** • Incidence of post-operative surgical site infection (SSI) including superficial/incisional, deep, and organ space, anastomotic dehiscence and leak [Time Frame: Up to 30 days post operation] **Secondary outcomes** • Incidence of post-operative *clostridium difficile* infection [Time Frame: Up to 30 days post operation] • Incidence of adynamic ileus [Time Frame: Up to 30 days post operation] • Incidence of cardiopulmonary complications [Time Frame: Up to 30 days post operation] • Incidence of urinary tract infection [Time Frame: Up to 30 days post operation] • Length of hospital stay [Time Frame: Up to 30 days post operation] • Incidence of mortality [Time Frame: Up to 30 days post operation]
Starting date	**Date of registration:** February 3, 2017 **Actual Study Start Date:** September 2016 **Estimated Primary Completion Date:** October 2020 (Last Update Posted: August 22, 2018) **Recruitment Status:** Unknown
Contact information	**Contact person:** Benjamin Phillips **Affiliation**: Thomas Jefferson University **Country of origin:** USA
Notes	**Ethics approval:** - **Source of funding:** -

NCT03491540

Study name	Mechanical Bowel Preparation and Oral Antibiotics Before Rectal Cancer Surgery (PREPACOL2)
Methods	**Study type:** - **Study design:** • Allocation: randomised • Intervention model: parallel assignment • Masking: double (participant, investigator) • Both participants and investigators are unaware of the intervention assignmentPrimary Purpose: prevention
Participants	**Condition or disease: r**ectal cancer surgery **Inclusion criteria** • Patients aged 18 or more

NCT03491540 *(Continued)*

- Scheduled to undergo elective restorative laparoscopic cancer of the rectal (<15 cm from the anal margin) with sphincter preservation
- With Signed consent
- And affiliated to the French social security system

Exclusion criteria

- Emergent surgery
- Scheduled total coloproctectomy
- Scheduled abdominoperineal resection with definitive colostomy
- Scheduled associated concomitant resection of another organ (liver, etc.)
- Active bacterial infection at the time of surgery or recent antibiotic therapy (up to 15 days before surgery)
- Associated inflammatory bowel disease
- Patients with known colonisation with multidrug-resistant enterobacteriaceae
- History of allergy or contraindication to the Ornidazole, Gentamycin, X-PREP or to any of the excipients of the drugs used.
- Cirrhosis of grade B and C (Child-Pugh classification)
- Myasthenia
- Allergy to one of the other treatments administered for the purpose of the trial (including betadine)
- Patient suffering from severe central neurologic diseases, fixed or progressive.
- Pregnant patients
- Refusal to participate or inability to provide informed consent

Target sample size: 400

Interventions	**Treatment arms** • Experimental: "MBP and oral antibiotics "group • Placebo Comparator: 2 "MBP alone " group **Mechanical bowel preparation** • Sennosides colonic preparation (X-PREP); 1 per day, on day -2 and day -1 **Oral antibiotics** • Gentamycin 80 mg, 4 per day, on day -2 and day -1; Liquid forms in individual vials • Ornidazole 1 g per day (2 tablets per day), on day -2 and day -1; In tablets
Outcomes	**Primary outcome** • Postoperative 30-day surgical site infection (SSI) **Secondary outcomes** • Overall postoperative morbidity • Severe postoperative morbidity • Postoperative mortality • Postoperative anastomotic leakage • Postoperative length of hospital stay • Unplanned hospitalisation • Tolerance of the colonic preparation • *Clostridium difficile* colitis occurrence • Rate of multiresistant bacteria carriage • Date of adjuvant chemotherapy beginning

NCT03491540 *(Continued)*

	• Temporary stoma closure rate
Starting date	**Date of registration:** April 9, 2018 **ActualStudy Start Date:** September 3, 2018 **Estimated Primary Completion Date:** May 31, 2023 **Recruitment Status:** Recruiting
Contact information	**Contact person:** Yves Panis and Massimo Giacca **Affiliation**: Service de chirurgie Colorectale/Hôpital Beaujon **Country of origin:** France
Notes	**Ethics approval:** - **Source of funding:** Assistance Publique - Hôpitaux de Paris

NCT03563586

Study name	Mechanical Bowel Preparation With or Without Oral Antibiotics for Colorectal Cancer Surgery (MEC-CA)
Methods	**Study type:** interventional (Clinical Trial) **Study design** • Allocation: randomised • Interventional model: Sequential Assignment • Masking: triple (Care Provider, Investigator, Outcomes Assessor) • Primary purpose: prevention
Participants	**Condition or disease:** Antibiotic, Bowel Cancer, Colorectal Cancer, Surgical Site Infection **Inclusion criteria** • Scheduled colorectal cancer surgery **Exclusion criteria** • Emergency surgery • Obstructive and perforated cancer • Intolerance to bowel preparation regimen • Allergies to orally administered antibiotics **Target sample size:** 105
Interventions	**Treatment arms** • Bowel Preparation plus antibiotics: preoperative oral antibiotic therapy with rifaximin 400 mg plus metronidazole 500 mg the day prior to surgery at 2:00, 3:00 and 10:00 pm, with mechanical bowel preparation (2 vials sodium phospate 45 mL at 1:00 and 7:00 pm) • Bowel preparation: preoperative mechanical bowel preparation (2 vials sodium phospate 45ml at 1:00 and 7:00 pm)
Outcomes	**Primary outcome**

NCT03563586 *(Continued)*

	• Surgical Site Infections [Time Frame: 30 days] **Secondary outcomes** • Anastomotic leaks [Time Frame: 30 days] • Other surgical and non-surgical complications [Time Frame: 30 days] • Hospital length of stay [Time Frame: 30 days] • Readmission rate [Time Frame: 30 days] • Patients' preparation tolerance [Time Frame: 30 days] • Preparation regimens side effects [Time Frame: 30 days] • Time to beginning of adjuvant treatment for colorectal cancer [Time Frame: 60 days]
Starting date	**Date of registration:** June 9, 2018 **Study Start Date:** April 1, 2018 **Estimated Primary Completion Date:** April 1, 2021 **Recruitment Status:** Recruiting (Last Update Posted: September 11, 2020)
Contact information	**Contact person:** George Theodoropoulos **Affiliation**: National and Kapodistrian University of Athens **Country of origin:** Greece
Notes	**Ethics approval:** - **Source of funding:** National and Kapodistrian University of Athens

NCT03856671

Study name	Prophylactic Effect Preoperative Antibiotics With Mechanical Bowel Preparation in SSIs
Methods	**Study type:** interventional **Study design** • Allocation: randomised • Intervention Model: parallel assignment • Masking d: no masking is to be conducted in the current study • Primary purpose: prevention
Participants	**Condition or disease:** Surgical Site Infection, Postoperative Complications, Bowel Preparation, Oral Antibiotics, Colorectal Cancer **Inclusion criteria** • Older than 18 years old • Undergoing laparoscopic colorectal surgery due to malignancy **Exclusion criteria** • No elective surgery • Intra-abdominal infection • Combination of other infectious surgery such as appendectomy, cholecystomy • Sever comorbidity such as uncontrolled hypertension and diabetes mellitus • Peritoneal implantation and metastasis

NCT03856671 *(Continued)*

	• Radiotherapy history • Colorectal surgery due to benign lesions • Allergic to antibiotics or PEG • Preoperative dermatosis may interfere wound healing • Long time application of corticosteroid • Autoimmune disease may affect wound healing • Patients refuse to enrol **Target sample size:** 360
Interventions	**Treatment arms** • Experimental: oral antibiotics+mechanical bowel preparationLiquid diet and polyethylene glycol with 2L water was administrated orally 1 day before surgery. A combination of neomycin 1g and metronidazole 0.2g every 6 hours was also administrated. Enteroclysis was conducted for patients on surgical morning. • No Intervention: simple mechanical bowel preparation. Only liquid diet and polyethylene glycol with 2L water was administrated orally 1 day before surgery. Enteroclysis was conducted for patients on surgical morning.
Outcomes	**Primary outcome** • Surgical site infection incidence [Time Frame: 30 days after surgery] **Secondary outcomes** • Antibiotics associated complications [Time Frame: 30 days after surgery] • Length of hospital stay after surgery [Time Frame: 30 days after surgery] • Bowel recovery time [Time Frame: 7 days after surgery] • Other postoperative complications [Time Frame: 30 days after surgery]
Starting date	**Date of registration:** February 27, 2019 **Actual Study Start Date:** January 17, 2019 **Estimated Primary Completion Date:** June 30, 2021 (Last Update Posted: February 5, 2020) **Recruitment Status:** Recruiting (Last Update Posted: February 5, 2020)
Contact information	**Contact person:** Purun Lei **Affiliation**: The Third Affiliated Hospital of Sun Yat-Sen university **Country of origin:** China
Notes	**Ethics approval:** - **Source of funding:** -

NCT04931173

Study name	Mechanical Bowel Prep Randomized Study
Methods	**Study type:** interventional **Study design** • Allocation: randomised

NCT04931173 *(Continued)*

- Intervention model: this is a multi-centre, parallel, two-arm, non-inferiority randomised controlled trial comparing IVA+OA+MBP versus IVA+OA to reduce surgical site infection following colon surgery
- Masking: none (Open Label)
- Primary purpose: other

Participants	**Condition or disease:** Colorectal surgery **Inclusion criteria** • Undergoing elective colon surgery for benign or malignant disease • Over the age of 18 years • Provides informed consent **Exclusion criteria** • Known anaphylaxis to neomycin or metronidazole • Pregnancy or lactation • Chronic renal failure (serum creatinine > 220 umol/L). **Target sample size:** 1062
Interventions	**Treatment arms** • Group A: IV and Oral antibiotics (IVA+OA)Patients will receive cefazolin 2g IV and metronidazole 500 mg IV administered by the anaesthesiologist within 60 minutes prior to the skin incision on the day of surgery. Standardised re-dosing of cefazolin 2g IV will occur every 4 hours and metronidazole 500 mg IV will occur every 8 hours during the surgical procedure. Following surgery, no further IVA will be given for SSI prophylaxis. In addition, patients will self-administer 1g neomycin and 1g metronidazole orally at 1500, 1700 and 2300 hours the day before surgery. Following this, they will not receive any further OAs for SSI prophylaxis. • Group B: IV antibiotics, MBP and oral antibiotics (IVA+MBP+OA) • Patients will receive IVA and OA per Group A. In addition, patients will stay on clear fluids and self-administer a 2L polyethylene glycol MBP orally, between 1500 and 2300 hours on the day before surgery.
Outcomes	**Primary outcome** • Surgical Site Infection Rate [Time Frame: 30 days following date of surgery] **Secondary outcomes** • Patient tolerability of the bowel preparation [Time Frame: 5 minutes (completed in pre-operative holding area on the day of surgery)] • Length of stay [Time Frame: 2-7 days] • 30-day ER rate [Time Frame: 30 days] • 30-day readmission rate [Time Frame: 30 days]
Starting date	**Date of registration:** June 18, 2021 **EstimatedStudy Start Date:** April 2022 **Estimated Primary Completion Date:** December 2025 **Recruitment Status:** not yet recruiting
Contact information	**Contact person:** Erin Kennedy **Affiliation**: Division of General Surgery, Mount Sinai Hospital, Canada

NCT04931173 *(Continued)*

	Country of origin: Canada
Notes	**Ethics approval:** - **Source of funding:** -

ORALEV2

Study name	Preoperative Oral Antibiotics With vs Without Mechanical Bowel Preparation to Reduce Surgical Site Infections Following Colonic Resection: an International Randomized Controlled Trial. (ORALEV2)
Methods	**Study type:** Interventional **Study design** • Allocation: randomised • Intervention model: parallel assignment • Masking: single (Outcomes Assessor) • Primary purpose: prevention
Participants	**Condition or disease:** Wounds and Injuries, Surgery--Complications **Inclusion criteria** • Patients of both genders, aged 18 years or above, with colonic disease without contraindications to surgical treatment, diagnosed with neoplasia or diverticular disease (diverticulosis with indication to elective surgery: stricture, chronic constipation), for whom a segmental or total colectomy is indicated. • Patients who voluntarily accept to join the study and sign a dedicated written consent. • Patients with capability of understanding the study and taking the medications prescribed. **Exclusion criteria** • Patients undergoing urgent surgery (within < 24 hours) • Patients who refuse to participate • Patients with rectal disease or neoplasia • Patients with pre-existing intra-abdominal sepsis (abscess, acute diverticulitis) • Patients who received preoperative antibiotic treatment for any other reasons during the 2 weeks before surgery • Patients with Crohn's disease or ulcerative colitis • Patients unlikely to adhere to the treatment prescribed • Patients with allergy or contraindication to the medications used in the study • Patients who need mechanical bowel preparation • Patients with contraindication to the bowel preparation used in the study (Citrafleet®) • Patients with kidney failure needing haemodialysis or with hypermagnesaemia • Patients with severe heart failurePatients with gastric or duodenal ulcer • Patients with mechanical obstruction • Patients with toxic megacolon • Patients with ascites or rhabdomyolysis **Target sample size:** 968
Interventions	**Treatment arms**

ORALEV2 *(Continued)*

- Group A (experimental): The day before surgery, patients will receive oral ciprofloxacin (750 mg/12 hours, meaning two doses at 12:00 PM and 0:00 PM) and oral metronidazole (250 mg/8 h, meaning three doses at 08:00 AM, 4:00 PM and 0:00 PM) and oral sodium picosulfate (sodium picosulfate/light magnesium oxide/anhydrous citric acid 10 mg/3.5 g/10.97 g per dose, two doses the day before surgery, Citrafleet®) (one sachet at 4:00 PM and one sachet at 7:00 PM). At anaesthetic induction, patients will receive iv cefuroxime 1.5 g and IV metronidazole 1 g.
- Group B (control): the day before surgery, patients will receive oral ciprofloxacin (750 mg/12 hours, meaning two doses at 12:00 PM and 0:00 PM) and oral metronidazole (250 mg/8 h, meaning three doses at 08:00 AM, 4:00 PM and 0:00 PM). At anaesthetic induction, patients will receive iv cefuroxime 1.5 g andIV metronidazole 1 g.

Outcomes	**Primary outcome** • SSIs (defined as the sum of superficial, deep and organ-space infections) occurring in each group within 30 days after surgery **Secondary outcomes** • Postoperative ileus • Anastomotic leak • Kidney failure • Complete postoperative recover • Length of hospital stay • Reintervention • Readmission • Patient satisfaction • Perioperative MBP-associated hypovolaemia
Starting date	**Date of registration:** November 13, 2019 **EstimatedStudy Start date:** September 14, 2021 **Estimated Primary Completion Date:** May 2023 **Recruitment Status:** Not yet recruiting (Last Update Posted: August 31, 2021)
Contact information	**Contact person:** Eloy Espín-Basany **Affiliation**: Colorectal Surgery Unit, Hospital Vall d'Hebron, **Country of origin:** Spain
Notes	**Ethics approval:** The study has been approved by the Ethics Committee of the Coordinating Centre and by the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) **Source of funding:** This study is funded by the Instituto de Salud Carlos III of the Spanish Ministry of Science and Innovation through grant PI20/00622

Panaiotti 2020

Study name	Mechanical Bowel Preparation with Oral Antibiotics Vs No Preparation Before Elective Colon Resection for Colon Cancer
Methods	**Study type:**

Panaiotti 2020 *(Continued)*

	Study design: randomised controlled trial
Participants	**Condition or disease:** elective colon resection **Inclusion criteria** • Signed the informed consent form, age above 18 years, with diagnosed primary colon cancer T1-4a N0-2 M0-1 (in case of resectable metastases), clinical indications for laparoscopic or open colonic resection with primary anastomosis planned. **Exclusion criteria** • Taking antibiotics within 30 days before surgery, previous colonic resection, expected stoma formation, renal or liver failure, allergic reactions to antibiotics or components of MBP drugs **Target sample size:** 712
Interventions	**Treatment arms** • Eligible patients will be randomised in 1:1 ratio to undergo surgery either with preoperative MBP +OA or without any bowel preparation
Outcomes	**Primary outcome** • Surgical site infection (SSI) rate (according to CDC definition divided to 3 groups: superficial incisional SSI, deep incisional SSI, organ/space SSI) **Secondary outcomes** • Duration of operation • Intraoperative complications rate • Surgeon's assessment of bowel preparation • Quality of operation
Starting date	**Date of registration:** - **EstimatedStudy Start date:** - **Estimated Primary Completion Date:** - **Recruitment Status:** -
Contact information	**Contact person:** Aleksandra Olkina **Affiliation**: Surgical department of abdominal oncology, Saint Petersburg **Country of origin:** Russia
Notes	**Ethics approval:** - **Source of funding:** -

REaCT-NSQIP

Study name	An RCT Protocol Using the REaCT and NSQIP Platforms to Compare Oral Antibiotics and No Mechanical Bowel Preparation for Surgical Site Infection in Colon Surgery
Methods	**Study type:** - **Study design:** multi-centre randomised controlled trail

REaCT-NSQIP *(Continued)*

Participants	**Condition or disease:** elective colon surgery **Inclusion criteria** - **Exclusion criteria** - **Target sample size:** -
Interventions	**Treatment arms** • No preparation before surgery • Oral antibiotics (neomycin and flagyl), to be taken the day before the surgery
Outcomes	**Primary outcome** • SSI rate **Secondary outcomes** • Length of stay • Hospital costs • Quality of life • *C. Difficile* infections • Increase of antibiotic-resistant
Starting date	**Date of registration: -** **ActualStudy Start Date: -** **Estimated Primary Completion Date: -** **Recruitment Status: -**
Contact information	**Contact person:** S.S. Apte **Affiliation**: The Ottawa Hospital, Ottawa **Country of origin:** Canada
Notes	**Ethics approval:** - **Source of funding:** -

Tagliaferri 2020

Study name	Combined mechanical and oral antibiotic bowel preparation versus oral antibiotics alone for the reduction of surgical site infection following elective colorectal resection: Interim analysis
Methods	**Study type:** - **Study design:** randomised controlled trial
Participants	**Condition or disease:** Elective colon resection **Inclusion criteria** All patients over 18 years of age undergoing elective colon resections were included in the study

Tagliaferri 2020 *(Continued)*

	Exclusion criteria - **Target sample size:** -
Interventions	**Treatment arms** • Intervention: Neomycin and Metronidazole for antibiotic preparation with polyethylene glycol. • Control: Neomycin and Metronidazole for antibiotic preparation without polyethylene glycol.
Outcomes	**Primary outcomes** • Superficial and deep SSI • Anastomotic leak **Secondary outcomes** • *Clostridium difficile* infection • Ileus • Cardiopulmonary complications • Urinary tract infectionLength of stay • Mortality
Starting date	**Date of registration:** - **Study Start Date:** - **Estimated Primary Completion Date:** - **Recruitment Status:** -
Contact information	**Contact person:** A. R. Tagliaferri **Affiliation**: - **Country of origin: USA**
Notes	**Ethics approval:** - **Source of funding:** -

BMI: body mass index; **IV:** intravenous; **ECOG:** Eastern Cooperative Oncology Group; **IBD:** irritable bowel disease; **MRI:** magnetic resonance imaging; **RCT:** randomised controlled trial; **SSI:** surgical site infections

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 SSI

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lau 1988	✓	✓	✓	✓	~	~
Takesue 2000	~	✓	✓	✓	~	~
Ishida 2001	✓	✓	✓	✓	~	~
Lewis 2002	✓	✓	✓	✓	~	~
Espin-Basany 2005	~	✓	✓	✓	~	~
Kobayashi 2007	✓	✓	✓	✓	~	~
Horie 2007	✓	✓	✓	✓	~	~
Oshima 2013	~	✓	✓	✓	~	~
Sadahiro 2014	✓	✓	✓	✓	✓	✓
Ikeda 2016	✓	✓	✓	✓	✓	✓
Hata 2016	✓	✓	✓	✓	✓	✓
Anjum 2017	✓	✓	✓	✓	~	~
Uchino 2019	✓	✓	✓	✓	✓	✓
Rybakov 2021	✓	✓	✓	✓	✓	✓
Papp 2021	✓	✓	✓	✓	✓	✓
Arezzo 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Anastomotic leakage

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lau 1988	✓	✓	✓	✓	~	~
Takesue 2000	~	✓	✓	✓	~	~
Ishida 2001	✓	✓	✓	✓	~	~
Horie 2007	✓	✓	✓	✓	~	~
Sadahiro 2014	✓	✓	✓	✓	✓	✓
Hata 2016	✓	✓	✓	✓	✓	✓
Ikeda 2016	✓	✓	✓	✓	✓	✓
Rybakov 2021	✓	✓	✓	✓	✓	✓
Papp 2021	✓	✓	✓	✓	✓	✓
Arezzo 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.5 Mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lazorthes 1982	~	✓	✓	✓	~	~
Arezzo 2021	✓	✓	✓	✓	✓	✓
Papp 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.8 Incidence of postoperative ileus

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Espin-Basany 2005	~	✓	✓	✓	~	~
Hata 2016	✓	✓	✓	✓	✓	✓
Ikeda 2016	✓	✓	✓	✓	✓	✓
Rybakov 2021	✓	✓	✓	✓	✓	✓
Papp 2021	✓	✓	✓	✓	✓	✓
Arezzo 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.9 Length of hospital stay

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lau 1988	✓	✓	✓	✓	~	~
Ikeda 2016	✓	✓	✓	✓	✓	✓
Arezzo 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.1 SSI

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Zmora 2003	✓	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ram 2005	✓	✓	✓	✓	~	~
Suzuki 2020	✓	✓	✓	✓	~	~

Risk of bias for analysis 2.2 Anastomotic leakage

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Zmora 2003	✓	✓	✓	✓	~	~
Ram 2005	✓	✓	✓	✓	~	~
Suzuki 2020	✓	✓	✓	✓	~	~

Risk of bias for analysis 2.3 Mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Zmora 2003	✓	✓	✓	✓	~	~
Ram 2005	✓	✓	✓	✓	~	~

Risk of bias for analysis 2.4 Incidence of postoperative ileus

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Zmora 2003	✓	✓	✓	✓	~	~
Ram 2005	✓	✓	✓	✓	~	~

Risk of bias for analysis 3.1 SSI

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Koskenvuo 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.4 Anastomotic leakage

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Koskenvuo 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.8 Incidence of postoperative ileus

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Koskenvuo 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.9 Length of hospital stay

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Koskenvuo 2019	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

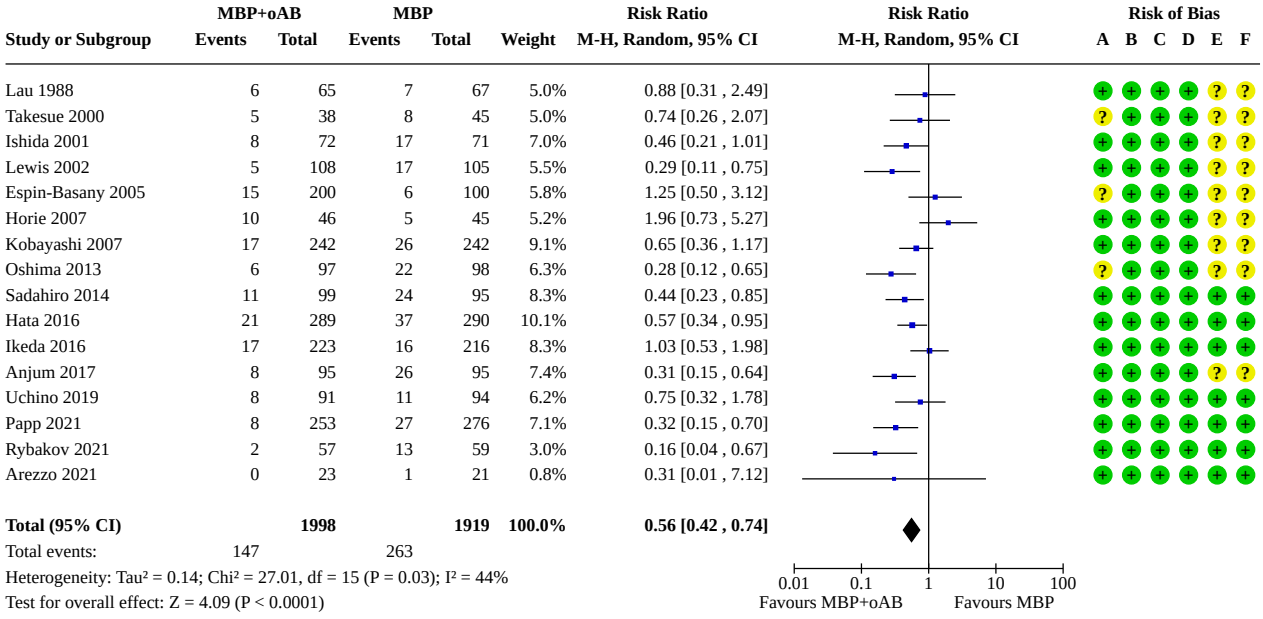
Comparison 1. MBP+oAB vs. MBP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 SSI	16	3917	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.74]
1.2 Incisional SSI	10	3054	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.66]
1.3 Organ/space SSI	10	3054	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.98]
1.4 Anastomotic leakage	10	2356	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 0.99]
1.5 Mortality	3	639	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.82]
1.6 Mild postoperative complications according to Clavien-Dindo(I + II)	3	695	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.29, 2.00]
1.7 Severe postoperative complications according to Clavien-Dindo (III + IV)	3	695	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.59, 1.70]
1.8 Incidence of postoperative ileus	6	2013	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.32]
1.9 Length of hospital stay	3	621	Mean Difference (IV, Random, 95% CI)	-0.19 [-1.81, 1.44]
1.10 Side effects of Intervention - Nausea/Vometing	3	545	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.33, 3.72]
1.11 Side effects of Intervention - Abdominal pain	3	545	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.67, 4.82]
1.12 C. difficile-related diarrhoea	3	1547	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.24, 3.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13 SSI_Subgroup analysis regarding surgery indication	16	3915	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.74]
1.13.1 Only malignant surgical indications	9	2160	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.96]
1.13.2 Only benign surgical indications	2	380	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.17, 1.22]
1.13.3 Both malignant and benign surgical indications	5	1375	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.26, 0.71]
1.14 SSI_Subgroup analysis regarding the type of surgery	14	3577	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.44, 0.80]
1.14.1 Colon and rectum resections	13	3461	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.46, 0.83]
1.14.3 Rectum resections only	1	116	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.67]
1.15 SSI_Subgroup analysis regarding the surgical approach	13	3075	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.41, 0.82]
1.15.1 Minimally invasive surgical approach	3	1062	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.46, 1.10]
1.15.2 Open surgical approach	5	684	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.39, 1.40]
1.15.3 Both open and minimally invasive surgical approach	5	1329	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.24, 0.72]
1.16 SSI_Subgroup analysis regarding the duration of mechanical bowel preparation	15	3871	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.74]
1.16.1 Bowel preparation on the day before surgery	13	3547	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.40, 0.77]
1.16.2 Bowel preparation over several days before the operation	2	324	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.30, 0.99]
1.17 SSI_Subgroup analysis regarding the agent combination of oral antibiotics	16	3915	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.74]
1.17.1 Combination of metronidazole and an aminoglycoside (neomycin or kanamycin)	9	2717	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.39, 0.78]
1.17.2 Combination of erythromycin and an aminoglycoside (neomycin or kanamycin)	3	757	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.40, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.17.3 Other oral antibiotic combinations	4	441	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.13, 1.59]
1.18 SSI_Subgroup analysis regarding the duration of intravenous antibiotic prophylaxis	16	3915	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.74]
1.18.1 Only perioperative intravenous antibiotic prophylaxis	9	2290	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.36, 0.72]
1.18.2 Continuation of perioperative intravenous antibiotic prophylaxis for 24 hours	3	824	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.19, 1.09]
1.18.3 Continuation of perioperative intravenous antibiotic prophylaxis beyond 24 hours	4	801	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.44, 1.30]

Analysis 1.1. Comparison 1: MBP+oAB vs. MBP, Outcome 1: SSI

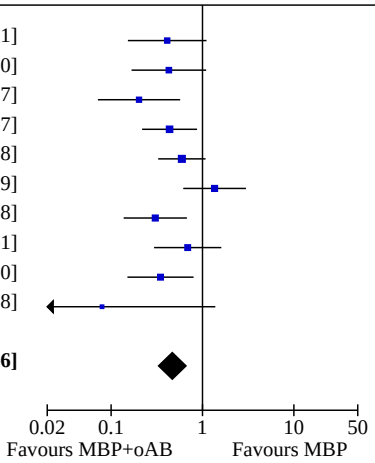


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: MBP+oAB vs. MBP, Outcome 2: Incisional SSI

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ishida 2001	5	72	12	71	8.5%	0.41 [0.15 , 1.11]
Kobayashi 2007	6	242	14	242	9.2%	0.43 [0.17 , 1.10]
Oshima 2013	4	97	20	98	8.0%	0.20 [0.07 , 0.57]
Sadahiro 2014	10	99	22	95	13.3%	0.44 [0.22 , 0.87]
Hata 2016	16	289	27	290	15.4%	0.59 [0.33 , 1.08]
Ikeda 2016	14	223	10	216	11.5%	1.36 [0.62 , 2.99]
Anjum 2017	7	95	23	95	11.4%	0.30 [0.14 , 0.68]
Uchino 2019	8	91	12	94	10.5%	0.69 [0.30 , 1.61]
Papp 2021	7	253	22	276	10.7%	0.35 [0.15 , 0.80]
Rybakov 2021	0	57	6	59	1.4%	0.08 [0.00 , 1.38]
Total (95% CI)		**1518**		**1536**	**100.0%**	**0.47 [0.33 , 0.66]**
Total events:	77		168			

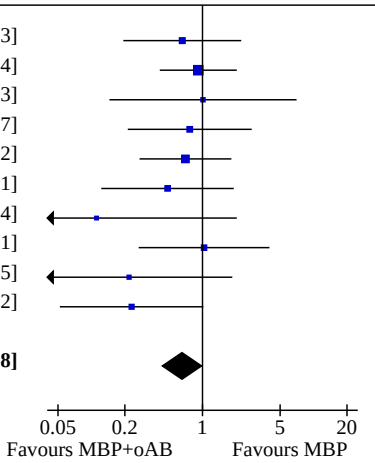
Heterogeneity: Tau² = 0.11; Chi² = 14.20, df = 9 (P = 0.12); I² = 37%
Test for overall effect: Z = 4.31 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: MBP+oAB vs. MBP, Outcome 3: Organ/space SSI

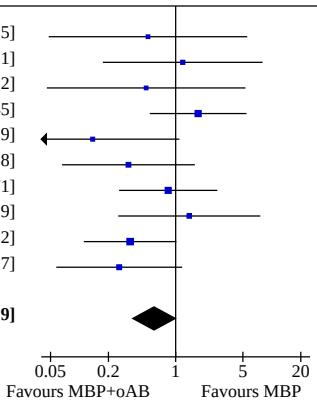
Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ishida 2001	4	72	6	71	11.0%	0.66 [0.19 , 2.23]
Kobayashi 2007	11	242	12	242	25.8%	0.92 [0.41 , 2.04]
Oshima 2013	2	97	2	98	4.4%	1.01 [0.15 , 7.03]
Sadahiro 2014	4	99	5	95	10.0%	0.77 [0.21 , 2.77]
Hata 2016	7	289	10	290	18.2%	0.70 [0.27 , 1.82]
Ikeda 2016	3	223	6	216	8.7%	0.48 [0.12 , 1.91]
Anjum 2017	0	95	4	95	1.9%	0.11 [0.01 , 2.04]
Uchino 2019	4	91	4	94	9.0%	1.03 [0.27 , 4.01]
Papp 2021	1	253	5	276	3.6%	0.22 [0.03 , 1.85]
Rybakov 2021	2	57	9	59	7.4%	0.23 [0.05 , 1.02]
Total (95% CI)		**1518**		**1536**	**100.0%**	**0.65 [0.44 , 0.98]**
Total events:	38		63			

Heterogeneity: Tau² = 0.00; Chi² = 6.03, df = 9 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: MBP+oAB vs. MBP, Outcome 4: Anastomotic leakage

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Lau 1988	1	65	2	67	4.4%	0.52 [0.05 , 5.55]	+	+	+	+	?	?
Takesue 2000	2	38	2	45	6.7%	1.18 [0.18 , 8.01]	?	+	+	+	?	?
Ishida 2001	1	72	2	71	4.4%	0.49 [0.05 , 5.32]	+	+	+	+	?	?
Horie 2007	7	46	4	45	16.6%	1.71 [0.54 , 5.45]	+	+	+	+	?	?
Sadahiro 2014	1	99	7	95	5.7%	0.14 [0.02 , 1.09]	+	+	+	+	+	+
Ikeda 2016	2	223	6	216	9.4%	0.32 [0.07 , 1.58]	+	+	+	+	+	+
Hata 2016	5	289	6	290	16.2%	0.84 [0.26 , 2.71]	+	+	+	+	+	+
Arezzo 2021	3	26	2	24	8.3%	1.38 [0.25 , 7.59]	+	+	+	+	+	+
Papp 2021	4	253	13	276	17.9%	0.34 [0.11 , 1.02]	+	+	+	+	+	+
Rybakov 2021	2	57	8	59	10.4%	0.26 [0.06 , 1.17]	+	+	+	+	+	+
Total (95% CI)		**1168**		**1188**	**100.0%**	**0.60 [0.36 , 0.99]**						
Total events:	28		52									

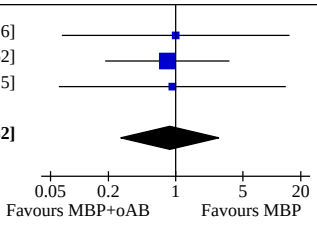


Heterogeneity: Tau² = 0.06; Chi² = 9.84, df = 9 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.99 (P = 0.05)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: MBP+oAB vs. MBP, Outcome 5: Mortality

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Lazorthes 1982	1	30	1	30	18.6%	1.00 [0.07 , 15.26]	?	+	+	+	?	?
Papp 2021	3	253	4	276	62.6%	0.82 [0.18 , 3.62]	+	+	+	+	+	+
Arezzo 2021	1	26	1	24	18.8%	0.92 [0.06 , 13.95]	+	+	+	+	+	+
Total (95% CI)		**309**		**330**	**100.0%**	**0.87 [0.27 , 2.82]**						
Total events:	5		6									



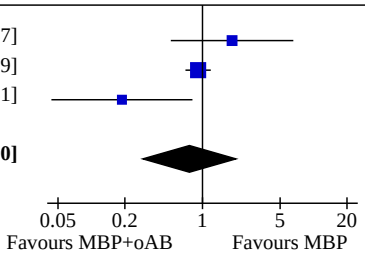
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.81)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: MBP+oAB vs. MBP, Outcome 6: Mild postoperative complications according to Clavien-Dindo(I + II)

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Arezzo 2021	6	26	3	24	27.1%	1.85 [0.52 , 6.57]
Papp 2021	72	253	86	276	49.4%	0.91 [0.70 , 1.19]
Rybakov 2021	2	57	11	59	23.5%	0.19 [0.04 , 0.81]
Total (95% CI)		**336**		**359**	**100.0%**	**0.76 [0.29 , 2.00]**
Total events:	80		100			

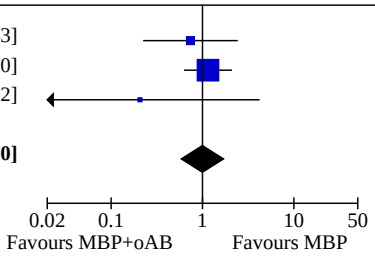
Heterogeneity: Tau² = 0.47; Chi² = 5.73, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: MBP+oAB vs. MBP, Outcome 7: Severe postoperative complications according to Clavien-Dindo (III + IV)

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Arezzo 2021	4	26	5	24	19.8%	0.74 [0.22 , 2.43]
Papp 2021	20	253	19	276	77.1%	1.15 [0.63 , 2.10]
Rybakov 2021	0	57	2	59	3.1%	0.21 [0.01 , 4.22]
Total (95% CI)		**336**		**359**	**100.0%**	**1.00 [0.59 , 1.70]**
Total events:	24		26			

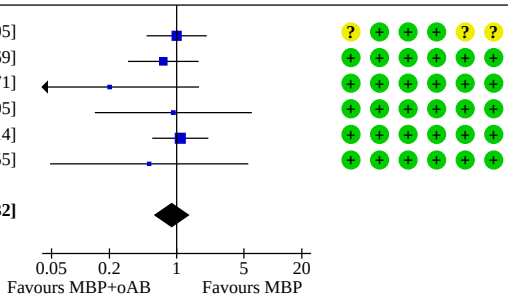
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: MBP+oAB vs. MBP, Outcome 8: Incidence of postoperative ileus

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Espin-Basany 2005	20	200	10	100	31.0%	1.00 [0.49 , 2.05]
Ikeda 2016	9	223	12	216	22.6%	0.73 [0.31 , 1.69]
Hata 2016	1	289	5	290	3.5%	0.20 [0.02 , 1.71]
Arezzo 2021	2	26	2	24	4.5%	0.92 [0.14 , 6.05]
Papp 2021	16	253	16	276	35.6%	1.09 [0.56 , 2.14]
Rybakov 2021	1	57	2	59	2.9%	0.52 [0.05 , 5.55]
Total (95% CI)		**1048**		**965**	**100.0%**	**0.89 [0.59 , 1.32]**
Total events:	49		47			

Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 5 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

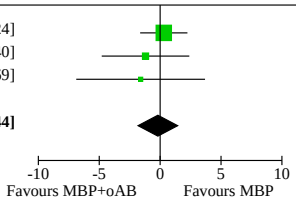


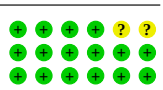
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: MBP+oAB vs. MBP, Outcome 9: Length of hospital stay

Study or Subgroup	MBP+oAB Mean	MBP+oAB SD	MBP+oAB Total	MBP Mean	MBP SD	MBP Total	Weight	Mean Difference IV, Random, 95% CI
Lau 1988	12.1	4.9	65	11.8	6.4	67	70.1%	0.30 [-1.64 , 2.24]
Ikeda 2016	12.2	8.9	223	13.4	25.5	216	20.4%	-1.20 [-4.80 , 2.40]
Arezzo 2021	10	7.3	26	11.6	11.2	24	9.5%	-1.60 [-6.89 , 3.69]
Total (95% CI)			**314**			**307**	**100.0%**	**-0.19 [-1.81 , 1.44]**

Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable



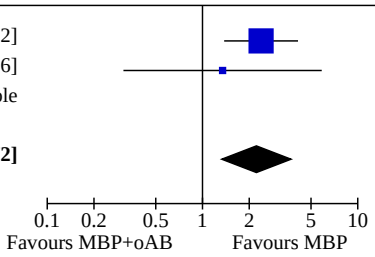


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: MBP+oAB vs. MBP, Outcome 10: Side effects of Intervention - Nausea/Vometing

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Espin-Basany 2005	62	200	13	100	87.8%	2.38 [1.38 , 4.12]
Oshima 2013	4	97	3	98	12.2%	1.35 [0.31 , 5.86]
Arezzo 2021	0	26	0	24		Not estimable
Total (95% CI)		**323**		**222**	**100.0%**	**2.22 [1.33 , 3.72]**
Total events:	66		16			

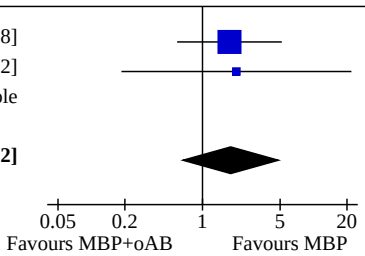
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.05 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: MBP+oAB vs. MBP, Outcome 11: Side effects of Intervention - Abdominal pain

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Espin-Basany 2005	14	200	4	100	82.8%	1.75 [0.59 , 5.18]
Oshima 2013	2	97	1	98	17.2%	2.02 [0.19 , 21.92]
Arezzo 2021	0	26	0	24		Not estimable
Total (95% CI)		**323**		**222**	**100.0%**	**1.79 [0.67 , 4.82]**
Total events:	16		5			

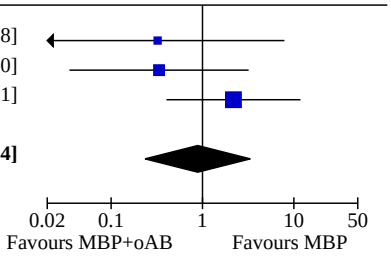
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: MBP+oAB vs. MBP, Outcome 12: C. difficile-related diarrhoea

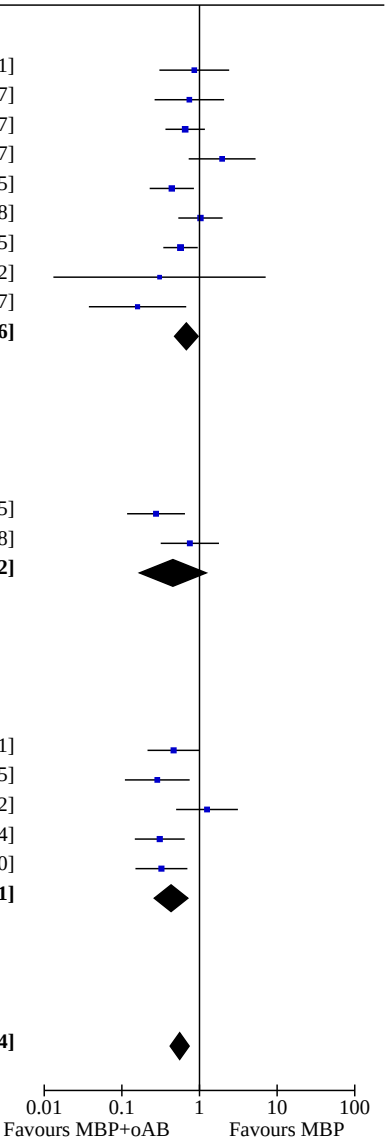
Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ikeda 2016	0	223	1	216	16.4%	0.32 [0.01 , 7.88]
Hata 2016	1	289	3	290	31.3%	0.33 [0.03 , 3.20]
Papp 2021	4	253	2	276	52.3%	2.18 [0.40 , 11.81]
Total (95% CI)		**765**		**782**	**100.0%**	**0.89 [0.24 , 3.34]**
Total events:	5		6			

Heterogeneity: Tau² = 0.13; Chi² = 2.19, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



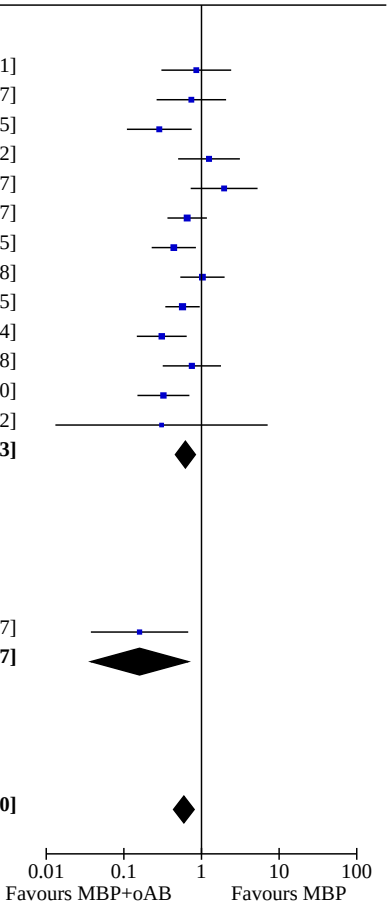
Analysis 1.13. Comparison 1: MBP+oAB vs. MBP, Outcome 13: SSI_Subgroup analysis regarding surgery indication

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Only malignant surgical indications						
Lau 1988	6	65	7	65	4.9%	0.86 [0.30 , 2.41]
Takesue 2000	5	38	8	45	5.0%	0.74 [0.26 , 2.07]
Kobayashi 2007	17	242	26	242	9.1%	0.65 [0.36 , 1.17]
Horie 2007	10	46	5	45	5.2%	1.96 [0.73 , 5.27]
Sadahiro 2014	11	99	24	95	8.3%	0.44 [0.23 , 0.85]
Ikeda 2016	17	223	16	216	8.3%	1.03 [0.53 , 1.98]
Hata 2016	21	289	37	290	10.1%	0.57 [0.34 , 0.95]
Arezzo 2021	0	23	1	21	0.8%	0.31 [0.01 , 7.12]
Rybakov 2021	2	57	13	59	3.0%	0.16 [0.04 , 0.67]
Subtotal (95% CI)		**1082**		**1078**	**54.8%**	**0.68 [0.48 , 0.96]**
Total events:	89		137			
Heterogeneity: Tau² = 0.09; Chi² = 12.45, df = 8 (P = 0.13); I² = 36%						
Test for overall effect: Z = 2.19 (P = 0.03)						
1.13.2 Only benign surgical indications						
Oshima 2013	6	97	22	98	6.3%	0.28 [0.12 , 0.65]
Uchino 2019	8	91	11	94	6.2%	0.75 [0.32 , 1.78]
Subtotal (95% CI)		**188**		**192**	**12.5%**	**0.45 [0.17 , 1.22]**
Total events:	14		33			
Heterogeneity: Tau² = 0.31; Chi² = 2.63, df = 1 (P = 0.10); I² = 62%						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.13.3 Both malignant and benign surgical indications						
Ishida 2001	8	72	17	71	7.0%	0.46 [0.21 , 1.01]
Lewis 2002	5	108	17	105	5.5%	0.29 [0.11 , 0.75]
Espin-Basany 2005	15	200	6	100	5.8%	1.25 [0.50 , 3.12]
Anjum 2017	8	95	26	95	7.4%	0.31 [0.15 , 0.64]
Papp 2021	8	253	27	276	7.1%	0.32 [0.15 , 0.70]
Subtotal (95% CI)		**728**		**647**	**32.8%**	**0.43 [0.26 , 0.71]**
Total events:	44		93			
Heterogeneity: Tau² = 0.14; Chi² = 7.26, df = 4 (P = 0.12); I² = 45%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
Total (95% CI)		**1998**		**1917**	**100.0%**	**0.56 [0.42 , 0.74]**
Total events:	147		263			
Heterogeneity: Tau² = 0.14; Chi² = 26.92, df = 15 (P = 0.03); I² = 44%						
Test for overall effect: Z = 4.11 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.37, df = 2 (P = 0.31), I² = 15.7%						



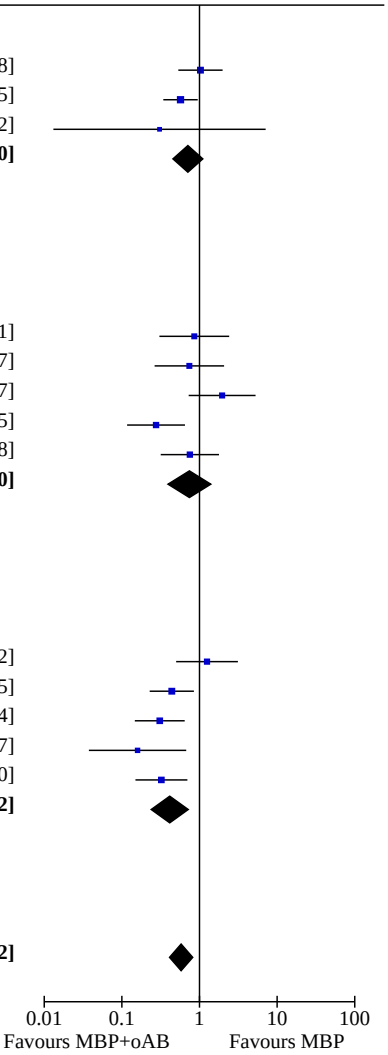
Analysis 1.14. Comparison 1: MBP+oAB vs. MBP, Outcome 14: SSI_Subgroup analysis regarding the type of surgery

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Colon and rectum resections						
Lau 1988	6	65	7	65	5.7%	0.86 [0.30 , 2.41]
Takesue 2000	5	38	8	45	5.8%	0.74 [0.26 , 2.07]
Lewis 2002	5	108	17	105	6.3%	0.29 [0.11 , 0.75]
Espin-Basany 2005	15	200	6	100	6.7%	1.25 [0.50 , 3.12]
Horie 2007	10	46	5	45	6.1%	1.96 [0.73 , 5.27]
Kobayashi 2007	17	242	26	242	10.5%	0.65 [0.36 , 1.17]
Sadahiro 2014	11	99	24	95	9.5%	0.44 [0.23 , 0.85]
Ikeda 2016	17	223	16	216	9.5%	1.03 [0.53 , 1.98]
Hata 2016	21	289	37	290	11.5%	0.57 [0.34 , 0.95]
Anjum 2017	8	95	26	95	8.5%	0.31 [0.15 , 0.64]
Uchino 2019	8	91	11	94	7.2%	0.75 [0.32 , 1.78]
Papp 2021	8	253	27	276	8.2%	0.32 [0.15 , 0.70]
Arezzo 2021	0	23	1	21	0.9%	0.31 [0.01 , 7.12]
Subtotal (95% CI)		**1772**		**1689**	**96.5%**	**0.62 [0.46 , 0.83]**
Total events:	131		211			
Heterogeneity: Tau² = 0.11; Chi² = 20.47, df = 12 (P = 0.06); I² = 41%						
Test for overall effect: Z = 3.17 (P = 0.002)						
1.14.3 Rectum resections only						
Rybakov 2021	2	57	13	59	3.5%	0.16 [0.04 , 0.67]
Subtotal (95% CI)		**57**		**59**	**3.5%**	**0.16 [0.04 , 0.67]**
Total events:	2		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.49 (P = 0.01)						
Total (95% CI)		**1829**		**1748**	**100.0%**	**0.59 [0.44 , 0.80]**
Total events:	133		224			
Heterogeneity: Tau² = 0.14; Chi² = 23.79, df = 13 (P = 0.03); I² = 45%						
Test for overall effect: Z = 3.37 (P = 0.0008)						
Test for subgroup differences: Chi² = 3.27, df = 1 (P = 0.07), I² = 69.4%						



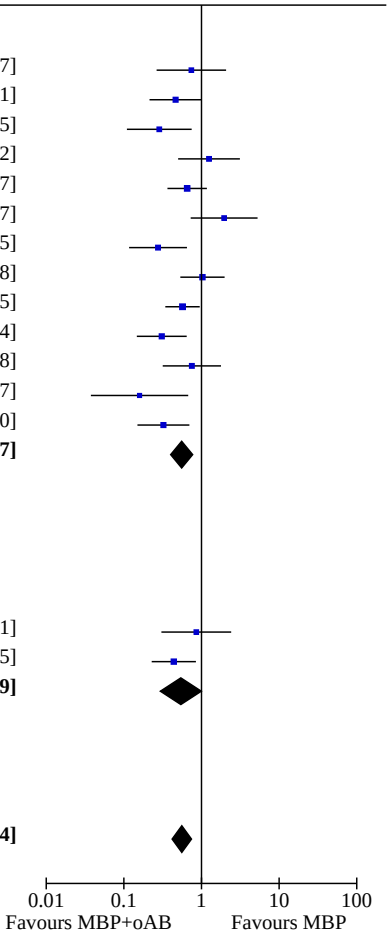
Analysis 1.15. Comparison 1: MBP+oAB vs. MBP, Outcome 15: SSI_Subgroup analysis regarding the surgical approach

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Minimally invasive surgical approach						
Ikeda 2016	17	223	16	216	10.2%	1.03 [0.53 , 1.98]
Hata 2016	21	289	37	290	12.0%	0.57 [0.34 , 0.95]
Arezzo 2021	0	23	1	21	1.1%	0.31 [0.01 , 7.12]
Subtotal (95% CI)		**535**		**527**	**23.4%**	**0.71 [0.46 , 1.10]**
Total events:	38		54			
Heterogeneity: Tau² = 0.02; Chi² = 2.22, df = 2 (P = 0.33); I² = 10%						
Test for overall effect: Z = 1.52 (P = 0.13)						
1.15.2 Open surgical approach						
Lau 1988	6	65	7	65	6.6%	0.86 [0.30 , 2.41]
Takesue 2000	5	38	8	45	6.6%	0.74 [0.26 , 2.07]
Horie 2007	10	46	5	45	6.9%	1.96 [0.73 , 5.27]
Oshima 2013	6	97	22	98	8.1%	0.28 [0.12 , 0.65]
Uchino 2019	8	91	11	94	8.0%	0.75 [0.32 , 1.78]
Subtotal (95% CI)		**337**		**347**	**36.3%**	**0.74 [0.39 , 1.40]**
Total events:	35		53			
Heterogeneity: Tau² = 0.29; Chi² = 8.89, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.15.3 Both open and minimally invasive surgical approach						
Espin-Basany 2005	15	200	6	100	7.6%	1.25 [0.50 , 3.12]
Sadahiro 2014	11	99	24	95	10.3%	0.44 [0.23 , 0.85]
Anjum 2017	8	95	26	95	9.3%	0.31 [0.15 , 0.64]
Rybakov 2021	2	57	13	59	4.2%	0.16 [0.04 , 0.67]
Papp 2021	8	253	27	276	9.0%	0.32 [0.15 , 0.70]
Subtotal (95% CI)		**704**		**625**	**40.3%**	**0.41 [0.24 , 0.72]**
Total events:	44		96			
Heterogeneity: Tau² = 0.20; Chi² = 8.35, df = 4 (P = 0.08); I² = 52%						
Test for overall effect: Z = 3.16 (P = 0.002)						
Total (95% CI)		**1576**		**1499**	**100.0%**	**0.58 [0.41 , 0.82]**
Total events:	117		203			
Heterogeneity: Tau² = 0.19; Chi² = 24.48, df = 12 (P = 0.02); I² = 51%						
Test for overall effect: Z = 3.11 (P = 0.002)						
Test for subgroup differences: Chi² = 2.73, df = 2 (P = 0.25), I² = 26.9%						



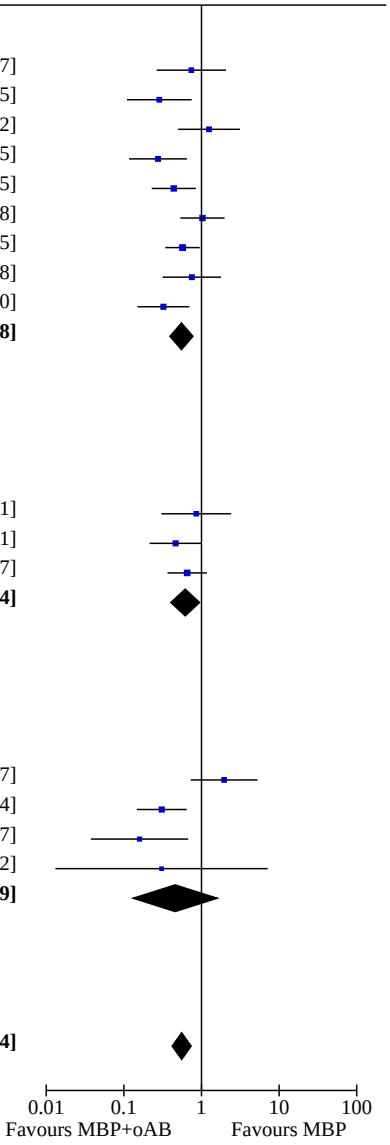
Analysis 1.16. Comparison 1: MBP+oAB vs. MBP, Outcome 16: SSI_Subgroup analysis regarding the duration of mechanical bowel preparation

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Bowel preparation on the day before surgery						
Takesue 2000	5	38	8	45	5.1%	0.74 [0.26 , 2.07]
Ishida 2001	8	72	17	71	7.1%	0.46 [0.21 , 1.01]
Lewis 2002	5	108	17	105	5.5%	0.29 [0.11 , 0.75]
Espin-Basany 2005	15	200	6	100	5.9%	1.25 [0.50 , 3.12]
Kobayashi 2007	17	242	26	242	9.1%	0.65 [0.36 , 1.17]
Horie 2007	10	46	5	45	5.3%	1.96 [0.73 , 5.27]
Oshima 2013	6	97	22	98	6.3%	0.28 [0.12 , 0.65]
Ikeda 2016	17	223	16	216	8.3%	1.03 [0.53 , 1.98]
Hata 2016	21	289	37	290	10.0%	0.57 [0.34 , 0.95]
Anjum 2017	8	95	26	95	7.4%	0.31 [0.15 , 0.64]
Uchino 2019	8	91	11	94	6.3%	0.75 [0.32 , 1.78]
Rybakov 2021	2	57	13	59	3.1%	0.16 [0.04 , 0.67]
Papp 2021	8	253	27	276	7.1%	0.32 [0.15 , 0.70]
Subtotal (95% CI)		**1811**		**1736**	**86.7%**	**0.56 [0.40 , 0.77]**
Total events:	130		231			
Heterogeneity: Tau² = 0.18; Chi² = 25.61, df = 12 (P = 0.01); I² = 53%						
Test for overall effect: Z = 3.54 (P = 0.0004)						
1.16.2 Bowel preparation over several days before the operation						
Lau 1988	6	65	7	65	5.0%	0.86 [0.30 , 2.41]
Sadahiro 2014	11	99	24	95	8.3%	0.44 [0.23 , 0.85]
Subtotal (95% CI)		**164**		**160**	**13.3%**	**0.54 [0.30 , 0.99]**
Total events:	17		31			
Heterogeneity: Tau² = 0.03; Chi² = 1.14, df = 1 (P = 0.29); I² = 12%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Total (95% CI)		**1975**		**1896**	**100.0%**	**0.56 [0.42 , 0.74]**
Total events:	147		262			
Heterogeneity: Tau² = 0.15; Chi² = 26.77, df = 14 (P = 0.02); I² = 48%						
Test for overall effect: Z = 3.99 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%						



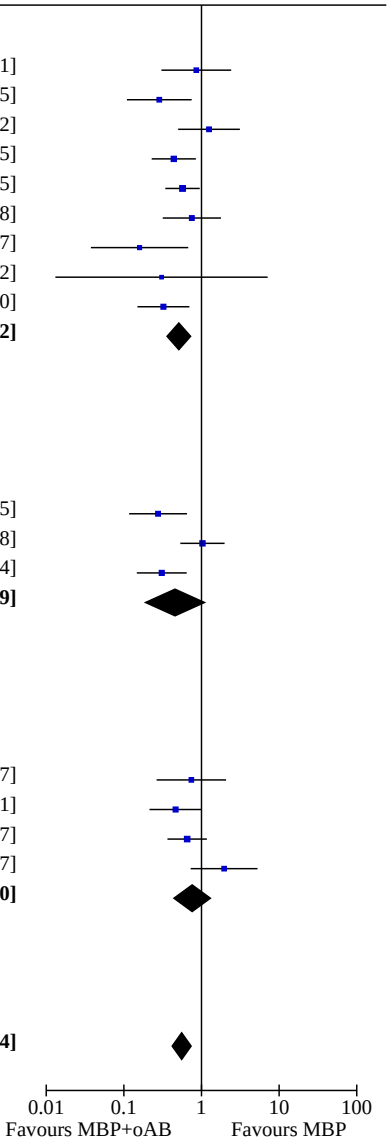
Analysis 1.17. Comparison 1: MBP+oAB vs. MBP, Outcome 17: SSI_Subgroup analysis regarding the agent combination of oral antibiotics

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Combination of metronidazole and an aminoglycoside (neomycin or kanamycin)						
Takesue 2000	5	38	8	45	5.0%	0.74 [0.26 , 2.07]
Lewis 2002	5	108	17	105	5.5%	0.29 [0.11 , 0.75]
Espin-Basany 2005	15	200	6	100	5.8%	1.25 [0.50 , 3.12]
Oshima 2013	6	97	22	98	6.3%	0.28 [0.12 , 0.65]
Sadahiro 2014	11	99	24	95	8.3%	0.44 [0.23 , 0.85]
Ikeda 2016	17	223	16	216	8.3%	1.03 [0.53 , 1.98]
Hata 2016	21	289	37	290	10.1%	0.57 [0.34 , 0.95]
Uchino 2019	8	91	11	94	6.2%	0.75 [0.32 , 1.78]
Papp 2021	8	253	27	276	7.1%	0.32 [0.15 , 0.70]
Subtotal (95% CI)		**1398**		**1319**	**62.5%**	**0.55 [0.39 , 0.78]**
Total events:	96		168			
Heterogeneity: Tau² = 0.11; Chi² = 14.01, df = 8 (P = 0.08); I² = 43%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
1.17.2 Combination of erythromycin and an aminoglycoside (neomycin or kanamycin)						
Lau 1988	6	65	7	65	4.9%	0.86 [0.30 , 2.41]
Ishida 2001	8	72	17	71	7.0%	0.46 [0.21 , 1.01]
Kobayashi 2007	17	242	26	242	9.1%	0.65 [0.36 , 1.17]
Subtotal (95% CI)		**379**		**378**	**21.1%**	**0.62 [0.40 , 0.94]**
Total events:	31		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.17.3 Other oral antibiotic combinations						
Horie 2007	10	46	5	45	5.2%	1.96 [0.73 , 5.27]
Anjum 2017	8	95	26	95	7.4%	0.31 [0.15 , 0.64]
Rybakov 2021	2	57	13	59	3.0%	0.16 [0.04 , 0.67]
Arezzo 2021	0	23	1	21	0.8%	0.31 [0.01 , 7.12]
Subtotal (95% CI)		**221**		**220**	**16.4%**	**0.46 [0.13 , 1.59]**
Total events:	20		45			
Heterogeneity: Tau² = 1.06; Chi² = 11.50, df = 3 (P = 0.009); I² = 74%						
Test for overall effect: Z = 1.23 (P = 0.22)						
Total (95% CI)		**1998**		**1917**	**100.0%**	**0.56 [0.42 , 0.74]**
Total events:	147		263			
Heterogeneity: Tau² = 0.14; Chi² = 26.92, df = 15 (P = 0.03); I² = 44%						
Test for overall effect: Z = 4.11 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.29, df = 2 (P = 0.87), I² = 0%						



Analysis 1.18. Comparison 1: MBP+oAB vs. MBP, Outcome 18: SSI_Subgroup analysis regarding the duration of intravenous antibiotic prophylaxis

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	MBP Events	MBP Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Only perioperative intravenous antibiotic prophylaxis						
Lau 1988	6	65	7	65	4.9%	0.86 [0.30 , 2.41]
Lewis 2002	5	108	17	105	5.5%	0.29 [0.11 , 0.75]
Espin-Basany 2005	15	200	6	100	5.8%	1.25 [0.50 , 3.12]
Sadahiro 2014	11	99	24	95	8.3%	0.44 [0.23 , 0.85]
Hata 2016	21	289	37	290	10.1%	0.57 [0.34 , 0.95]
Uchino 2019	8	91	11	94	6.2%	0.75 [0.32 , 1.78]
Rybakov 2021	2	57	13	59	3.0%	0.16 [0.04 , 0.67]
Arezzo 2021	0	23	1	21	0.8%	0.31 [0.01 , 7.12]
Papp 2021	8	253	27	276	7.1%	0.32 [0.15 , 0.70]
Subtotal (95% CI)		**1185**		**1105**	**51.7%**	**0.51 [0.36 , 0.72]**
Total events:	76		143			
Heterogeneity: Tau² = 0.08; Chi² = 11.21, df = 8 (P = 0.19); I² = 29%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
1.18.2 Continuation of perioperative intravenous antibiotic prophylaxis for 24 hours						
Oshima 2013	6	97	22	98	6.3%	0.28 [0.12 , 0.65]
Ikeda 2016	17	223	16	216	8.3%	1.03 [0.53 , 1.98]
Anjum 2017	8	95	26	95	7.4%	0.31 [0.15 , 0.64]
Subtotal (95% CI)		**415**		**409**	**21.9%**	**0.46 [0.19 , 1.09]**
Total events:	31		64			
Heterogeneity: Tau² = 0.45; Chi² = 8.18, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 1.76 (P = 0.08)						
1.18.3 Continuation of perioperative intravenous antibiotic prophylaxis beyond 24 hours						
Takesue 2000	5	38	8	45	5.0%	0.74 [0.26 , 2.07]
Ishida 2001	8	72	17	71	7.0%	0.46 [0.21 , 1.01]
Kobayashi 2007	17	242	26	242	9.1%	0.65 [0.36 , 1.17]
Horie 2007	10	46	5	45	5.2%	1.96 [0.73 , 5.27]
Subtotal (95% CI)		**398**		**403**	**26.4%**	**0.76 [0.44 , 1.30]**
Total events:	40		56			
Heterogeneity: Tau² = 0.13; Chi² = 5.25, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**1998**		**1917**	**100.0%**	**0.56 [0.42 , 0.74]**
Total events:	147		263			
Heterogeneity: Tau² = 0.14; Chi² = 26.92, df = 15 (P = 0.03); I² = 44%						
Test for overall effect: Z = 4.11 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.69, df = 2 (P = 0.43), I² = 0%						



Comparison 2. MBP+oAB vs. oAB

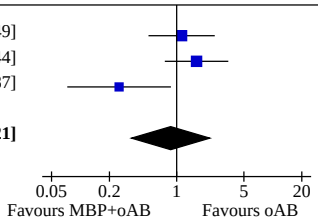
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 SSI	3	960	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.34, 2.21]
2.2 Anastomotic leakage	3	960	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.21, 3.45]
2.3 Mortality	2	709	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.30, 3.50]

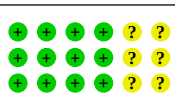
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Incidence of postoperative ileus	2	709	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.68, 2.33]

Analysis 2.1. Comparison 2: MBP+oAB vs. oAB, Outcome 1: SSI

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	oAB Events	oAB Total	Weight	Risk Ratio M-H, Random, 95% CI
Zmora 2003	12	187	11	193	36.4%	1.13 [0.51 , 2.49]
Ram 2005	16	164	10	165	37.2%	1.61 [0.75 , 3.44]
Suzuki 2020	3	125	12	126	26.4%	0.25 [0.07 , 0.87]
Total (95% CI)		**476**		**484**	**100.0%**	**0.87 [0.34 , 2.21]**
Total events:	31		33			

Heterogeneity: Tau² = 0.46; Chi² = 6.41, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



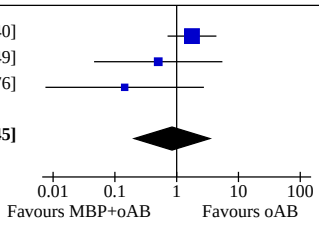


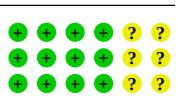
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: MBP+oAB vs. oAB, Outcome 2: Anastomotic leakage

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	oAB Events	oAB Total	Weight	Risk Ratio M-H, Random, 95% CI
Zmora 2003	12	187	7	193	58.4%	1.77 [0.71 , 4.40]
Ram 2005	1	164	2	165	24.0%	0.50 [0.05 , 5.49]
Suzuki 2020	0	125	3	126	17.6%	0.14 [0.01 , 2.76]
Total (95% CI)		**476**		**484**	**100.0%**	**0.84 [0.21 , 3.45]**
Total events:	13		12			

Heterogeneity: Tau² = 0.67; Chi² = 3.27, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



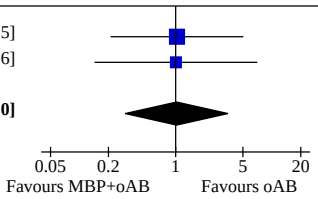


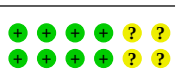
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: MBP+oAB vs. oAB, Outcome 3: Mortality

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	oAB Events	oAB Total	Weight	Risk Ratio M-H, Random, 95% CI
Zmora 2003	3	187	3	193	60.1%	1.03 [0.21 , 5.05]
Ram 2005	2	164	2	165	39.9%	1.01 [0.14 , 7.06]
Total (95% CI)		**351**		**358**	**100.0%**	**1.02 [0.30 , 3.50]**
Total events:	5		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



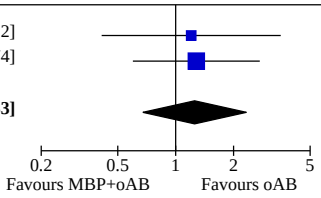


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: MBP+oAB vs. oAB, Outcome 4: Incidence of postoperative ileus

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	oAB Events	oAB Total	Weight	Risk Ratio M-H, Random, 95% CI
Zmora 2003	7	187	6	193	33.4%	1.20 [0.41 , 3.52]
Ram 2005	14	164	11	165	66.6%	1.28 [0.60 , 2.74]
Total (95% CI)		**351**		**358**	**100.0%**	**1.25 [0.68 , 2.33]**
Total events:	21		17			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



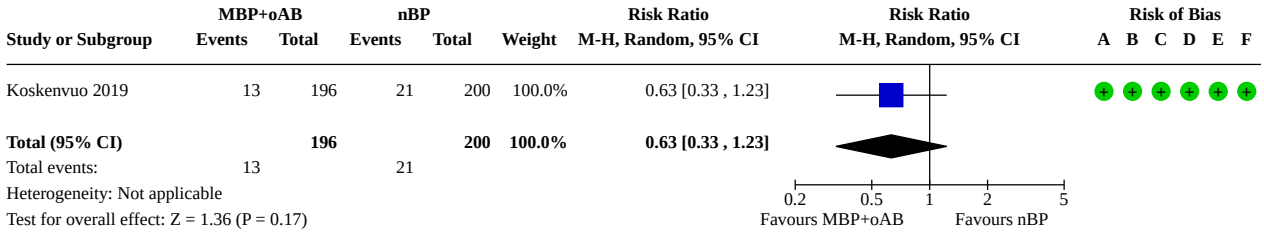
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. MBP+oAB vs. nBP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 SSI	1	396	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.33, 1.23]
3.2 Incisional SSI	1	396	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.14, 1.45]
3.3 Organ/space SSI	1	396	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.33, 1.78]
3.4 Anastomotic leakage	1	396	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 Mortality	1	396	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.22]
3.6 Mild postoperative complications according to Clavien-Dindo(I + II)	1	396	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.41]
3.7 Severe postoperative complications according to Clavien-Dindo(III + IV)	1	396	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.80, 2.69]
3.8 Incidence of postoperative ileus	1	396	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.77, 1.81]
3.9 Length of hospital stay	1	396	Mean Difference (IV, Random, 95% CI)	0.10 [-0.80, 1.00]
3.10 Side effects of Intervention	1	396	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.44, 2.01]
3.11 C. difficile-related diarrhoea	1	396	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.30]

Analysis 3.1. Comparison 3: MBP+oAB vs. nBP, Outcome 1: SSI

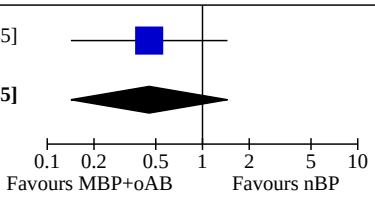


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: MBP+oAB vs. nBP, Outcome 2: Incisional SSI

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	4	196	9	200	100.0%	0.45 [0.14 , 1.45]
Total (95% CI)		**196**		**200**	**100.0%**	**0.45 [0.14 , 1.45]**
Total events:	4		9			

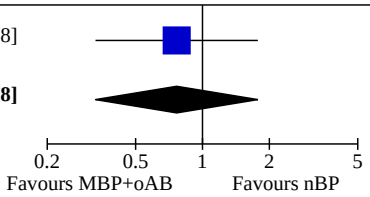
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: MBP+oAB vs. nBP, Outcome 3: Organ/space SSI

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	9	196	12	200	100.0%	0.77 [0.33 , 1.78]
Total (95% CI)		**196**		**200**	**100.0%**	**0.77 [0.33 , 1.78]**
Total events:	9		12			

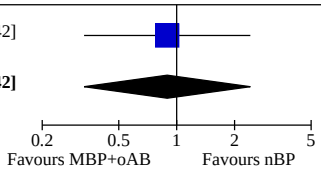
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: MBP+oAB vs. nBP, Outcome 4: Anastomotic leakage

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Koskenvuo 2019	7	196	8	200	100.0%	0.89 [0.33 , 2.42]	+ + + + + +
Total (95% CI)		**196**		**200**	**100.0%**	**0.89 [0.33 , 2.42]**	
Total events:	7		8				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable

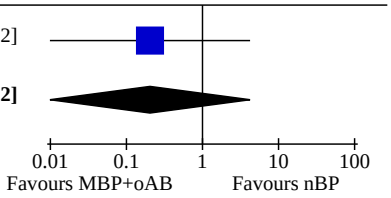


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.5. Comparison 3: MBP+oAB vs. nBP, Outcome 5: Mortality

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	0	196	2	200	100.0%	0.20 [0.01 , 4.22]
Total (95% CI)		**196**		**200**	**100.0%**	**0.20 [0.01 , 4.22]**
Total events:	0		2			

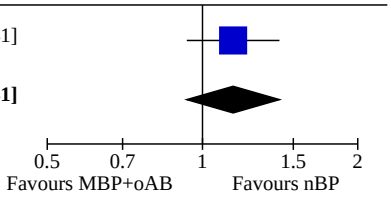
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: MBP+oAB vs. nBP, Outcome 6: Mild postoperative complications according to Clavien-Dindo(I + II)

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	100	196	89	200	100.0%	1.15 [0.93 , 1.41]
Total (95% CI)		**196**		**200**	**100.0%**	**1.15 [0.93 , 1.41]**
Total events:	100		89			

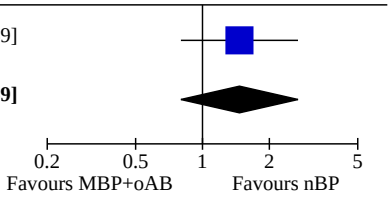
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: MBP+oAB vs. nBP, Outcome 7: Severe postoperative complications according to Clavien-Dindo(III + IV)

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	23	196	16	200	100.0%	1.47 [0.80 , 2.69]
Total (95% CI)		**196**		**200**	**100.0%**	**1.47 [0.80 , 2.69]**
Total events:	23		16			

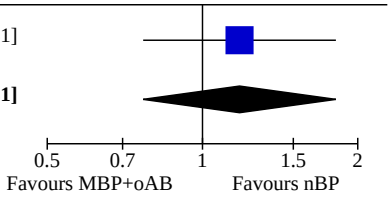
Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: MBP+oAB vs. nBP, Outcome 8: Incidence of postoperative ileus

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	37	196	32	200	100.0%	1.18 [0.77 , 1.81]
Total (95% CI)		**196**		**200**	**100.0%**	**1.18 [0.77 , 1.81]**
Total events:	37		32			

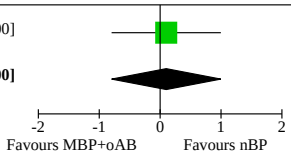
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: MBP+oAB vs. nBP, Outcome 9: Length of hospital stay

Study or Subgroup	MBP+oAB Mean	MBP+oAB SD	MBP+oAB Total	nBP Mean	nBP SD	nBP Total	Weight	Mean Difference IV, Random, 95% CI
Koskenvuo 2019	5.4	4.7	196	5.3	4.4	200	100.0%	0.10 [-0.80 , 1.00]
Total (95% CI)			**196**			**200**	**100.0%**	**0.10 [-0.80 , 1.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable

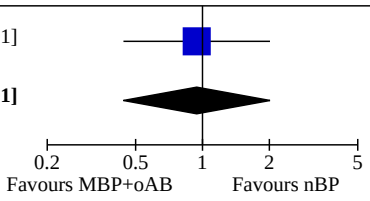


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.10. Comparison 3: MBP+oAB vs. nBP, Outcome 10: Side effects of Intervention

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	12	196	13	200	100.0%	0.94 [0.44 , 2.01]
Total (95% CI)		**196**		**200**	**100.0%**	**0.94 [0.44 , 2.01]**
Total events:	12		13			

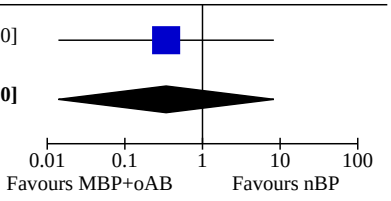
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: MBP+oAB vs. nBP, Outcome 11: C. difficile-related diarrhoea

Study or Subgroup	MBP+oAB Events	MBP+oAB Total	nBP Events	nBP Total	Weight	Risk Ratio M-H, Random, 95% CI
Koskenvuo 2019	0	196	1	200	100.0%	0.34 [0.01 , 8.30]
Total (95% CI)		**196**		**200**	**100.0%**	**0.34 [0.01 , 8.30]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Summary of outcomes reported per study

StudyID	SSI	Subdivision in incisional and organ/space SSI	Anastomotic leakage	Mortality	Mild and severe postoperative complications according to Clavien-Dindo	Incidence of postoperative ileus	LOS	Side effect of Intervention	C. difficile-related diarrhoea
MBP+oAB vs. MBP									
Anjum 2017	yes	yes	no	no	no	no	no	no	no
Arezzo 2021	yes	no	yes	yes	yes	yes	yes	yes	yes
Espin-Basany 2005	yes	no	no	no	no	yes	no	yes	no
Hata 2016	yes	yes	yes	no	no	yes	no	no	yes
Horie 2007	yes	no	yes	no	no	no	no	no	no
Ikeda 2016	yes	yes	yes	no	no	yes	yes	no	yes
Ishida 2001	yes	yes	yes	no	no	no	no	no	no
Kobayashi 2007	yes	yes	no	no	no	no	no	no	no
Lau 1988	yes	no	yes	no	no	no	yes	no	no
Lazorthes 1982	incorrect*	no	no	yes	no	no	incorrect**	no	no
Lewis 2002	yes	no	no	no	no	no	no	no	no
Oshima 2013	yes	yes	no	no	no	no	no	yes	no
Papp 2021	yes	yes	yes	yes	yes	yes	no	no	yes
Rybakov 2021	yes	yes	yes	no	yes	yes	no	no	incorrect***
Sadahiro 2014	yes	yes	yes	no	no	no	no	no	incorrect****

Table 1. Summary of outcomes reported per study *(Continued)*

Takesue 2000	yes	no	yes	no	no	no	no	no	no
Uchino 2019	yes	yes	no	no	no	no	no	no	no
MBP+oAB vs. oAB									
Ram 2005	yes	no	yes	yes	no	yes	yes	no	no
Suzuki 2020	yes	yes	yes	no	no	no	no	no	yes
Zmora 2003	yes	no	yes	yes	no	yes	incorrect**	no	no
MBP+oAB vs. nBP									
Koskenvuo 2019	yes	yes	yes	yes	yes	yes	yes	yes	yes

* Wound infections were classified into major and minor, but only data from major wound infections are reported
**Only the numerical value given with no unit of measurement specified, no information about range or standard deviation
*** Detection of Clostridia in general, not specific for C. difficile
**** Detection rate of C. difficile toxin pre- and postoperatively, regardless of whether diarrhoea was present

APPENDICES

Appendix 1. Search strategies

CENTRAL was searched via the Cochrane library using the following search string:

#1 [mh "colorectal surgery"] OR [mh "colectomy"] OR [mh "proctectomy"]

#2 (colorectal OR colon OR rectal OR proctolog* OR proctocolonic):ti,ab,kw

#3 (surger* OR surgical* OR resect* OR incisi* OR excisi* OR invasive* OR restorati* OR operation* OR operative* OR perioperati* OR peri-operati*):ti,ab,kw OR [mh "elective surgical procedures"]

#4 #2 AND #3

#5 #4 OR #1

#6 [mh "laxatives"] OR [mh "cathartics"] OR [mh "enema"] OR [mh "antibiotic prophylaxis"] OR [mh "Anti-Bacterial Agents"]

#7 (antibacterial* OR anti bacterial* OR antibiotic* OR neomycin OR metronidazole OR ciprofloxacin OR colistin OR tobramycin OR paromomycin OR erythromycin OR levofloxacin):ti,ab,kw

#8 (oral OR orally):ti,ab,kw

#9 #7 AND #8

#10 (bowel preparat* OR intestine preparat* OR colon preparat* OR gut preparat* OR bowel cleansing OR intestine cleansing OR colon cleansing OR gut cleansing OR laxative* OR purgative OR enema):ti,ab,kw

#11 #9 AND #10

#12 #6 OR #11

#13 #5 AND #12

MEDLINE was searched via PubMed using the following search string:

#1 "Colorectal Surgery"[MeSH Terms] OR "Colectomy"[Mesh]

#2 colorectal [tiab] OR colon [tiab] OR rectal [tiab] OR proctolog* [tiab] OR proctocolonic [tiab]

#3 surger* [tiab] OR surgical* [tiab] OR resect* [tiab] OR incisi* [tiab] OR excisi* [tiab] OR invasive* [tiab] OR restorati* [tiab] OR operation* [tiab] OR operative* [tiab] OR perioperati* [tiab] OR peri-operati* [tiab] OR "surgery"[Subheading] OR "Surgical Procedures, Operative"[Mesh]

#4 #2 AND #3

#5 #4 OR #1

#6 "Gastrointestinal Agents"[Mesh] OR "Laxatives" [Pharmacological Action] OR "Enema"[Mesh] OR "Cathartics"[Mesh] OR "Laxatives"[Mesh] OR "Antibiotic Prophylaxis"[Mesh] OR "Anti-Bacterial Agents"[Mesh]

#7 antibacterial* [tiab] OR anti bacterial* [tiab] OR antibiotic* [tiab] OR neomycin [tiab] OR metronidazole [tiab] OR ciprofloxacin [tiab] OR colistin [tiab] OR tobramycin [tiab] OR paromomycin [tiab] OR erythromycin [tiab] OR levofloxacin [tiab]

#8 oral [tiab] OR orally [tiab]

#9 #7 AND #8

#10 bowel preparat* [tiab] OR intestine preparat* [tiab] OR colon preparat* [tiab] OR gut preparat* [tiab] OR bowel cleansing [tiab] OR intestine cleansing [tiab] OR colon cleansing [tiab] OR gut cleansing [tiab] OR laxative* [tiab] OR purgative [tiab] OR enema [tiab]

#11 #9 AND #10

#12 #6 OR #11

#13 #5 AND #12

#14 ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

#15 #13 AND #14

Embase was searched via Ovid using the following search string:

#1 exp *colorectal surgery/ or exp *colon resection/ or exp *rectum resection/

#2 (colorectal or colon or rectal or proctolog* or proctocolonic).ti,ab,kw.

#3 (surger* or surgical* or resect* or incisi* or excisi* or invasive* or restorati* or operation* or operative* or perioperati* or peri-operati*).ti,ab,kw. or exp *elective surgery/

#4 2 and 3

#5 1 or 4

#6 exp *laxative/ or exp *intestine preparation/ or exp *enema/ or exp *antibiotic prophylaxis/ or exp *antiinfective agent/

#7 (antibacterial* or anti bacterial* or antibiotic* or neomycin or metronidazole or ciprofloxacin or colistin or tobramycin or paromomycin or erythromycin or levofloxacin).ti,ab,kw.

#8 (oral or orally).ti,ab,kw.

#9 7 and 8

#10 (bowel preparat* or intestine preparat* or colon preparat* or gut preparat* or bowel cleansing or intestine cleansing or colon cleansing or gut cleansing or laxative* or purgative or enema).ti,ab,kw.

#11 9 and 10

#12 6 or 11

#13 5 and 12

#14 limit 13 to (clinical trial or randomized controlled trial)

ClinicalTrials.gov was searched using the following search strategies:

Advanced Search
Condition or disease: colorectal surgery
Other terms: bowel preparation AND oral antibiotic
Study type: Interventional Studies (Clinical Trails)
Study Results: All Studies
Eligibility Criteria: Adult (18-64) , Older Adult (65+)
Sex: all

Expert Search
((Colorectal Surgery OR colectomy OR proctectomy OR ((colorectal OR colon OR rectal OR proctolog* OR proctocolonic) AND (surger* OR surgical* OR resect* OR incisi* OR excisi* OR invasive* OR restorati* OR operation* OR operative* OR perioperati* OR peri-operati))) AND ((bowel preparat* OR intestine preparat* OR colon preparat* OR gut preparat* OR bowel cleansing OR intestine cleansing OR colon cleansing OR gut cleansing OR laxative* OR purgative OR enema) AND ((oral OR orally) AND (antibacterial* OR anti bacterial* OR antibiotic* OR neomycin OR metronidazole OR ciprofloxacin OR colistin OR tobramycin OR paromomycin OR erythromycin OR levofloxacin))))

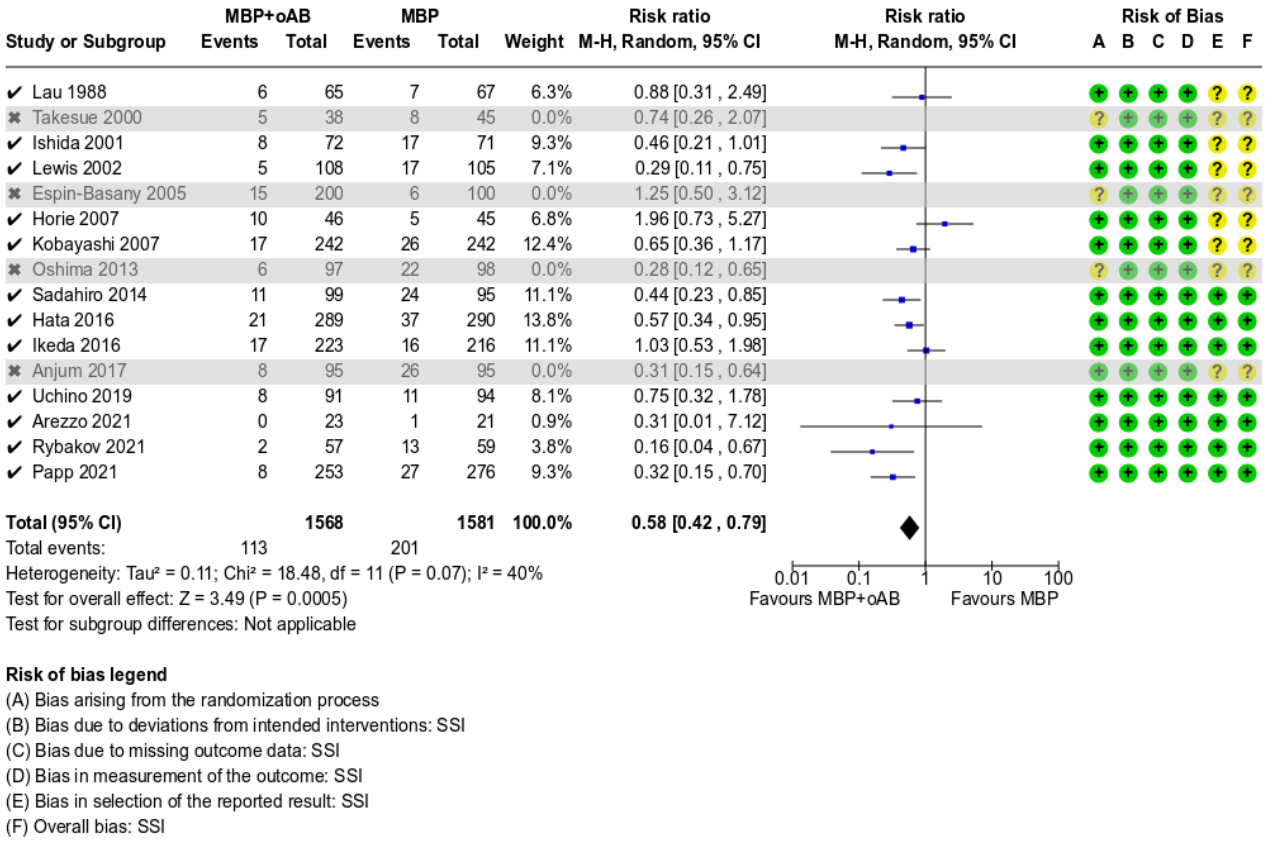
The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) was searched using the following search strategy:

mechanical bowel preparation AND oral antibio* AND ((colorectal OR colo* OR rectal*) AND (surgery OR operat*))

Appendix 2. Sensitivity analysis

Investigate sensitivity - 1.1 SSI: Figure 4

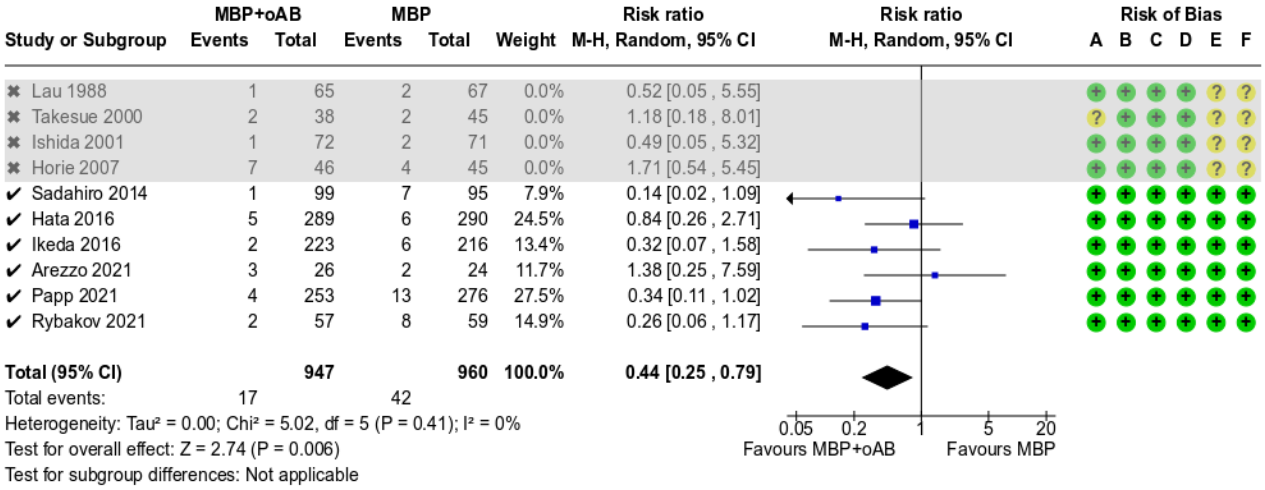
Figure 4. Investigate sensitivity - 1.1 SSI



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: SSI
(C) Bias due to missing outcome data: SSI
(D) Bias in measurement of the outcome: SSI
(E) Bias in selection of the reported result: SSI
(F) Overall bias: SSI

Investigate sensitivity - 1.4 Anastomotic leakage: Figure 5

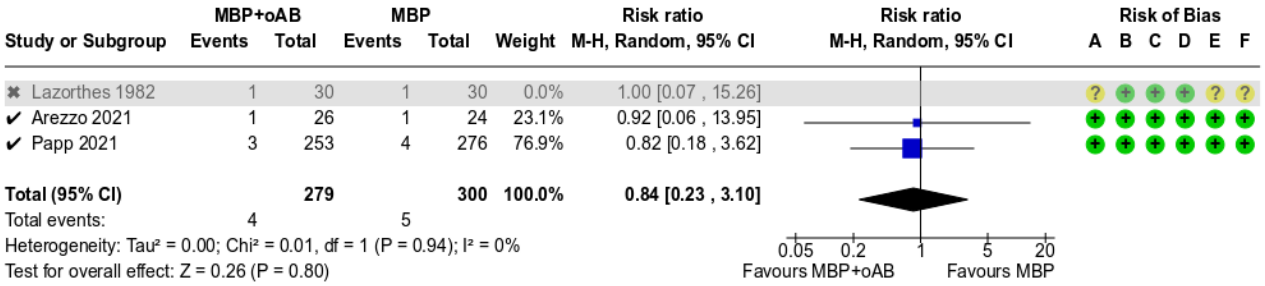
Figure 5. Investigate sensitivity - 1.4 Anastomotic leakage



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Anastomotic leakage
(C) Bias due to missing outcome data: Anastomotic leakage
(D) Bias in measurement of the outcome: Anastomotic leakage
(E) Bias in selection of the reported result: Anastomotic leakage
(F) Overall bias: Anastomotic leakage

Investigate sensitivity - 1.5 Mortality: Figure 6

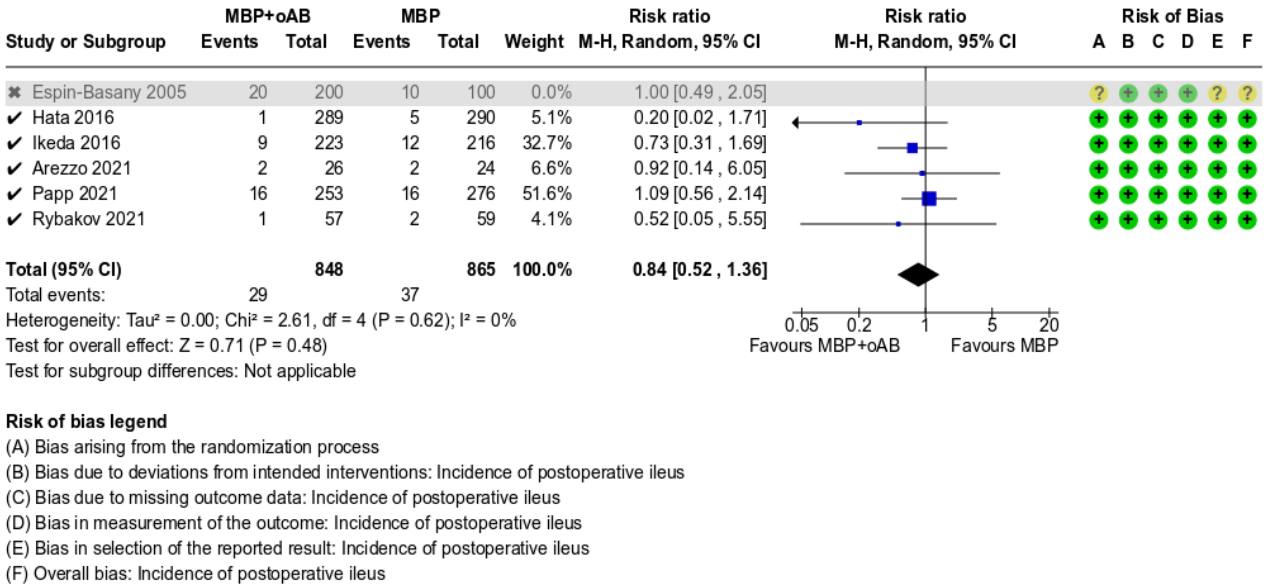
Figure 6. Investigate sensitivity - 1.5 Mortality



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Mortality
(C) Bias due to missing outcome data: Mortality
(D) Bias in measurement of the outcome: Mortality
(E) Bias in selection of the reported result: Mortality
(F) Overall bias: Mortality

Investigate sensitivity - 1.8 Incidence of postoperative ileus: Figure 7

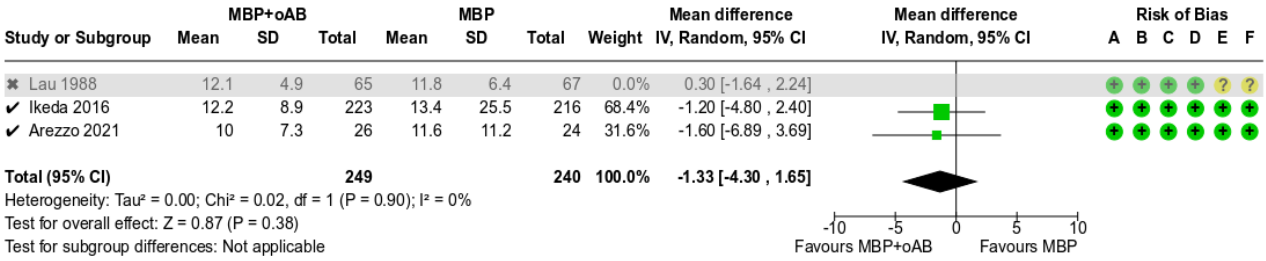
Figure 7. Investigate sensitivity - 1.8 Incidence of postoperative ileus



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Incidence of postoperative ileus
(C) Bias due to missing outcome data: Incidence of postoperative ileus
(D) Bias in measurement of the outcome: Incidence of postoperative ileus
(E) Bias in selection of the reported result: Incidence of postoperative ileus
(F) Overall bias: Incidence of postoperative ileus

Investigate sensitivity - 1.9 Length of hospital stay: Figure 8

Figure 8. Investigate sensitivity - 1.9 Length of hospital stay



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Length of hospital stay
(C) Bias due to missing outcome data: Length of hospital stay
(D) Bias in measurement of the outcome: Length of hospital stay
(E) Bias in selection of the reported result: Length of hospital stay
(F) Overall bias: Length of hospital stay

HISTORY

Protocol first published: Issue 1, 2022

CONTRIBUTIONS OF AUTHORS

Maria A Willis (MW): Conception of the review, search strategy development, acquisition of trial reports, trial selection, data extraction, risk of bias assessment, data analysis, data interpretation, review drafting.

Ingrid Toews (IT): Methodological advice and revision of the review.

Sophia LV Soltau (SS): Data extraction and risk of bias assessment.

Joerg C Kalff (JK): Clinical advice on the conception of the review and revision of the review.

Joerg J Meerpohl (JM): Data interpretation, final revision of the review, in particular with regard to the methodology.

Tim O Vilz (TV): Conception of the review, trial selection, revision of the review.

All authors have read and approved the final manuscript and declare that they are accountable for all aspects of the review.

DECLARATIONS OF INTEREST

MW: Surgical resident at the University Hospital Bonn. This review is intended as a partial aspect of the evidence workup for a new guideline on perioperative medicine for gastrointestinal tumours. This guideline is being developed with the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.) and the German Guideline Program in Oncology, and is funded by the German Cancer Aid (see Sources of support).

IT: None.

SS: None.

JK: None.

JM: None.

TV: Scientific grant from the German Cancer Aid to create a guideline for 'Perioperative Management of Gastrointestinal Tumours (POMGAT)' (see Sources of support); publications in the field of perioperative medicine; head of the Colorectal Surgery and Proctology section at the University Hospital Bonn.

SOURCES OF SUPPORT

Internal sources

- Department of General, Visceral, Thorax and Vascular Surgery, University Hospital Bonn, Bonn, Germany, Germany

  Salary (TV); Salary (MW before and after the nine-month leave to work full time on the review)
- Institute for Evidence in Medicine, Freiburg, Germany

  Salary (IT andJM)

External sources

- German Cancer Aid, Germany

  Scientific grant for the development of a guideline on 'Perioperative Management of Gastrointestinal Tumours (POMGAT)' including salary payment for MW during a nine-month leave of absence from clinical practice to complete the review in collaboration with Cochrane Germany and funding for a student assistant (SS) to support the guideline project.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Ms Sophia Soltau (SS) was included as an additional author and carried out the data extraction and risk of bias assessment together with MW instead of TV. Together with IT, TV took on the role of the third reviewer and was consulted in case of disagreements between MW and SS. The reasons for this were, firstly, to involve SS in the project so that she could learn how to conduct a systematic review and, secondly, to add another person to the project resources to ensure that the schedule was adhered to.
2. The planned subdivision of SSI into superficial, deep and organ/space infections had to be adjusted because most studies that made a subdivision only distinguished between incisional and organ/space SSI. For those studies that reported superficial SSI and deep SSI separately, these data were combined into incisional SSI for inclusion in the meta-analysis.
3. The secondary outcome "treatment-related adverse events", including its sub-items, was replaced by the two outcomes "side effect of the intervention" and "*C. Difficile*-related diarrhoea". Adverse events of the intervention were mainly reported as nausea/vomiting or abdominal pain. Information on dehydration, electrolyte imbalance, renal failure or cardiac dysfunction due to MBP, or the number of participants who discontinued the intervention due to side effects and the number of participants for whom therapy was initiated to treat the complications, were not reported in any of the included studies. Furthermore, the identified studies did not distinguish between MBP or oAB as a trigger for the side effect of the intervention.
4. The planned subgroup analyses also had to be adjusted based on the data available to us. For example, the planned subdivision into (extended) right-sided versus (extended) left-sided versus rectal resections was not possible. A meaningful subdivision into colon versus rectal resections could also not be made, as most studies reported a mixed collective (Analysis 1.14). The comparison of operations with restoration of bowel continuity (primary anastomosis) with or without creation of a protective stoma, could also not be performed due to lack of data.
5. For the primary endpoint anastomotic leakage, no subgroup analysis was performed for the comparison MBP+oAB versus MBP as no statistical heterogeneity was found ($Chi^2 = 9.84$, $df = 9$ ($P = 0.36$); $I^2 = 9\%$; Analysis 1.4).

6. The sensitivity analyses were also conducted differently than intended in the protocol. As no study with a high risk of bias was identified, an analysis with only those studies that were found to have a low risk of bias was conducted as a sensitivity analysis for the first comparison. The planned sensitivity analysis with exclusion of all studies that had > 20% missing data was not performed, as only one study (Rybakov 2021) analysed less than 80% of randomised patients, and the reasons for this are well explained. The missing data is not due to loss to follow-up, but partly due to the fact that no surgery was performed, inoperability was given, or no anastomosis was done, so that the patients no longer fulfilled the inclusion criteria of the study.
7. The MID for SSI and anastomotic leakage given in the protocol had to be revised because the derivation of the given values led to conflicting estimates of clinical relefance. The premise that an intervention must lead to an absolute risk reduction of 5% to achieve a clinically important difference was retained. From the formula RRR = 100% x (1- RR) it can be deduced that we achieve an absolute risk reduction of 5% with a risk reduction of less than or equal to 0.95, so this value was reported as the new MID for both SSIs and anastomotic leaks.

INDEX TERMS

Medical Subject Headings (MeSH)

Anastomotic Leak [drug therapy] [prevention & control]; *Anti-Bacterial Agents [administration & dosage] [therapeutic use]; *Colorectal Surgery [adverse effects]; *Ileus [drug therapy] [prevention & control]; Preoperative Care; *Surgical Wound Infection [drug therapy] [prevention & control]

MeSH check words

Adult; Humans