

Draft Comparative Effectiveness Review

Number XX

Oral Mechanical Bowel Preparation for Colorectal Surgery

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Abstract

Background: In the United States oral mechanical bowel preparation (OMBP) is often prescribed preoperatively for patients undergoing elective colorectal surgery.

Objectives: We conducted a systematic review to summarize the evidence on the comparative effectiveness and safety of OMBP strategies versus no preparation, OMBP versus enema only, and among different OMBP strategies.

Data Sources: We searched MEDLINE®, the Cochrane Central Register of Controlled Trials®, EMBASE®, and CINAHL® without any language restriction (last search on November 29, 2012). We also did a targeted search of the FDA Web site (last search on May 17, 2013). We supplemented searches by asking technical experts and perusing reference lists. We searched the ClinicalTrials.gov Web site (last search on May 15, 2013) for ongoing comparative trials.

Study Eligibility Criteria, Participants and Interventions: We included English-language full-text reports of randomized controlled trials (RCTs; at least 10 patients per arm), and nonrandomized comparative studies (NRCSs; at least 100 patients per arm) of OMBP strategies in adults or children undergoing elective colon or rectal surgery. For harms we also included cohort studies or case series of at least 200 participants. Eligible comparative studies reported on predetermined clinical outcomes, including overall mortality, infectious outcomes, and anastomotic leakage; health system and resource utilization outcomes such as readmissions after surgery or length of stay, and patient-centered outcomes such as patient satisfaction, and quality of life.

Study Appraisal and Synthesis Methods: A single investigator extracted data from each study; quantitative results and intervention descriptions were verified by a second reviewer. We assessed the risk of bias for each outcome and the strength of the evidence following the processes described in the *AHRQ Methods Guide*. For each Key Question, we synthesized results qualitatively by means of tables and graphs, and did both pairwise and network meta-analysis. Estimation was done in the generalized linear mixed model framework, with binomial family and a logit link function. Models accounted for between-study heterogeneity.

Results: Forty RCTs, 8 NRCSs; and 6 single-group cohorts were eligible. Of those, 15 RCTs were included in meta-analyses comparing OMBP versus enema versus no preparation. Both pairwise and network meta-analyses found no statistically significant differences between OMBP and either no preparation or enema for overall mortality, anastomotic leakage, wound infection, surgical site infection and reoperation. However confidence (credibility) intervals did not exclude clinically important differences in either direction. OMBP appeared to be protective compared to no preparation for “peritonitis or intraabdominal abscess” in pairwise frequentist analyses, but Bayesian network analyses which modeled between-study heterogeneity more fully provided weaker evidence of benefit. The few studies comparing active OMBP strategies between them assessed highly diverse outcomes and most pertained to interventions that are no longer in clinical use. Therefore, although the studies did not suggest much difference among strategies, the evidence is too weak to support definitive conclusions of relevance to current practice. Evidence on the harms of OMBP was too poorly reported in the surgical literature to draw conclusions as well.

Limitations: The evidence regarding OMBP for colorectal surgery is limited in the following ways: (1) most studies enrolled small numbers of patients and reported low event rates for major clinical events; (2) studies did not report results for important clinical subgroups, particularly those defined by anatomic location of surgery (colon versus rectal surgery) and the type of surgical procedure performed (e.g., open versus laparoscopic surgery); (3) studies comparing

alternative active OMBP strategies used a large number of diverse preparation regimes and reported results for heterogeneous, often poorly defined, outcomes; (4) nonrandomized trials, and particularly observational studies, could not effectively supplement the results of randomized trials because of shortcomings in their design and analysis (e.g., diversity of outcomes and suboptimal confounding control).

Conclusions: Studies comparing OMBP versus either no preparation or enema did not find statistically significant differences for most outcomes; however, the confidence (or credibility) intervals around summary estimates could not exclude clinically significant effects. The effectiveness of different active OMBP strategies could not be assessed because the studies compared interventions that are no longer used, and data on harms were too sparse for analysis. Therefore, there is a clear need for new comparative studies (both randomized and nonrandomized) of the currently used interventions and appropriate reporting of subgroups, and consideration of patient preferences to provide definitive answers to these questions. It may also be possible to get better data on harms associated with OMBP from studies of indications other than elective colorectal surgery, e.g., colonoscopy.

The PROSPERO registration number of the protocol is CRD42013004381.

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Appendix A: Search Strategy

Appendix B: List of Excluded Studies by Reason for Exclusion

Appendix C: Sensitivity Analysis for Pairwise Contrasts

Appendix D: List of Ongoing Studies

Executive Summary

Background

In the U.S. oral mechanical bowel preparation (OMBP), defined as an oral preparation given prior to surgery to clear fecal material from the bowel lumen, is often prescribed preoperatively for patients undergoing elective colorectal surgery.¹ OMBP is sometimes used as a precaution in anticipation of possible iatrogenic bowel injury during abdominal and pelvic surgeries that do not entail resection of the colon or rectum (e.g., urologic or gynecologic procedures). OMBP is also routinely prescribed prior to colonoscopy, to allow maximal visualization of the intraluminal bowel during the procedure.²

In 2009, more than 250,000 colorectal surgeries were recorded,³ most commonly for cancer or diverticulitis,⁴ and—in the vast majority of cases—in adults. In the context of colorectal surgery many have considered OMBP necessary for decreasing infectious complications, in particular by lowering anastomosis leak rates associated with surgery.⁵ Gross spillage of fecal material in the operative field increases the need for a stoma, which can impact patients' quality of life. Moreover, a stoma requires additional surgery to reverse, and possibly other surgeries should complications such as bowel obstructions or incisional hernia arise.^{6,7} Complication rates for elective colorectal surgery range between 4 and 36 percent.^{8,9} A surgical site infection can substantially lengthen hospital stay from approximately 4 days to 21 days and increase costs from approximately \$11,000 to \$43,000.⁸ Therefore, reducing complication rates of elective colorectal surgery is a very important goal.

However OMBP is not risk free. Most patients start the OMBP at home the day before surgery. Elderly and frail patients may undergo OMBP in the hospital. OMBP is at the least a hassle for patients (some preparations are unpleasant-tasting; ingesting large quantities of fluids and spending long periods in the toilet is also unpleasant) and can also lead to complications. Some patients experience vomiting and dehydration that are severe enough to require medical attention, or even to reschedule the surgery. Additionally, liquid bowel contents from OMBP use may be less safely handled during surgery than solid contents, and may result in infections. Individuals who may be at greater risk of adverse effects of OMBP are the elderly (for example, ≥ 65 years of age) and those with comorbidities such as cardiovascular and pulmonary disease, diabetes, kidney disease, and compromised immune conditions.

OMBP for colon or rectal surgery appears to be widespread practice in the United States. A 2003 survey found that more than 99 percent of colorectal surgeons routinely employed OMBP,¹⁰ and a recent study (2007–2009) of 24 Michigan hospitals reported use on OMBP in 86 percent of all colorectal surgeries.¹¹ The initial adoption of OMBP prior to colorectal surgery was not based on high quality evidence but rather on expert opinion and observational data.^{12,13} Several recent trials (mostly conducted in Europe) failed to identify a statistically significant benefit for using versus not using OMBP prior to colon surgery.^{14,15} Citing some of these trials, the 2010 guidelines of the Canadian Society of Colon and Rectal Surgeons favored omitting OMBP in the preoperative management of patients undergoing elective right-sided and left-sided colorectal surgical resections,¹⁶ but deemed that evidence was insufficient to support or refute omitting OMBP for patients undergoing low anterior resection (with or without diverting stomas).

Over time, both the OMBP strategies and adjunctive therapies have changed. The U.S. Food and Drug Administration has approved several OMBP regimens that are available over the counter. Most commonly used are large volume (approximately 4 liters) osmotically-balanced

polyethylene glycol (PEG) solutions (e.g., MiraLAX®, GoLYTELY®, NuLYTELY®), or reduced-volume PEG (approximately 2 liters) plus bisacodyl (HalfLyte®). PEG solutions evacuate the bowel by washout, with no substantial fluid or electrolyte shifts.⁸ Bisacodyl, a poorly absorbed diphenylmethane, stimulates colonic peristalsis.² Hyperosmotic preparations (e.g., Fleet®) that draw water into the bowel to achieve washout are largely discontinued because of concern about electrolyte imbalances.² Older, more aggressive OMBP strategies such as whole gut irrigation through nasogastric tubes, or multi-day strategies, are no longer used. An enema is sometimes given the night before or the morning of surgery. Antibiotics, parenteral or oral, are also often administered preoperatively for systemic coverage and for reducing the concentration of anaerobic bacteria in the gut.^{17, 18} A recent Cochrane systematic review (covering studies up to December 1, 2010) found no benefit for OMBP in terms of anastomotic leaks, other surgical complications, or mortality for mixed populations of patients undergoing colon or rectal resection.¹ Several studies have been published since the last search of the Cochrane review, suggesting that an updated synthesis is needed. Furthermore, there is reason to believe that OMBP could have a different impact depending on the anatomic location of surgery (left versus right), type of surgery (open versus laparoscopic), and whether the OMBP includes an enema or not. Finally, large variation in practice exists in different parts of the world, perhaps suggesting that existing syntheses of the evidence do not adequately address all major decisionmaking uncertainties.

The purpose of this review was to systematically evaluate experimental and observational evidence on the benefits and harms associated with the use of OMBP in patients undergoing elective colorectal surgery. We also aimed to identify patient and procedural characteristics that modify the effect of OMBP on outcomes.

Key Questions

On the basis of the original topic nomination and an extensive stakeholder-driven process of topic development and refinement, we formulated the following Key Questions to guide the review:

Key Question 1: How do various preoperative OMBP strategies compare with either no OMBP or with each other with respect to their effectiveness for preventing surgical or postsurgical complications? Does the effect vary by elective (a) right colon, (b) left colon, and (c) rectal surgery?

Key Question 2: How do various preoperative OMBP strategies compare with either no OMBP or with each other with respect to presurgical and postsurgical adverse events? How do comparative adverse events vary (a) by OMBP strategy, and (b) by subgroup of especially susceptible patients.

Methods

We performed a systematic review of the published literature using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*^a). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in the reporting of this review.¹⁹ A full description of all review

^a Available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>; last accessed May 1th, 2013.

steps is included in the full report and the study protocol. The PROSPERO registration number of the protocol is CRD42013004381.

External Stakeholder Input

A Technical Expert Panel (TEP) provided input to help refine the Key Questions, identify important issues, and define parameters for the review of evidence. The nine TEP members included representatives of professional societies, experts in colorectal surgery, experts on the preoperative preparation of patients undergoing elective surgery, and an infectious disease specialist.

Literature Search and Abstract Screening

We searched MEDLINE®, the Cochrane Central Trials Registry®, EMBASE®, and CINAHL® without any language or publication date restriction (last search on November 29, 2012). See **Appendix A** of the full report for the exact search queries. We also did a targeted search of the FDA Web site (last search performed on May 17th, 2013).^b We supplemented searches by asking technical experts to provide additional relevant citations, and perusing reference lists of eligible studies, clinical practice guidelines, and narrative and systematic reviews. We requested supplementary information from OMBP preparation manufacturers. Finally, we searched the ClinicalTrials.gov Web site (with the last search performed on May 16th, 2013) to identify ongoing comparative trials of alternative OMBP strategies. We did not consider unpublished data other than that included in FDA documents or ClinicalTrials.gov. Abstracts were manually screened in duplicate following a standardization exercise.

Study Selection and Eligibility Criteria

Two investigators reviewed full-text articles independently for eligibility. Disagreements were resolved by consensus including at least one additional investigator.

We included English-language full-text reports of randomized controlled trials (RCTs; at least 10 patients per arm), and nonrandomized comparative studies (NRCSS; at least 100 patients per arm) in adults or children undergoing elective colon or rectal surgery. Studies reporting on both colorectal and non-colorectal surgery were included if results were presented by anatomic site, or if at least 80 percent of surgeries involved the large bowel. For harms we also included cohort studies or case series of at least 200 participants.

We defined as OMBP any preparation for surgery that was administered orally or through a nasogastric tube, but without need for other (e.g., endoscopic) intervention. Cointerventions could include oral or parenteral antibiotics, dietary modification, or enema. Eligible studies compared OMBP-based strategies between them, or versus no preparation.

We included studies reporting on a predetermined set of **clinical outcomes**, including overall and cause-specific survival, infectious outcomes, anastomotic leakage, planned and unplanned ostomies; failed attempts to restore bowel continuity, venous thromboembolism; **health system and resource utilization outcomes** such as readmissions after surgery, reoperation, additional interventional procedures, length of stay, admission to intensive care unit/ nursing care; and **patient-centered outcomes** such as patient satisfaction, and quality of life. For Key Question 2 we considered the following prespecified **harms or adverse events**: nausea, vomiting, dehydration, electrolyte imbalance, kidney damage, emergency admissions prior to surgery;

^b During the peer review of this draft searches will be updated to include data indexed through June 2013.

cancelled, delayed, or rescheduled surgeries, allergic reactions, seizures. Studies reporting harms were included regardless of causal attribution to OMBP.

Data Extraction

A single investigator extracted data from each study; quantitative results were verified by a second reviewer. Disagreements were resolved by consensus involving a third investigator. Following pilot testing, data were extracted into electronic forms stored in the Systematic Review Data Repository using separate forms per Key Question.²⁰ We took particular care to avoid double counting (both in qualitative and quantitative analyses) when published papers reported on potentially (fully or partially) overlapping patient populations. Potential overlap was assessed on the basis of the sampling population of each study, the enrollment period for each publication, the patient selection criteria, and information on overlap provided by the authors in the published papers.

Risk of Bias and Completeness of Reporting of Individual Studies

We assessed the risk of bias for each outcome following the processes described in the *Methods Guide*. For RCTs, we based our assessment on items from the Cochrane risk of bias tool.²¹ For NRCSs and single-group studies, we used items from the Newcastle-Ottawa tool, with the addition of items relevant to statistical analysis.²² We provide qualitative dispositions regarding publication bias based on the number of available studies, the number of studies contributing information for each outcome, sample size, and the statistical significance of reported comparisons.

Synthesis

For each Key Question, we synthesized results qualitatively and assessed whether studies were sufficiently similar to be combined in a meta-analysis.

We used both pairwise and network meta-analysis. We did pairwise meta-analyses for outcome comparisons with more than three nonoverlapping studies. For outcomes with at least six studies, we used Bayesian network meta-analysis to jointly analyze evidence for “OMBP with or without enema”, “enema alone” and “no OMBP or enema”. Bayesian methods incorporate uncertainty in the summary estimates of treatment effects more fully than frequentist methods. Studies comparing “enema alone” and “no OMBP or enema” were not in the scope of this report, and such studies (if any exist) are not included in the analyses. In structural sensitivity analyses we split the “OMBP with or without enema” strategy into “OMBP alone” and “OMBP plus enema” interventions. We did not construct or analyze networks that include comparisons between alternative “active” OMBP interventions, because of substantial concerns that head-to-head studies between “active” OMBP strategies are not similar to studies included in the above network. We assessed for inconsistency qualitatively, by comparing results from pairwise and network meta-analyses, because formal tests for inconsistency are known to be very underpowered.

Estimation was done in the generalized linear mixed model framework, with binomial families and a logit link function.²³ Models accounted for between-study heterogeneity. In network meta-analyses we assumed homogeneity of the random effects variances at the between-study level, because few studies provided information for each comparison in the network.

For all statistical tests, except those for heterogeneity, statistical significance was defined as a two-sided P-value where $P < 0.05$. Heterogeneity was considered statistically significant when the P-value of Cochran’s Q statistic was $P < 0.10$ to account for the low statistical power of the

test. Between-study heterogeneity was quantified with the I^2 statistic.²⁴ All network meta-analysis models were fit using Bayesian MCMC methods. Prior distributions for all model parameters were noninformative.

Subgroup and Sensitivity Analyses

We planned to explore between-study heterogeneity using subgroup and meta-regression analyses. However, we observed little between study heterogeneity and for each comparison of interest few studies were available, rendering such analyses inappropriate. We did sensitivity analyses, such as leave-one-out analyses, analyses assuming a fixed effects model, analyses including a retracted study, and analyses evaluating alternative network topologies.

Software

All analyses were performed using Stata IC (version 12.1 Stata Corp., College Station, TX). We did not perform any adjustments for multiple comparisons. Markov Chain Monte Carlo estimation for Bayesian analysis was done in Winbugs (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK), through calls from Stata. Graphs were generated in Stata.

Grading the Body of Evidence and Assessing Applicability

We followed the *Methods Guide* to evaluate the strength of the body of evidence (high, moderate, low, and insufficient) for each Key Question with respect to the following domains: risk of bias, consistency, directness, precision, and reporting bias. We followed the *Methods Guide*²⁵ to evaluate the applicability of included studies to patient populations of interest, as guided by the Key Questions.

Results

Our literature search yielded 8759 citations, of which 804 were reviewed in full text. In the end 54 unique studies (in 60 publications^{9, 12, 14, 15, 26-82}) were eligible (40 RCTs; 8 NRCSS; and 6 single-group cohorts – see full report for details on the literature flow). The most common reasons for exclusion of articles were related to study design (e.g., we excluded small uncontrolled case series) and language of publication. Up to 2010 only four relevant non-English language studies were available. These studies reported on few patients and very low numbers of events; as such, their inclusion does not affect our results. See **Appendix B** of the full report for a list of the excluded studies and reasons for exclusion. Data extraction forms and summary tables for all included studies are available online on the Systematic Review Data Repository (<http://srdp.ahrq.gov/>).

Comparative effectiveness of OMBP versus no OMBP or enema, and among OMBP strategies (Key Question 1)

Forty RCTs and eight NRCSS met criteria for Key Question 1. The published report of one of these RCTs has been retracted and is not considered in main analyses.^{67, 83} Two RCTs were in children and one RCT compared inpatient versus outpatient preparation. The remaining 36 RCTs were classified into two mutually exclusive groups: trials comparing OMBP versus no OMBP (with or without enema) –active versus inactive comparison; and trials comparing alternative active OMBP strategies –active versus active comparison.

Compared to studies of OMBP versus no OMBP, studies of active OMBP regimens were conducted in earlier years (median year of enrollment start was 1987 versus 1999), and employed more often, or even exclusively, preparations that have fallen out of use (e.g., several-day-long preparations, multiple enemas, and whole gut irrigation with large volumes administered through nasogastric tubes). Most importantly, perioperative parenteral antibiotics were used in all arms of OMBP versus no OMBP studies, compared to only 26 of the 46 OMBP-treated arms. Because of these differences, we considered comparisons of OMBP versus no OMBP separately from comparisons among alternative active OMBP strategies. The former appear applicable to contemporary decisionmaking regarding preoperative preparation, whereas the later less so.

OMBP versus no OMBP

Fifteen RCTs and 5 NRCSs (20 in adult populations and 1 in a mixed population of adults and children) contributed relevant information to the main analysis. Common indications for surgery were colorectal cancer and diverticular disease. Details on the surgical approach (e.g., operation types, anastomosis methods, open versus surgical surgery) were generally poorly reported. With respect to stratification by surgical site, one study enrolled only patients undergoing rectal surgery, two studies enrolled only patients undergoing left-sided colorectal surgeries, and three studies reported stratified results.

RCTs

Fifteen RCTs compared OMBP versus no OMBP. Studies used a variety of OMBP regimens: seven used PEG, one study used hyperosmotic sodium solutions, three studies used other laxatives or cathartics, and four studies used other methods (including combinations of the aforementioned regimens). All studies reported using intravenous antibiotics in the perioperative period and two studies reported also using oral antibiotics.

The majority of RCTs were considered to be at moderate risk of bias. Overall, based on the number of items considered indicative of “low” risk, six studies were considered to be at high risk of bias, eight to be at moderate risk of bias, and one to be at low risk of bias.

In order to extract the maximum amount of information from the available RCTs, we performed 3 different meta-analyses: (1) a conventional meta-analysis of trials directly comparing OMBP with either enema or no preparation; (2) a network meta-analysis of the same trials as the basis for calculating the probability that each intervention was best/second best/worst; and (3) a 4-node network meta-analysis allowing us to estimate the effects of OMBP with enema and OMBP without enema. We base our assessment of the evidence on the results of all these analyses.

Table ES-1 shows pairwise random effects meta-analyses of RCTs for six clinical outcomes, stratified by whether enema was administered in the comparator group. There was no statistically significant difference between OMBP and no preparation or enema for all but one outcome, but confidence intervals did not exclude clinically important differences in either direction. The single exception was for the outcome category “peritonitis or intraabdominal abscess”, for which OMBP appeared to be protective compared to no preparation (OR=0.58, 95% confidence interval 0.37 to 0.89). We caution however that the outcome definition was quite diverse across studies. The 95% credible interval for this comparison included 1 when we used analyses that are better in incorporating the uncertainty in the synthesis of the data (Bayesian network meta-analyses, see below).

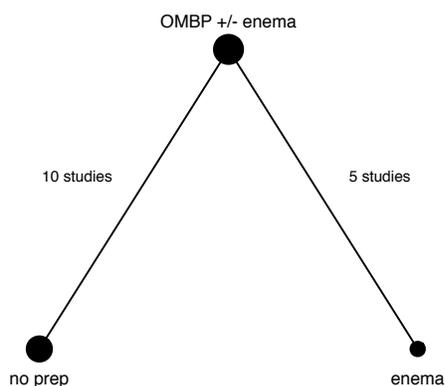
Table ES-1: Meta-analysis Results for the Comparison of OMBP Versus Enema or No Preparation

Outcome	Comparison	N studies (N events / N patients, per group)	OR (95% CI); P value	Heterogeneity (P value; I ² %)
All-cause mortality	OMBP ± enema vs. no prep	9 (37 / 1973 vs. 39 / 1963)	0.94 (0.59, 1.48); P = 0.78	0.80; 0%
	OMBP ± enema vs. enema	4 (7 / 526 vs. 4 / 530)	1.67 (0.45, 6.13); P = 0.44	0.32; 0%
Anastomotic leakage	OMBP ± enema vs. no prep	9 (82 / 1968 vs. 93 / 1950)	0.88 (0.64, 1.20); P = 0.41	0.66; 0%
	OMBP ± enema vs. enema	4 (24 / 526 vs. 21 / 530)	1.16 (0.51, 2.64); P = 0.71	0.21; 34%
Wound Infection	OMBP ± enema vs. no prep	11 (206 / 2035 vs. 182 / 2022)	1.15 (0.93, 1.43); P = 0.19	0.67; 0%
	OMBP ± enema vs. enema	4 (48 / 526 vs. 49 / 530)	1.02 (0.53, 1.93); P = 0.96	0.11; 50%
Peritonitis/ intraabdominal abscess	OMBP ± enema vs. no prep	8 (36 / 1756 vs. 60 / 1733)	0.58 (0.37, 0.89); P = 0.01	0.52; 0%
	OMBP ± enema vs. enema	4 (6 / 526 vs. 6 / 530)	1.00 (0.31, 3.24); P = 0.99	0.87; 0%
Reoperation	OMBP ± enema vs. no prep	5 (112 / 1691 vs. 108 / 1672)	1.02 (0.78, 1.35); P = 0.86	0.42; 0%
	OMBP ± enema vs. enema	2 (7 / 225 vs. 8 / 222)	0.61 (0.01, 32.65); P = 0.81	0.02; 83%
SSI	OMBP ± enema vs. no prep	4 (150 / 978 vs. 161 / 939)	0.90 (0.48, 1.70); P = 0.74	0.01; 75%
	OMBP ± enema vs. enema	2 (33 / 192 vs. 26 / 190)	1.51 (0.38, 6.06); P = 0.56	0.02; 81%

OR values lower than 1 indicate that events are less common among OMBP-treated groups (i.e., that OMBP is beneficial). CI = confidence interval; no prep = no OMBP and no enema; OMBP = oral mechanical bowel preparation (with or without enema); OR = odds ratio; SSI = surgical site infection.

The main network meta-analysis compared “OMBP with or without enema”, “enema”, and “no preparation” (**Figure ES-1**). The network meta-analysis “respects” the randomization procedure within each study and allows us to “borrow strength” from all studies in estimating between-study heterogeneity. Because it integrates over the distribution of the between-study heterogeneity parameter, it incorporates the uncertainties of data synthesis more fully than the aforementioned pairwise analyses. The point estimates in **Table ES-2** are similar to those from pairwise meta-analyses (**Table ES-1**), but the 95% credible intervals are generally wider than the corresponding 95% confidence intervals. (The credible intervals are the Bayesian analogue of the confidence intervals.) As expected, uncertainty is most striking for the indirectly estimated effect sizes (i.e., those comparing enema versus no preparation).

Figure ES-1: 3-node network structure



Network structure for the 3-node network meta-analysis comparing OMBP +/- enema vs. enema alone vs. no preparation. Nodes indicate the treatments compared and have size proportional to the total number of patients enrolled in the corresponding trial groups. Connecting lines depict direct comparisons and are labeled with the total number of available studies (not all studies contributed data for all outcomes).

Table ES-2. Summary Estimates from the 3-node Network Meta-analysis.

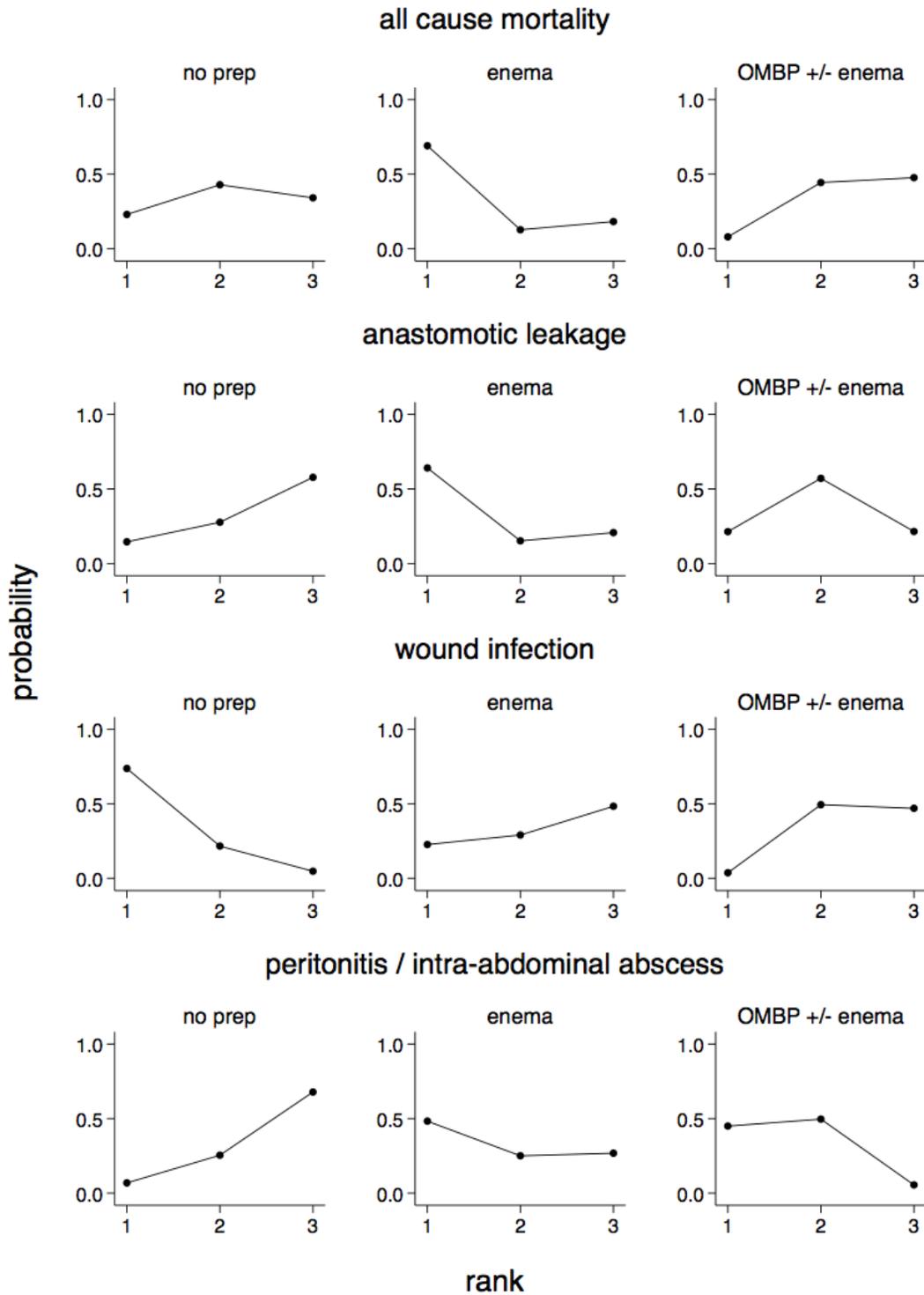
Outcome	Comparison	OR (95% CrI)
All-cause mortality	Enema vs. no preparation*	0.60 (0.09, 4.83)
	OMBP ± enema vs. no preparation	1.10 (0.55, 3.76)
	OMBP ± enema vs. enema	1.87 (0.37, 11.43)
Anastomotic leakage	Enema vs. no preparation*	0.76 (0.32, 1.80)
	OMBP ± enema vs. no preparation	0.90 (0.60, 1.46)
	OMBP ± enema vs. enema	1.19 (0.57, 2.57)
Wound infection	Enema vs. no preparation*	1.25 (0.66, 2.52)
	OMBP ± enema vs. no preparation	1.25 (0.91, 1.95)
	OMBP ± enema vs. enema	1.01 (0.58, 1.80)
Peritonitis/ Intra-abdominal abscess	Enema vs. no preparation*	0.65 (0.15, 3.28)
	OMBP ± enema vs. no preparation	0.64 (0.35, 1.47)
	OMBP ± enema vs. enema	0.99 (0.25, 3.89)

OR values lower than 1 indicate that events are less common among treatment groups receiving the first listed treatment for each comparison. CrI = credible interval; OR = odds ratio.

* Results based only on indirect comparisons. Outcomes with fewer than 6 studies were not analyzed with network meta-analysis; analyses for reoperation (7 studies) and surgical site infections (6 studies) produced very wide credible intervals and are not shown here.

Based on the network analysis, **Figure ES-2** shows the probability that each treatment is the “best”, “second best”, or “last” with respect to all-cause mortality, anastomotic leakage, wound infection, and peritonitis or intra-abdominal abscess. The rank probabilities take into account the difference in the point estimates of the treatment effects and the uncertainty around them but does not say anything about the magnitude of the differences between treatments. Therefore, rank probabilities should be interpreted with caution. Overall, across outcomes, no intervention appears to be uniformly better or worse than the others, although OMBP never appears to be the most likely best choice.

Figure ES-2: Ranking of Treatments Based on the 3-node Network Meta-Analysis



Each panel depicts the estimated probability that a given treatment is the best (rank = 1), second best (rank = 2), or last (rank = 3), for each of the outcomes of interest.

Finally, we separated the “OMBP with or without enema” strategy into “OMBP with enema” and “OMBP without enema” in a second network meta-analysis (a 4-node network). The results of the 4-node network meta-analysis generally suggested that data are not adequate to draw definitive conclusions due to imprecision. Results were robust in all sensitivity analyses listed in the methods section (see main report).

NRCSs

Five NRCSs reported information on the comparison of OMBP versus omission of preparation. Because of heterogeneity in patient selection and outcomes reported, differences in study design, and concerns regarding risk for residual confounding we did not perform meta-analysis. In sum, the NRCSs reported results consistent with those of RCTs and did not demonstrate significant differences between OMBP and no-OMBP strategies. At the same time, confidence intervals were generally broad (e.g., could not exclude a 50% change in odds in either direction). Studies were at substantial risk of bias, mostly due to confounding factors that had not been adequately controlled in the design or analysis of these investigations.

Comparisons of Alternative Active OMBP strategies

Twenty-three RCTs and two NRCSs (reported in 25 publications) provided information on comparisons among active OMBP strategies for patients undergoing elective colorectal surgery. We first examine the findings of RCTs, followed by the findings of NRCSs.

RCTS in adults

Twenty-one of the 23 RCTs enrolled adult patients and two enrolled exclusively children. The most common indications for surgery were colorectal cancer and diverticular disease. Information on the surgical approach (e.g., operation types, anastomosis methods, open versus surgical surgery) and on the breakdown of surgical sites into right colon, left colon and rectum was generally not reported.

The majority of RCTs (20 out of 23) had two treatment groups; three had three groups and one had four groups, for a total of 51 active OMBP groups and 35 possible pairwise contrasts. Studies compared diverse OMBP strategies. We grouped OMBP strategies into seven grand categories to facilitate synthesis and presentation: PEG, PEG combined with laxatives or cathartics, hyperosmotic sodium solutions, other laxatives or cathartics, whole gut irrigation with electrolyte solutions (other than PEG), mixed/other (e.g., combinations of OMBP drugs), and dietary interventions. The most common comparisons were between PEG versus whole-gut-irrigation-based OMBP (examined in 5 RCTs) and PEG-based versus laxative/cathartic-based OMBP (3 RCTs).

Many items necessary for detailed assessment of all risk of bias were not reported in most studies. Overall, based on the number of items considered indicative of “low” risk, 10 studies were considered to be at high risk of bias, 12 to be at intermediate risk of bias, and one to be at low risk of bias.

We did not perform a meta-analysis because of extensive diversity of the employed OMBP strategies, the heterogeneity in the assessed outcomes, and concerns regarding selective outcome reporting (and other risk of bias dimensions). Instead, we summarize the information extracted from studies qualitatively. Briefly, we observed that

1. **Only 17 out of the 28 possible comparisons had some empirical information**, i.e., have at least one study. The “density” of observed versus possible comparisons is somewhat optimistic: we have been quite lenient in categorizing the individual active OMBP

comparisons into the seven conceptual categories represented by rows and columns in each panel.

2. **Outcomes were assessed or reported in sufficient detail in a minority of the conducted studies**, perhaps with the exception of wound infection. Where two or more studies provided information for the same outcome no conclusions could be reached regarding the comparative effectiveness of interventions.
3. **Some of the outcomes of interest to this review, such as surgical site infections, pulmonary embolism, and venous thrombosis were not reported in any study.** The empirical evidence that is available to a literature-based review is but a small fraction of what could have been available. This represents a “lost opportunity”.
4. **The majority of the available studies were small, and probably underpowered to detect modest or small effect sizes, let alone relatively rare harms.** Across all 74 analyzable results (outcome/comparison combinations) four were statistically significant. This proportion (4.1%) is near the 5% that would be expected by chance if the null hypothesis of no association were true. Because the true distribution of effects in this body of literature is unknown, and because these analyses are not independent (per study, they are in the same patients), one cannot simply infer that all identified statistically significant findings are false. Nevertheless, this observation is congruent with the notion that very few, if any, genuine differences exist among active OMBP strategies in the included studies.

RCTS in children

Two studies, both conducted in India, compared alternative active OMBP strategies in children undergoing colorectal surgery. The first study compared whole gut irrigation with normal saline with added potassium versus PEG. The second study compared whole gut irrigation with a NaCl solution, PEG, or Ringer’s lactate. Both studies were considered to be at high risk of bias and did not provide conclusive evidence on the comparative effectiveness of the OMBP strategies they evaluated.

NRCSs

Only two NRCSs reported information on the comparison of alternative active OMBP strategies, including preparations that are no longer in clinical use (e.g., mannitol). The same observations that apply to the RCTs of active versus active interventions apply here as well.

Comparisons of Inpatient versus Outpatient OMBP

One RCT and one retrospective NRCS compared inpatient versus outpatient use of OMBP using PEG. Both studies were considered to be at high risk of bias. No statistically significant differences among arms were reported, however results were inconclusive due to the very small number of events for all reported outcomes.

Comparative harms of OMBP versus no OMBP or enema, and among OMBP strategies (Key Question 2)

To address Key Question 2 we summarize the evidence on the following predefined potential adverse events of OMBP: nausea, vomiting, dehydration, electrolyte imbalance, kidney damage, emergency admissions prior to surgery, cancelled, delayed, or rescheduled surgeries, allergic reactions, and seizures. The organization of the subsequent sections follows that of Key Question

1. We first discuss comparative studies of OMBP versus enema or no preparation, followed by comparative and noncomparative (single group) studies of alternative active OMBP strategies. We did not attempt a meta-analysis because of the substantial diversity in outcome definitions, and variation in the reporting of adverse events.

Comparisons of OMBP versus no OMBP

Of the 15 RCTs comparing OMBP with or without enema versus enema alone or no preparation, only two provided information on harms (1 for nausea and 1 for renal failure). In the study reporting data on nausea,²⁹ nine out of 95 OMBP-treated patients and eight of 90 controls reported experiencing nausea ($P = 0.77$). In the other study,³⁰ three of 89 patients receiving OMBP versus one of 89 patients receiving no preparation experienced acute renal failure ($P = 0.62$).

None of the five NRCSs comparing OMBP versus no preparation reported information on the prespecified adverse events.

Comparisons of Alternative Active OMBP strategies

RCTs in adults

As discussed in the corresponding section of Key Question 1, studies of alternative active OMBP strategies used very diverse OMBP strategies, assessed heterogeneous outcomes, and raised concerns of selective outcome reporting (and other risk of bias dimensions). Regarding the assessment of adverse events, studies utilized a diverse set of symptom scales to measure severity of patient reported adverse events (nausea, vomiting, fatigue, bloating, cramping, etc.). In most studies adverse event definitions were not clearly described, making it impossible to consistently compare outcomes across studies. For these reasons, we have used the same approach as in Key Question 1 and summarize findings qualitatively.

We make the similar observations as in Key Question 1: empirical information is available only for some out of many possible contrasts, and when provided, it is poorly reported. For example, most reported data fall into the outcome category “other patient-reported adverse events”, which is indicative of the nonstandardized reporting. Renal failure, an outcome considered important given that many OMBP strategies involve ingestion of large volumes of electrolyte solutions, was not reported in any study. Further, the majority of the available studies were small, and probably underpowered to detect modest or small effect sizes, let alone relatively rare harms. Across all 81 analyzable results (outcome/comparison combinations), 23 were statistically significant. However, there is no readily discernible pattern. Because the true distribution of effects in this body of literature is unknown, and because many of these analyses are not independent, one cannot make statements on whether the identified statistically significant findings are more than what would be expected by chance.

RCTs in children

The studies comparing alternative active OMBP strategies in children undergoing colorectal surgery did not provide conclusive evidence on the adverse events of the OMBP strategies they evaluated.

NRCSs

The two NRCSs comparing alternative active OMBP strategies versus no preparation did not report information on the prespecified adverse events.

Single-group Cohorts

Six studies met our inclusion criteria for single group cohorts and reported results on at least one of the prespecified adverse events of pertaining to Key Question 2. Overall, reporting of adverse events was partial and was limited to vomiting, nausea, vomiting and nausea, and allergic reactions. Almost universally, the rates of reported adverse events were below four percent. The exception was a cohort⁴¹ of patients receiving OMBP with sodium phosphate with or without oral antibiotics, where the rate of vomiting was approximately 17 percent (51 of 300 patients). No study made causal attributions of the adverse events to the OMBP drugs or to the cointerventions (antibiotics 5 cohorts, enema in 1).

No studies reported adverse events by any of the prespecified subgroups of interest.

Comparisons of Inpatient versus Outpatient OMBP

The two studies (1 RCT and 1 NRCS) comparing inpatient versus outpatient administration of OMBP did not report information on the prespecified adverse events of interest.

Discussion

Key Findings

We reviewed almost 60 studies spanning 40 years of empirical research on the benefits and harms of alternative OMBP strategies for elective colorectal surgery and noted a striking shift in the design and focus of research over time. In the early 1970's OMBP was widely considered highly desirable, on the basis of pathophysiological arguments rather than empirical evidence, and the majority of research focused on determining which OMBP strategy was best.⁵ It appears that those earlier assumptions are being questioned by an increasing number of studies comparing OMBP with no OMBP, while the number of comparisons among active OMBP strategies has declined. It is probably fair to state that the question is whether or not to perform OMBP, with any of the relatively short duration preparation regimes that are used in practice.

After examining the literature for a wide range of clinical outcomes, we found no evidence that OMBP with or without enema differs from enemas or no preparation. However, for all outcomes, the uncertainty accompanying the treatment effects was large. Based on the boundaries of the confidence intervals, for many outcomes one cannot exclude a modest (e.g., 30 to 50 percent) change in odds in either direction. Uncertainty is largely because the studies were relatively small, and the key clinical events such as mortality, anastomotic leakage, reoperation, and severe infection are relatively rare. OMBP did appear protective for the outcome of peritonitis or intra-abdominal abscess, but this association disappeared when inter-study heterogeneity was taken into account. Of more concern is that important subgroups, such as anatomic location (right colon versus left colon versus rectum) and type of surgery (laparoscopic versus open) were sparsely reported in the published literature.

We attempted to assess the comparative effectiveness of different OMBP strategies, but the studies were too small and heterogeneous for firm conclusions, and in any case most of the strategies compared are no longer in use, rendering the results non-applicable.

Similarly we attempted to assess harms, but too few studies collected harms consistently.

Assessment of the Strength of Evidence

Table ES-4 presents a summary of the report's key findings for each Key Question. When appropriate, results are presented separately for each of the populations and outcomes of interest.

Please see the Methods section for a detailed discussion of our approach to rating the strength of evidence.

Table ES-4. Summary Assessment of the Strength of Evidence

Population	Outcome	Comparison	Assessment of the strength of evidence	Key findings and comments*
KQ1: Adult patients undergoing colorectal surgery	All-cause mortality	OMBP versus no preparation	Insufficient	The OR in network meta-analysis of 9 studies was 1.10 (95% CrI 0.55 to 3.76), indicating substantial uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
		OMBP versus enema	Insufficient	The OR in network meta-analysis of 4 studies was 1.87 (95% CrI 0.37 to 11.43), indicating substantial uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
	Anastomotic leakage	OMBP versus no preparation	Low (for lack of difference)	The OR in network meta-analysis of 9 studies was 0.90 (95% CrI 0.60 to 1.46), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
		OMBP versus enema	Low (for lack of difference)	The OR in network meta-analysis of 4 studies was 1.19 (95% CrI 0.56 to 2.57), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
	Wound infection	OMBP versus no preparation	Low (for lack of difference)	The OR in network meta-analysis of 11 studies was 1.25 (95% CrI 0.91 to 1.95), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
		OMBP versus enema	Low (for lack of difference)	The OR in network meta-analysis of 4 studies was 1.01 (95% CrI 0.58 to 1.80), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was some evidence of inconsistency; the test for heterogeneity was not statistically significant (P = 0.11) but the I ² index was 50%
	Peritonitis/Intra-	OMBP versus no	Low (for lack of	The OR in network meta-analysis of 8 studies was 0.64 (95% CrI 0.35 to 1.47), indicating moderate uncertainty in the summary estimate. Pairwise analysis indicated that OMBP was

abdominal infection	preparation	difference)	significantly associated with a reduction in peritonitis but that analysis does not fully reflect the statistical uncertainty of the data and therefore is less reliable. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected	
	OMBP versus enema	Low (for lack of difference)	The OR in network meta-analysis of 4 studies was 0.99 (95% CrI 0.25 to 3.89), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected	
Reoperation	OMBP versus no preparation	Low (for lack of difference)	No network analysis possible. The OR in pairwise meta-analysis of 5 studies was 0.78 (95% CI 0.78 to 1.35), indicating substantial uncertainty in the summary estimate Studies were at low-moderate ROB There was some concern regarding selective outcome reporting There was evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected	
	OMBP versus enema	Insufficient	No network analysis possible. The OR in pairwise meta-analysis of 2 studies was 0.61 (95% CI 0.01 to 32.65), indicating substantial uncertainty in the summary estimate. Studies were at low-moderate ROB There was some concern regarding selective outcome reporting There was statistical evidence of inconsistency; the test for heterogeneity was statistically significant (P=0.02) and the I ² index was 83%	
All other effectiveness outcomes	OMBP versus no preparation	Insufficient	Few if any studies reported information; study-specific results were imprecise There was concern about selective outcome reporting	
	OMBP versus enema	Insufficient	Few if any studies reported information; study-specific results were imprecise There was concern about selective outcome reporting	
All outcomes	Alternative active OMBP strategies versus each other	Insufficient	Individual studies compared diverse interventions and reported outcomes heterogeneously, precluding synthesis Study specific results were imprecise Studies were at moderate-high ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected	
All outcomes	Inpatient vs. outpatient OMBP	Insufficient	Only two studies were available (1 RCT, at moderate ROB, and 1 NRCS, at high ROB) Study specific estimates were imprecise	
KQ1: Children undergoing elective colorectal	All outcomes	All comparisons	Insufficient	Only 2 studies provided evidence on children undergoing elective colorectal surgery Studies reported information only for wound infection (no other effectiveness outcomes were assessed) and produced imprecise results

surgery				
KQ1: Patients undergoing elective surgery for right-sided or left-sided colon, or rectal surgery	All outcomes	All comparisons	Insufficient	Only a small minority of studies provided anatomic location specific results (and only for a single outcome) There is concern regarding selective analysis reporting
KQ2: Patients undergoing elective colorectal surgery (unselected)	Adverse events	All comparisons	Insufficient	When interpreting the data available for this review results are insufficient: most prespecified adverse events of interest were evaluated by a small minority of studies or not examined at all; when reported study specific results did not lead to definitive conclusions due to imprecise results, and lack of validation of the measurement scales used (for patient symptom scores) However, the evolution of the preparation strategies used in trials (with most recent studies using PEG-based strategies, possibly in combination with laxatives) indicates that these preparations may be considered safest or more palatable for patients
KQ2: Patients undergoing elective surgery who may be at particular risk for adverse events	Adverse events	All comparisons	Insufficient	No relevant studies were identified

*Unless otherwise stated, summary estimates reported in this table are those from the network meta-analysis. We believe that these results better reflect statistical uncertainty.

CI = confidence interval; CrI = credibility interval; KQ = key question; NRCS = nonrandomized comparative study; OR = odds ratio; PEG = polyethylene glycol; RCT = randomized controlled trial; ROB = risk of bias.

Strengths and Limitations of This Review

Compared with the most recent Cochrane Review of OMBP, we have included a broader spectrum of study designs (including NRCSs and single group cohorts) and have performed more extensive data analyses using Bayesian network meta-analysis. As a result of using analyses that more fully account for the uncertainties in the synthesis of evidence, our interpretation of the evidence base is more conservative than that of the Cochrane review and other recent meta-analyses.^{1, 84-8687} Similarly to those reviews, we did not find evidence of clear benefit from OMBP, but the wide confidence intervals around our results leads us to conclude that clinically significant benefit or harm cannot be excluded and therefore further research is urgently needed to provide a definitive answer. While our results are consistent with no difference between using and not using OMBP, the confidence or credible intervals cannot exclude a modest difference in either direction.

Nonetheless, several limitations need to be considered when interpreting our results. First, our conclusions, to a large extent, reflect limitations of the underlying evidence base. Our ability to perform important subgroup analyses to explore the impact of patient-, disease-, or system-level characteristics on the effectiveness of OMBP is limited by the incomplete reporting of relevant information in the published papers. Second, we excluded studies not published in English, although this is unlikely to cause major bias since previous work studies identified only three relevant non-English language publications including a total of 219 patients. Third, we have relied mainly on electronic database searches and perusal of reference lists to identify relevant studies. Unpublished relevant studies may have been missed. Fourth, indexing of non-randomized studies – and single-group cohort studies in particular – is less complete than that of randomized trials and we may have failed to identify relevant studies. However, we did not use search filters that limit results to specific study designs, in order to increase the sensitivity of our searches.

Applicability

The existing evidence base comparing OMBP with or without enema, versus enema or no preparation, appears to be applicable to US settings. Studies enrolled patients with an age distribution similar to that of patients undergoing colorectal surgery in the US, and for indications that represent the most prevalent indications in US clinical practice. However, none of these studies has been conducted in the US, raising some concern that system-level differences may render findings less applicable to surgical practice. Findings may be most applicable to patients undergoing colon surgery; data on patients undergoing rectal surgery were sparse, and thus the applicability of findings to this population is at best unclear. Similarly, the applicability of our findings to patients undergoing laparoscopic colorectal surgery is unclear, because few studies reported relevant information. Regarding studies comparing alternative active OMBP strategies, applicability appears to be severely limited, because they examined OMBP regimens that have fallen out of use modern practice, such as whole gut irrigation with non-PEG electrolyte solutions, and mannitol.

Limitations of the Evidence

On the basis of the reviewed studies, we believe that the evidence regarding OMBP for colorectal surgery is limited in the following ways:

- *Most studies enrolled small numbers of patients and reported low event rates for major clinical events during followup.*

- Studies *did not report results for important clinical subgroups*, particularly those defined by anatomic location of surgery (colon versus rectal surgery) and the type of surgical procedure performed (e.g., open versus laparoscopic surgery).
- The *literature comparing alternative active OMBP strategies for colorectal strategy was fragmented* because studies used a large number of diverse preparation regimes and reported results for heterogeneous, often poorly defined, outcomes.
- *Nonrandomized trials, and particularly observational studies, could not effectively supplement the results of randomized trials* because of shortcomings in their analysis.

Evidence Gaps

Given the uncertainty of the evidence base, all the key questions addressed in this review remain evidence gaps. In addition, there is particularly limited and incomplete information on those undergoing elective rectal surgery or laparoscopic surgery. The examined literature provided only limited information for key adverse events of interest, and none on whether the adverse events associated with OMBP use are more common in frail patients and patients with very compromised function of major systems (e.g., cardiac, pulmonary, renal, immune).

Ongoing Research

A search on May 15, 2013, in the ClinicalTrials.gov registry identified 6 records of studies that are expected to provide information relevant to the Key Questions of this report. These may provide more data on OMBP for laparoscopic surgery and rectal surgery, OMBP versus enema, comparisons among alternative OMBP strategies. Additional trials will be needed to answer all the questions that remain.

Future Research

This review has identified major gaps in the published evidence on the comparative effectiveness and safety of OMBP for elective colorectal surgery. We believe that there is need for *a large, pragmatic and definitive RCT examining all combinations of using versus not using OMBP, oral antibiotics, and enema prior to colorectal surgery*. Such a study should be very feasible in the US setting, given the large volume of the procedures, that the interventions to be tested are low cost (or already part of standard care), and that only short followup is needed. It would be very important that data is collected according to anatomic location and type of surgery. *Although an individual patient data meta-analysis of existing trials of OMBP* is a lower cost alternative for obtaining information on important subgroups it would likely not succeed in reducing the uncertainty around the effectiveness of OMBP given the poor reporting. Its results could be used to inform the design of future primary trials. Future research is also needed to better understand *patient preferences*; given the current uncertainty regarding the comparative effectiveness of interventions. *Developing decision aids (decision support tools)* may help inform and facilitate the shared decisionmaking process. Informative decision aids could be developed using *decision analysis* methods to incorporate evidence on treatment benefits and adverse events with patient preferences. Finally, *observational studies* can inform the comparative effectiveness of alternative OMBP strategies, particularly for susceptible groups that have not been represented in the RCTs thus far. Such studies should have large sample sizes (to account for the low incidence of most outcome events) chosen on the basis of prospective power analyses, include patients representative of those seen in clinical practice, and use strong methods to address confounding bias (e.g., propensity score or instrumental variable methods). Further, exposure assessment should include the collection of details regarding the preparation

strategy (i.e., the OMBP regimen and any cointerventions) and outcome ascertainment should be done using standardized definitions for all outcomes of interest. Although the use of observational data always requires additional assumptions for valid inference on treatment effects (compared to randomized designs), well designed observational studies can offer valuable information both regarding the effectiveness and adverse effects of OMBP.

Conclusions

In summary, we found limited evidence to support or refute the use of OMBP for elective colorectal surgery. Studies comparing OMBP versus enema or no preparation provided limited evidence regarding the comparative effectiveness of these interventions. Although differences between were not statistically significant, confidence (or credibility) intervals around summary estimates could not exclude clinically significant effects) for most outcomes. The large body of literature on alternative active OMBP strategies was largely irrelevant to current surgical decisionmaking because the trials were underpowered, reported poorly defined outcomes, and compared preparations no longer in use. Future studies, including pooled reanalyses of existing data, new comparative studies (both randomized and nonrandomized), elicitation of patient preferences, and decision modeling hold promise for informing future studies.

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Background

Oral Mechanical Preparation for Colorectal Surgery

In the U.S. oral mechanical bowel preparation (OMBP), defined as an oral preparation given prior to surgery to clear fecal material from the bowel lumen, is often prescribed preoperatively for patients undergoing elective colorectal surgery.¹ OMBP is sometimes used as a precaution in anticipation of possible iatrogenic bowel injury during abdominal and pelvic surgeries that do not entail resection of the colon or rectum (e.g., urologic or gynecologic procedures). OMBP is also routinely prescribed prior to colonoscopy, to allow maximal visualization of the intraluminal bowel during the procedure.²

In 2009 there were 254,000 surgeries categorized as partial excisions of the large intestine;³ of these, 99.2 percent were for patients 15 years of age or older, and 50.4 percent were for patients 65 years of age or older. An analysis of claims from one large insurer demonstrated that the most common indication for colorectal surgery was cancer (43.9 percent), followed by diverticulitis (30.4 percent), and inflammatory bowel disease (4.5 percent).⁴

In the context of colorectal surgery, many have considered OMBP necessary to prevent infectious complications, mainly based on the belief that postoperative infectious morbidities are related to spillage of septic bowel contents during surgery and anastomotic leakage immediately after surgery.⁵ Gross spillage of fecal material in the operative field typically induces many surgeons to create an ostomy, which impacts patients' quality of life. An ostomy, in turn, requires additional surgery to reverse it and possibly other surgeries for complications such as bowel obstructions, incisional hernia repairs, and concomitant readmissions due to complications from these surgeries.^{6,7} Complication rates for elective colorectal surgery range between 4 and 36 percent.^{8,9} A surgical site infection can increase the hospitalization stay from approximately 4 to 21 days and increase costs from approximately \$11,000 to \$43,000.⁸ A recent analysis of more than 10,000 patients from a commercial insurance database reported that the 90-day readmission rate was 23.3 percent and the 30-day surgical site infection rate was 18.8 percent, following colorectal surgery.⁴ The median cost of a surgical site infection readmission was \$12,835.

The initial adoption of OMBP prior to colorectal surgery was not based on high quality evidence but rather on expert opinion and observational data.^{12,13} Recently, several trials (mostly conducted in Europe) found no statistically significant benefit for OMBP with colon surgery. For example, a recent large randomized trial of found that the rate of anastomotic leakage, wound

infections, and mortality did not differ by more than 3% between patients assigned to OMBP as compared to those assigned to the control group. On the basis of these data, utilization of OMBP has declined in Europe, but less so in the U.S.¹⁴ A 2003 U.S. survey showed that more than 99 percent of colorectal surgeons routinely employed OMBP.¹⁰ A recent study (2007–2009) of 24 Michigan hospitals reported that 86 percent of all colorectal surgeries were preceded by OMBP (49.6 percent without oral antibiotics and 36.4 percent with oral antibiotics).¹¹ In addition, anecdotal data from a recent meeting of the American Society of Colon and Rectal Surgeons indicated that OMBP use is widespread in the U.S. although recent surveys indicate that some surgeons have discontinued use of OMBP for right-side colon surgery.

Clinical guidelines reflect this uncertainty. For example, the 2010 guidelines of the Canadian Society of Colon and Rectal Surgeons stated that good evidence supported the omission of OMBP in the preoperative management of patients undergoing open elective right-sided and left-sided colorectal surgical resections.¹⁵ However, the guidelines also stated that there was insufficient evidence to support or refute the omission of OMBP for patients undergoing low anterior resection (with or without diverting stomas) or for patients undergoing laparoscopic colorectal surgery. The evidence regarding the use of enemas was also considered insufficient.

Clinical Use of OMBP Regimens

In the U.S. commonly used OMBP agents are approved by the U.S. Food and Drug Administration and are available over the counter. OMBP regimens in clinical use differ with respect to their mechanism of action, volume of preparation that needs to be ingested, and duration of use. The most commonly used oral laxative agents currently are over-the-counter, large-volume, osmotically balanced polyethylene glycol (PEG) solutions (e.g., MiraLAX®, GoLYTELY®, NuLYTELY®) or reduced-volume PEG with the addition of bisacodyl (HalfLyte®). PEG solutions evacuate the bowel by washout of ingested fluid (approximately 4 liters), with no substantial fluid or electrolyte shifts.⁸ Bisacodyl, a poorly absorbed diphenylmethane, stimulates colonic peristalsis and requires a smaller volume of ingested fluid (approximately 2 liters).² In contrast, hyperosmotic preparations draw water into the bowel to achieve washout.² Previously, sodium phosphate hyperosmotic preparations (Fleet®) were used, but this has been largely discontinued because of concern about electrolyte imbalance.

Typically, the patient starts the OMBP at home the day before surgery. Elderly and frail patients may undergo OMBP in the hospital. Patients dislike the large quantities of unpleasant-tasting laxative solutions required and the long time spent on the toilet. A minority of patients requires medical attention for vomiting, dehydration, and other reactions to OMBP; this may require cancellation and rescheduling of surgery. Additionally, liquid bowel contents from OMBP use may be less safely handled during surgery than solid contents and may represent a source of infection. Individuals who may be at greater risk of adverse effects of OMBP are the elderly (for example, ≥ 65 years of age) and those with comorbidities such as cardiovascular and pulmonary disease, diabetes, kidney disease, and compromised immune conditions.

Cointerventions

Evaluation of the effectiveness of OMBP needs to take into account the effects of cointerventions, such as enemas or antibiotics, on clinical outcomes. An enema is sometimes given the night before or the morning of surgery. Oral or intravenous antibiotics are also often

administered in preparation for surgery. Mechanical cleansing of the large intestine decreases the total volume of stool in the colon but does not change the concentration of bacteria.¹⁶ For this reason, in addition to the intravenous antibiotics routinely given immediately before and during colorectal surgery, some surgeons also prescribe oral antibiotics.¹⁷ A common oral antibiotic regimen (Nichols-Condon) consists of neomycin and erythromycin given the day before surgery.¹⁸ Metronidazole is often substituted for erythromycin because of its increased effectiveness against anaerobic organisms in the gut. Differences in antibiotic regimens between trials may confound comparisons of postoperative infection rates among trials that otherwise have similar preoperative preparation regimens. Decreased infection rates have been reported when oral antibiotics are added to intravenous antibiotics and OMBP,^{11, 17} and it was conjectured that oral antibiotics may be more effective when the burden of colonic bacteria has been reduced by means of OMBP.¹⁷

Current Uncertainties Regarding OMBP

A recent Cochrane systematic review (covering studies up to December 1, 2010 and using a fixed-effect meta-analysis model) found no benefit for OMBP in terms of anastomotic leaks, other surgical complications, or mortality for mixed populations of patients undergoing colon or rectal resection.¹ Several studies have been published since the last search of the Cochrane review, suggesting that an updated synthesis is needed. Furthermore, large variation in practice exists in different parts of the world, perhaps suggesting that existing syntheses of the evidence do not adequately address all decisionmaking uncertainties.^{19, 20} Specifically, current reviews do not adequately examine the comparative effectiveness of all feasible alternative bowel preparation strategies and have relied on pairwise comparisons between interventions, often lumping different OMBP methods or combining control groups who receive no intervention with groups using enemas. This approach may introduce heterogeneity (if alternative OMBP methods have different effectiveness or if enemas are superior to no intervention) and is not helpful in identifying the best OMBP approach. By contrast, a joint synthesis of data on all relevant treatment options, including direct comparisons between alternative OMBP strategies, could provide information on which treatment is likely best.

Scope of the Review

The purpose of this review was to systematically evaluate experimental and observational evidence on the benefits and harms associated with the use of OMBP in patients undergoing elective colorectal surgery. We also aimed to identify patient and procedural characteristics that modify the effect of OMBP on outcomes.

Key Questions

On the basis of the original topic nomination and an extensive process of topic development and refinement, we formulated the following Key Questions to guide the review:

Key Question 1: How do various preoperative OMBP strategies compare between them and versus a control with respect to their effectiveness for preventing surgical or postsurgical complications?

- a) For elective *right colon* surgery?
- b) For elective *left colon* surgery?
- c) For elective rectal surgery?

Key Question 2: How does the use of OMBP, with or without cointerventions (e.g., antibiotics, rectal enema), compare with no OMBP or with OMBP plus different cointerventions with respect to presurgical and postsurgical adverse events?

- a) What are the comparative adverse events of the various OMBP strategies?
- b) What are the comparative adverse events of OMBP in subgroups of patients especially susceptible to the potential adverse events?

Methods

This comparative effectiveness review evaluated the impact of alternative oral mechanical bowel preparation (OMBP) strategies for patients undergoing elective colorectal surgery. We considered comparisons between use of OMBP and its omission, as well as comparisons among alternative OMBP strategies.

We performed a systematic review of the published literature using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*³). The main sections in this chapter reflect the elements of the protocol established for the comparative effectiveness review. We followed the reporting requirements listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.²¹ All methods and analyses were determined *a priori*. The protocol was developed with input from external clinical and methodological experts and in consultation with the AHRQ task order officer (TOO); it was posted online to solicit additional public comments. Its PROSPERO registration number is CRD42013004381.

AHRQ Task Order Officer

The AHRQ TOO assigned to this project was responsible for overseeing all aspects of this report. The TOO facilitated a common understanding among all parties involved in the project, resolved ambiguities, and fielded all queries from the Evidence-based Practice Center (EPC) regarding the scope and processes of the project. The TOO and other staff at AHRQ reviewed the report for consistency, clarity, and to ensure that it conforms to AHRQ standards.

External Stakeholder Input

An initial set of questions for evidence review were nominated to the Effective Healthcare Program by a representative of a professional society. During a topic refinement phase, the initial questions that had previously been nominated for this report were refined with input from a panel of Key Informants representing clinicians, patients, and payers. After a public review of the proposed Key Questions, a group of experts was convened to form the Technical Expert Panel (TEP), which provided input to help refine the Key Questions, identify important issues, and define parameters for the review of evidence. TEP members included representatives of professional societies, experts in colorectal surgery, experts on the preoperative preparation of patients undergoing elective surgery, and an infectious disease specialist. Several of the TEP members have methodological expertise in health technology assessment. In addition, input from the TEP was sought during compilation of the report when questions arose about the scope of the review.

Key Questions

Two Key Questions were posed. Key Question 1 pertained to the comparative effectiveness of alternative OMBP strategies, including a strategy of no preparation. Key Question 2 pertained

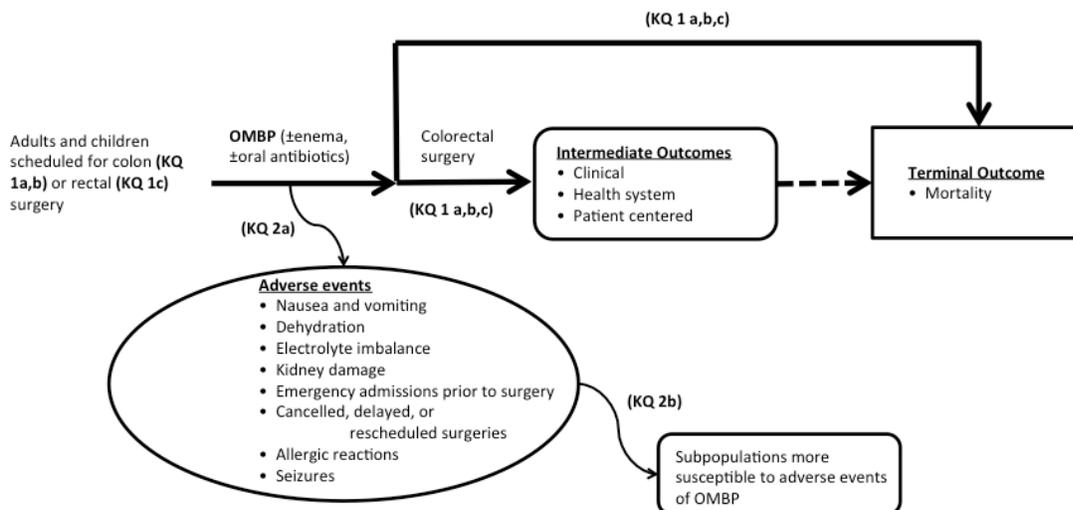
³ Available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>; last accessed May 1th, 2013.

to adverse events of alternative OMBP strategies, including a strategy of no preparation. The complete Key Questions have been presented at the end of the Introduction section.

Analytic Framework

We developed an analytic framework (**Figure 1**) that maps the Key Questions within the context of populations, interventions, comparators, and outcomes of interest, as well as the chain of logic that evidence must support to link the interventions to health outcomes. Briefly, the framework illustrates that OMBP, together with various cointerventions (e.g., enemas, oral or intravenous antibiotics, nutritional modifications), can impact intermediate and terminal outcomes (e.g., surgical site infections, anastomotic leakage, mortality), and can also be associated with adverse events (e.g., nausea and vomiting, electrolyte imbalance).

Figure 1: Analytic Framework



Key Questions are shown within the context of the PICO (**P**opulation, **I**ntervention, **C**omparators, and **O**utcomes) formalism. Interventions (alternative OMBP strategies or no OMBP) are compared in relevant clinical populations (patients undergoing elective large bowel surgery) with regard to intermediate outcomes (e.g., anastomotic leakage, reoperation, costs, etc.), final outcomes (mortality), or adverse events (e.g., nausea, vomiting, etc.). The intervention effect may be modified by several patient-level factors (e.g., cointerventions, anatomic location of the surgery, use of antibiotics, etc.). See the preceding section for a detailed description of the populations, interventions, and outcomes of interest. Abbreviations: KQ = Key Question; OMBP = oral mechanical bowel preparation.

Literature Search and Abstract Screening

We searched MEDLINE®, the Cochrane Central Trials Registry®, EMBASE®, and CINAHL® without any language or publication date restriction to identify literature relevant to the report. Searches were conducted on November 29, 2012. Search strings included terms for the populations and treatments of interest (see **Appendix A** for the exact search queries, which were extensively validated against previous reviews on the treatments of interest). We also performed a targeted search of the FDA Web site (last search performed on May 17th, 2013). All

searches will be updated to include data indexed up to June 2013; evidence from studies published since our original search will be incorporated in the final report, which will be prepared after the peer review of the current draft.

To supplement searches, we asked technical experts to provide additional citations of potentially relevant articles. We identified additional studies by perusing reference lists of eligible studies, published clinical practice guidelines, and relevant narrative and systematic reviews. On the basis of preliminary searches conducted during topic refinement, we provided the Scientific Resource Center (SRC, an entity within the Effective Health Care Program unrelated to the Brown EPC) with a list of relevant technologies and manufacturers. Per EPC procedures, the SRC solicits information from the manufacturers and organizes all obtained material into submission information packages (SIPs). However, as of May 17, 2013 no documents were sent to the SRC from outside sources.^a All articles identified through sources other than electronic database searches were reviewed for eligibility in full text, using the same criteria as for articles identified through our database searches. Finally, we searched the ClinicalTrials.gov Web site (with the last search performed on May 15, 2013) for ongoing comparative trials of alternative OMBP strategies. We did not consider unpublished data other than the information included in the FDA documents or ClinicalTrials.gov.

A common set of 200 abstracts was first screened by three investigators and discrepancies were discussed in order to standardize screening practices and ensure understanding of the criteria by all team members. Two hundred additional abstracts were screened by all investigators to ensure that selection criteria were standardized. The remaining citations were split into nonoverlapping sets, each screened by a single reviewer. Abstracts were manually screened, using *Abstrackr*.²² Reviewers aimed to be inclusive in order to increase the sensitivity of abstract screening. All abstracts were reviewed by two team members and discrepancies were resolved by consensus.

Study Selection and Eligibility Criteria

Full-text articles were reviewed independently by two investigators to determine eligibility. Disagreements regarding inclusion or relevance to a specific question were resolved by consensus including at least one additional investigator. Below we detail the study selection criteria for each Key Question.

We did not include studies in languages other than English but we recorded the number of such studies. We excluded narrative reviews, editorials, letters to the editor, and other papers not presenting primary research data. We also excluded studies reporting exclusively on healthy individuals or studies reporting exclusively the results of animal experiments. **Appendix B** lists all the studies excluded after full-text screening and the reason for exclusion.

Populations and Conditions of Interest

For Key Question 1 the population of interest was adults and children who underwent elective colon (Key Questions 1a and 1b) or rectal surgery (Key Question 1c). Subgroups of interest were those defined by anastomosis location and type (e.g., based on the bowel segments anastomosed or the method of anastomosis, hand-sewn versus stapled), type of surgical

^a During the peer review period the EPC team will review any additional documents that may be provided from reviewers, or late-arriving SIPs from manufacturers.

procedure (open versus laparoscopic), patient age (children versus adults), and indications for surgery (cancer versus inflammatory bowel disease versus diverticulitis versus other).

For Key Question 2a the population of interest was adults and children who undergo elective colon or rectal surgery. Key Question 2b focused specifically on adverse events in susceptible patient groups undergoing elective colorectal surgery, including adults and children with cardiovascular or pulmonary disease, those at the extremes of age (young children and the elderly), patients who have undergone adjuvant chemotherapy or radiotherapy, and patients with diabetes, kidney disease, or compromised immune function (including drug-induced immunosuppression).

We considered out of the scope of this review studies of patients receiving OMBP in preparation for endoscopic procedures or studies in patients who presented with complete bowel obstruction requiring surgical or endoscopic intervention to initiate OMBP. We also excluded studies of patients undergoing emergency colorectal surgery, and studies reporting results on the use of OMBP on patients undergoing noncolorectal surgery or on mixed populations in which less than 80 percent of patients underwent colorectal surgery (unless data on the subgroup undergoing colorectal surgery were reported separately).

Interventions

For all Key Questions, the intervention of interest was OMBP administered before colon or rectal surgery. Studies in which the preparation was administered via nasogastric tube were also considered eligible. Mechanical bowel preparation delivered through other routes (e.g., retrograde preparation) was not considered within the scope of the review.

We considered the following cointerventions to be of interest when administered along with OMBP: oral or intravenous antibiotics administered before surgery (e.g., neomycin, erythromycin, metronidazole, various cephalosporins), rectal enemas, and dietary modification in preparation for surgery.

Comparators

We considered alternative OMBP strategies (with or without cointerventions), including a strategy of not using OMBP as the comparators of interest.

Outcomes

For Key Question 1 we considered the following intermediate outcomes: **clinical outcomes** [infectious outcomes (whenever possible, these were classified according to the definitions proposed by the Centers for Disease Control and Prevention^b), anastomotic leakage, planned and unplanned ostomies; failed attempts to restore bowel continuity, venous thromboembolism (deep venous thrombosis and pulmonary embolism)]; **health system and resource utilization outcomes** [readmissions after surgery, reoperation, additional interventional procedures (endoscopy, interventional radiology), length of stay (postoperative and overall), admission to intensive care unit, admission to nursing care]; and **patient-centered outcomes**: (patient satisfaction, and quality of life). We also extracted data on mortality, which was considered the terminal clinical outcome of interest (including all-cause and cause specific mortality).

^b Available at www.cdc.gov/hicpac/SSI/002_SSI.html#IB1; last accessed February 11, 2013

For Key Question 2 we considered the following adverse events: nausea, vomiting, dehydration, electrolyte imbalance (e.g., hypokalemia, hypernatremia), kidney damage, emergency admissions prior to surgery; cancelled, delayed, or rescheduled surgeries, allergic reactions, seizures. Studies reporting any of these prespecified outcomes were included, regardless of causal attribution to OMBP (i.e., regardless of whether the authors of individual reports considered them to be related to OMBP use as opposed to any of the cointerventions); however, we collected information on causal attribution, when available.

Timing, Followup Duration, and Setting

We did not select studies on the basis of followup duration and, when possible, outcome data (for all outcomes) were evaluated separately for the preoperative and postoperative periods. We also did not use the setting where studies were conducted as a selection criterion.

Study Designs

For both Key Questions we considered randomized controlled trials (RCTs) comparing at least two of the interventions of interest in patient populations undergoing elective colon or rectal surgery. We required that RCTs enrolled at least 10 subjects per arm; smaller sample sizes were considered unlikely to provide estimates of treatment effects that are adequately precise. We also considered nonrandomized comparative studies (NRCS, prospective or retrospective; observational or experimental) comparing at least two of the interventions of interest in patients undergoing elective colon or rectal surgery. We required that NRCS enrolled at least 100 subjects (per arm); this cutoff was chosen because we expected that adjustments for confounders would be made, and that these would require a minimum sample size. This cutoff is probably lenient.^c

For Key Question 2, in addition to RCTs and NRCS, we also considered single-group studies (i.e., cohort studies where all patients are managed with OMBP and followed up longitudinally) and then undergo elective colon or rectal surgery. We required that single group studies reported results on at least 200 patients. This cutoff was chosen to ensure that studies would be likely to observe events that have relatively low incidence rates.^d For Key Question 2b (adverse events in susceptible subgroups) we specifically required that studies reported formal interaction tests or allowed for the calculation of statistics that compare the treatment effect among strata of the modifier of interest.

Data Extraction

A single investigator extracted data from each study; quantitative results were verified by a second reviewer. Disagreements were resolved by consensus involving a third investigator. Data were extracted into electronic forms stored in the Systematic Review Data Repository²³; separate forms were generated for each Key Question. Extraction forms were piloted on three to five articles for each Key Question and revisions were made as needed. We extracted information on

^c Assuming that at least three potential confounders are to be considered, regression models have to include at least four predictor variables (one per confounder and the treatment indicator). Using the (fairly optimistic) rule of 10, this means that a study should include at least 40 ($= 4 \times 10$) outcome events for statistical analysis. This implies relatively large sample sizes, especially for low incidence rate events: Even if the outcome rate is relatively high, e.g. 10 percent, the sample size needs to be >400 patients, which is much larger than the cutoff employed here.

^d For example, assuming the true incidence proportion is 0.01 (=1%) the probability of observing at least one event is >85 percent for a study of 200 patients.

the following items: patient selection criteria, population characteristics, sample size, study design, analytic details, and outcomes.

We prespecified that we would contact authors for the following reasons: (1) to clarify information reported in the papers that is hard to interpret (e.g., inconsistencies between tables and text); (2) to obtain missing data on key subgroups of interest when not available in the published reports (e.g., location of the surgery—right or left colon, rectum); and (3) to verify suspected overlap between study populations in publications from the same group of investigators. We contacted the corresponding author of each study by email or regular mail to collect additional information. We made a primary contact attempt (once all eligible studies had been identified) and will use up to two reminder emails (approximately 2 and 4 weeks after the first attempt). Information provided directly by the authors will be incorporated in the Final Report.

Population Overlap Across Publications

We took particular care to avoid double counting (both in qualitative and quantitative analyses) when published papers reported on potentially (fully or partially) overlapping patient populations. Potential overlap was assessed on the basis of the sampling population of each study, the enrollment period for each publication, the patient selection criteria, and information on overlap provided by the authors in the published papers. When overlap could not be ruled out on the basis of the above criteria, we used a conservative approach of considering as potentially overlapping in any studies conducted by the same investigators. In the presence of suspected overlap we based our analysis on the study reporting the largest number of outcome events (typically, the study reporting on the longest followup for longitudinal studies).

Risk of Bias and Completeness of Reporting of Individual Studies

For assessing the risk of bias, we followed recently updated guidance from the *Methods Guide*. We used different criteria for assessing the risk of bias (and when appropriate, the completeness of reporting) for each study design. For RCTs, we based our assessment on items from the Cochrane risk of bias tool.²⁴ For NRCSS and single-group studies, we used items from the Newcastle-Ottawa tool^c, with the addition of items relevant to statistical analysis.²⁵

We did not merge items into composite quality scores. Instead, we assessed and reported each methodological quality item (as Yes, No, or Unclear/Not Reported) for each eligible study. We rated each study as being of low, intermediate, or high risk of bias on the basis of these items. Generally, studies with low risk of bias have the following features: lowest likelihood of confounding due to comparison to a randomized controlled group; a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; clear reporting of dropouts and a dropout rate less than 20 percent; and no apparent bias. Studies with moderate risk of bias are susceptible to some bias but not sufficiently to invalidate results. They do not meet all the criteria for low risk of bias owing to some deficiencies, but none are likely to introduce major bias. Studies with moderate risk of bias may not be randomized or may be missing information, making it difficult to assess limitations and potential problems. Studies with high risk of bias are those with indications of bias that may invalidate the reported findings (e.g.,

^c Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp; last accessed May 30, 2013

observational studies not adjusting for any confounders, studies using historical controls, or studies with very high dropout rates). These studies have serious errors in design, analysis, or reporting and contain discrepancies in reporting or have large amounts of missing information.

Assessment of risk of bias was outcome specific. For example, a given study that was well designed, conducted and reported with respect to its primary outcome, but did a suboptimal analysis for a secondary outcome was graded of different quality for the two outcomes.

Data Synthesis

Qualitative Synthesis

We summarized the findings of the report according to the order of the Key Questions. Within each Key Question, results were organized for each appropriate subgroup on the basis of the populations assessed, comparisons performed (e.g., OMBP versus no OMBP; or comparisons among alternative OMBP strategies), and outcomes assessed. We used tables and graphs (e.g., weighted scatterplots) to synthesize information across studies.

Single-group studies of OMBP were used to obtain ranges of adverse event rates among patients receiving the interventions of interest. These ranges were used as a reference to help contextualize the relative effects observed in comparative studies, and inform on their applicability.

Quantitative Synthesis

Meta-analysis

For each comparison of interest, we assessed whether the eligible studies were sufficiently similar to be combined in a meta-analysis on the basis of clinical heterogeneity of patient populations and interventions, as well as methodological heterogeneity of study designs and outcomes reported. RCTs and nonrandomized designs (NRCSs and single group studies) were not combined quantitatively because of heterogeneity in the comparisons and outcomes reported, as well as on the basis of concerns regarding risk of bias in nonrandomized studies.

The determination on the appropriateness of meta-analysis was made *before* any data analysis; we did not base the decision to perform a meta-analysis on statistical criteria for heterogeneity. Such criteria are often inadequate (e.g., have low power when the number of studies is small) and do not account for the ability to explore and explain heterogeneity by examining study-level characteristics. Main analyses included all relevant studies (e.g., studies of colon and rectum surgeries and those with mixed populations); subgroup analyses (e.g., separately by anatomic site of surgery, or by year when study enrollment was started) were performed, when possible. In cases where only a subset of the available studies could be quantitatively combined (e.g., when some studies were judged to be so clinically different from others as to be excluded from meta-analysis) we synthesized findings qualitatively by taking into account the magnitude and direction of effects.

Pairwise Meta-analyses

Direct pairwise meta-analyses were undertaken when there were more than three non-overlapping studies evaluating the same intervention and comparator and reporting the same outcomes. All meta-analyses used random effects models. Sensitivity analyses (including leave-

one-out analyses, analyses assuming a fixed effects model, and reanalyses after excluding a group of studies) where undertaken when deemed important (e.g., in the presence of studies with outlying effect sizes or evidence of temporal changes in effect sizes). For all statistical tests, except those for heterogeneity, statistical significance was defined as a two-sided P-value where $P < 0.05$. Heterogeneity was considered statistically significant when the P-value of Cochran's Q statistic was $P < 0.1$ to account for the low statistical power of the test. Between-study inconsistency was quantified with the I^2 statistic.²⁶ We attempted to explore between-study heterogeneity using subgroup and meta-regression analyses.

Network Meta-analysis

Network Topology

We used network meta-analysis to jointly analyze evidence on the effectiveness of the following treatment strategies: OMBP plus enema, OMBP alone, enema alone and no preparation. Studies comparing enema alone and no OMBP or enema were not in the scope of this report, and such studies (if any exist) are not included in the analyses. This does not induce any bias in estimates of the treatment effects obtained from comparisons reported in the included studies.

The topology of the network corresponds to the separate meta-analyses reported in a recent Cochrane Systematic Review.¹ Specifically, in the main analysis we considered OMBP-treated groups as a single network node (i.e., we constructed a 3-node network, comprising OMBP, with or without enema, versus enema alone versus no preparation). We believe that this analysis represents a compromise between obtaining informative estimates of the relative effects of interventions when few trials are available and the desire for more granular groupings of these interventions. It is also consistent with previous work on the topic.¹ In structural sensitivity analyses, we evaluated a 4-node specification of the network structure, considering groups receiving OMBP with enema and those receiving OMBP without enema as separate nodes.

We did not construct or analyze networks that include comparisons between alternative active OMBP interventions, because of substantial concerns that head-to-head studies between active OMBP strategies are not similar to studies included in the above network. Specifically, we observed substantial heterogeneity in the cointerventions, the details of the OMBP strategies, and in the examined outcomes. We also observed that most studies with head-to-head comparisons of OMBP regimens were conducted more than two decades ago (e.g., 60 percent finished enrollment in or before 1990). By contrast, most comparisons of OMBP versus no OMBP (with or without enema) were conducted in more recent years (e.g., 86 percent begun enrollment after 1990).

This temporal pattern in the design of OMBP studies parallels evolving trends in surgical practice (e.g., the use of enhanced recovery protocols, use of intravenous antibiotics), and suggests that secular changes have occurred in the characteristics of the enrolled populations and the typical cointerventions/preparation for surgery. This was deemed substantial ground for disputing the similarity between older studies comparing active OMBP strategies, and the more recent ones that compare using versus not using OMBP.

Models and Estimation

We fit models in the familiar generalized linear mixed model framework using the binomial family for within study variability and a logit link function (i.e., the odds ratio is the metric of choice). Network meta-analyses were performed for all outcomes of interest where several studies (at least 6 studies for at least one of the direct contrasts) existed.²⁷ Models accounted for between-study heterogeneity and assumed homogeneity of the random effects variances at the between-study level. This assumption is typical especially when few studies provide information for each edge of the network.

In the main analysis (3-node network) no included study reported a comparison of enema versus no enema. Because the effect size for this comparison is only indirectly estimated, no assessment of consistency between direct and indirect effects is possible. In sensitivity analysis (4-node network), we had a closed loop and therefore the opportunity to test for inconsistency. We did not perform a formal test for inconsistency, but evaluated its presence qualitatively by comparing results from pairwise meta-analyses (direct effects) with results from the network analyses (combined direct and indirect effects). This is because in networks with relatively few and small studies quantitative assessments of inconsistency are very uncertain, and almost noninformative.

All network meta-analysis models were fit using Bayesian Markov Chain Monte Carlo (MCMC) methods because they offer additional modeling flexibility (when compared with maximum likelihood approaches) and because they allowed direct probabilistic statements regarding the magnitude and direction of the treatment effect. Prior distributions for all model parameters (including treatment effects and between-study variance components) were noninformative. For example, treatment effect priors did not exclude very large benefits or very large harms, as the variance in the prior for the true log odds ratio was set to 1000. Similarly, priors for variance components were consistent with no heterogeneity as well as very large heterogeneity. The prior for the between-study variance ranged from 0 to 25 on the log-odds ratio scale.

Reporting of results

We obtained estimates of the treatment effects of interest (e.g., odds ratios for anastomotic leakage comparing OMBP versus no OMBP), as well as the rank probabilities for each treatment strategy (e.g., probability that OMBP is the best treatment). We also estimated probabilities that the difference (in the odds ratio scale) between pairs of treatments was larger than 1.00, 1.10, 1.25, 1.50, 2.00, 3.00, and 5.00 (or smaller than the inverse of these values, to capture extreme effects in the other direction). These cutoffs were chosen after discussion with the TEP.

Subgroup and Meta-regression Analysis

To assess the impact of study-level characteristics on estimates of the effect size, we planned to perform random effects meta-regression. However, in pairwise meta-analyses we found limited evidence of heterogeneity and the total number of available studies for each comparison was relatively small, rendering the use of such methods inappropriate.

Small-Study Effects and Publication Bias

We did not use funnel plots or statistical tests of funnel plot asymmetry to assess the presence of small-study effects in pairwise meta-analyses — that is, differences between larger (more precise) and smaller (less precise) studies. Although these methods are sometimes considered as

diagnostics for publication bias, theoretical and empirical studies show that they cannot differentiate publication bias from genuine heterogeneity.^{28, 29} Furthermore, selective outcome reporting, other biases, or chance can also lead to significant results. Because of these reasons, we only provide qualitative dispositions regarding publication bias.

Software

All analyses were performed using Stata IC (version 12.1 Stata Corp., College Station, TX). All frequentist tests were two-sided (except those for heterogeneity) and statistical significance was defined as a P value of less than 0.05. We did not perform any adjustments for multiple comparisons. Results from Bayesian analyses are reported as medians and 95% central credible intervals (CrI) from the posterior distributions. MCMC methods were implemented in Winbugs (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK), through calls from Stata. Graphs were generated in Stata.

Grading the Body of Evidence

We followed the *Methods Guide* to evaluate the strength of the body of evidence for each Key Question with respect to the following domains: risk of bias, consistency, directness, precision, and reporting bias.

Briefly, we determined *risk of bias* (low, medium, or high) on the basis of the study design and the methodological quality of the studies.

We rated the *consistency* of the data as no inconsistency, inconsistency present, or not applicable (if there is only one study available). We did not use rigid counts of studies as standards of evaluation (e.g., four of five studies agree, therefore the data are consistent); instead, we assessed the direction, magnitude, and statistical significance of all studies and made a determination. We described our logic when studies were not unanimous.

We assessed *directness* of the evidence (direct versus indirect) on the basis of the use of surrogate outcomes or the need for indirect comparisons (e.g., when treatments had not been directly compared and inference was based on observations across studies).

We assessed the *precision* of the evidence as precise or imprecise on the basis of the degree of certainty surrounding each effect estimate. Generally, a precise estimate is one that allows for a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions and that therefore precludes a conclusion.

The potential for *reporting bias* (suspected versus not suspected) was evaluated with respect to publication bias, selective outcome reporting bias, and selective analysis reporting bias. For reporting bias, we provided qualitative dispositions rather than perform formal statistical tests to evaluate differences in the effect sizes between more precise (larger) and less precise (smaller) studies (see above, under Small-Study Effects and Publication Bias). We evaluated the reported results across studies qualitatively, on the basis of completeness of reporting (separately for each outcome of interest), number of enrolled patients, and numbers of observed events. Judgment on the potential for selective outcome reporting bias will be based on reporting patterns for each outcome of interest across studies. We acknowledge that both types of reporting bias are difficult to reliably detect on the basis of data available in published research studies (i.e., without access to study protocols and detailed analysis plans). Although some degree of subjectivity is unavoidable in this assessment, we present explicitly all operational decisions and provide the rationale for our judgment on reporting bias.

Finally, we rated the body of evidence using four strength of evidence levels: high, moderate,

low, and insufficient. These ratings describe our level of confidence that the evidence reflects the true effect for the major comparisons of interest.

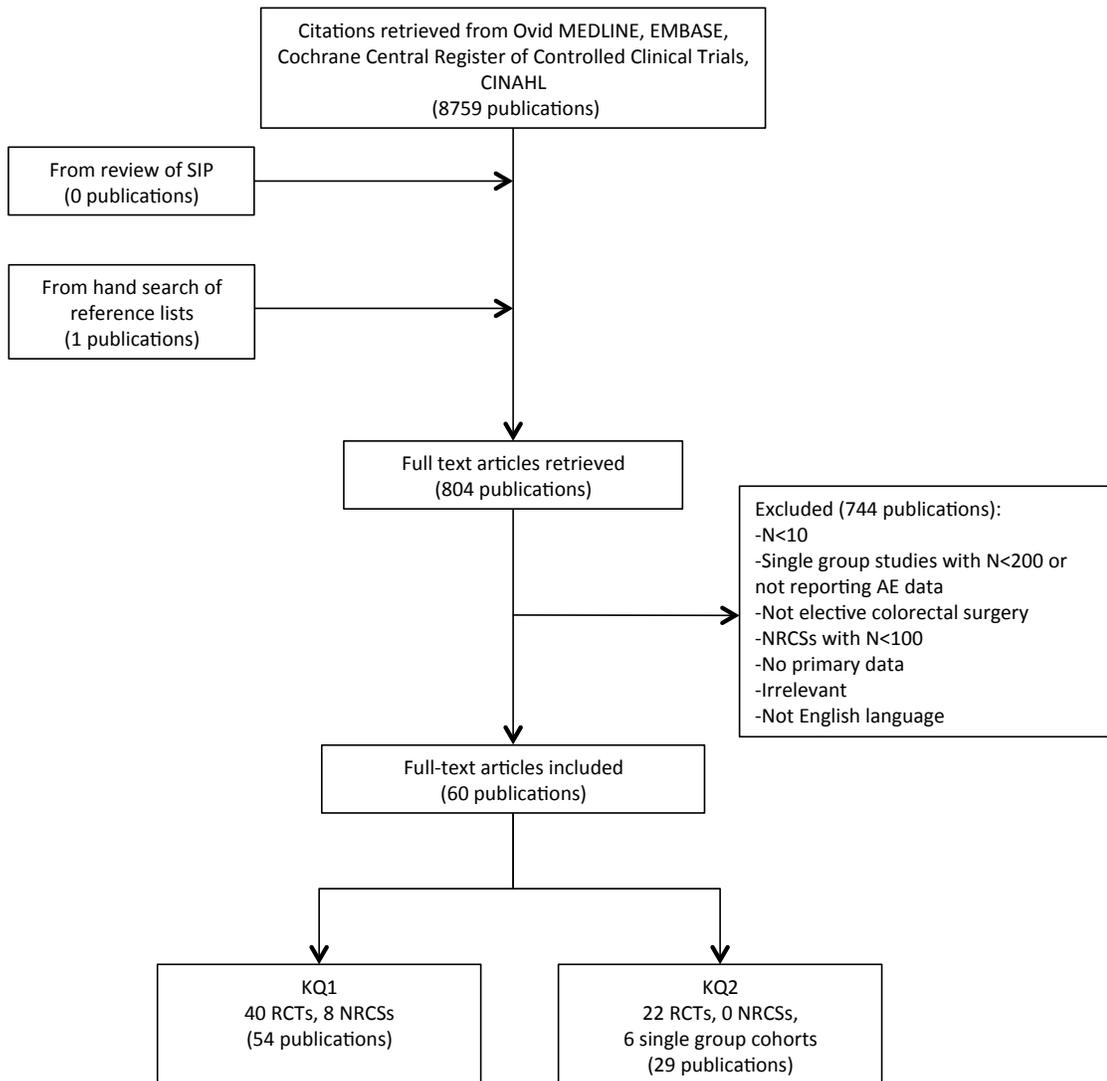
Assessing Applicability

We followed the Methods Guide³⁰ to evaluate the applicability of included studies to patient populations of interest. We evaluated studies (or subgroups of studies) of elderly adults (operationally defined as patients 65 years of age or older) separately if data are available. Applicability will also be judged separately for various indications of OMBP use (e.g., left-sided versus right-sided colon surgery, rectal surgery), characteristics of the OMBP preparation strategy (e.g., total duration of preparation, inpatient versus outpatient use); patient sex (men versus women), and setting of care.

Results

Our literature search yielded 8759 citations (8758 from electronic databases and 1 from hand-searching; no submission information packages were received; **Figure 2**). Of these, 804 articles were reviewed in full text. After full text review, 54 unique studies (reported in 60 publications^{9, 12, 31-89}) were judged to have met the inclusion criteria for at least one of the Key Questions (40 RCTs; 8 NRCSs; and 6 single-group cohorts). The most common reasons for exclusion of articles were related to study design (e.g., we excluded uncontrolled case series and NRCSs not meeting the sample size cutoffs) and language of publication. See **Appendix B** for a list of the excluded studies with the reason for exclusion. Data extraction forms and summary tables for all included studies are available online on the Systematic Review Data Repository (<http://srdp.ahrq.gov/>).

Figure 2: Literature Flow Diagram



KQ = Key Question; SIP = submission information package. Some publications reported data from the same study. Detailed reasons for exclusion of studies reviewed in full text but not considered further are presented in **Appendix B**.

Key Question 1. How do various preoperative OMBP strategies compare between them and versus a control with respect to their effectiveness for preventing surgical or postsurgical complications?

- a. For elective right colon surgery?
- b. For elective left colon surgery?
- c. For elective rectal surgery?

Forty RCTs (**Table 1**) and eight NRCSs met criteria for Key Question 1. Twenty-one studies compared OMBP versus enema or no preparation (16 RCTs; 5 NRCSs); 25 compared alternative active OMBP strategies (23 RCTs and 2 NRCSs); two studies compared inpatient vs. outpatient preparation (1 RCT and 1 NRCS).

One RCT comparing OMBP versus no OMBP has been retracted,^f and was not included in the main analyses.^{74, 90} In extensive sensitivity analyses, inclusion of the retracted study did not impact appreciably impact results or conclusions. Two RCTs that enrolled exclusively children are discussed separately. Among studies enrolling adults, one RCT⁵⁰ and one NRCS⁶⁰ compared the same OMBP regimen in the inpatient versus outpatient setting, and are also described separately.

Table 1: Bowel Preparation Strategies in Included RCTs

Author, Year [PMID]	OMBP (per arm)	Enema used (per arm)	Oral antibiotics used (per arm)	Parenteral antibiotics used (per arm)
Comparisons of OMBP vs. enema or no preparation				
Hughes, 1972 ⁵⁴ [4621021]	bisacodyl / no OMBP	yes / no	unclear / unclear	yes / yes
Burke, 1994 ³⁸ [8044619]	Na picosulphate / no OMBP	no / no	no / no	yes / yes
Santos, 1994 ⁷² [7827905]	mineral oil, agar, phenolphthalein + mannitol / no OMBP	yes / no	no / no	yes / yes
Miettinen, 2000 ⁶³ [10826429]	PEG / no OMBP	no / no	no / no	yes / yes
Zmora, 2003 ^{86, 87} [12616120]	PEG / no OMBP	selective / selective	yes / yes	yes / yes
Bucher, 2005 ³⁷ [15786427]	PEG / no OMBP	no / selective	no / no	yes / yes
Fa-Si-Oen, 2005 ⁴⁸ [15981065]	PEG / no OMBP	no / no	no / no	yes / yes
Platell, 2006 ⁶⁹ [16491463]	PEG / no OMBP	no / yes	no / no	yes / yes
Contant, 2007 ^{43, 79, 80} [18156032]	PEG or NaP / no OMBP	no / no	no / no	yes / yes
Jung, 2007 ^{55, 56} [17514668]	PEG or NaP / no OMBP	no / no	yes / yes	yes / yes
Pena-Soria, 2008 ^{9, 68} [18820977]	PEG / no OMBP	yes / no	no / no	yes / yes
Bretagnol, 2010 ³⁵ [21037443]	senna / no OMBP	yes / no	no / no	yes / yes

^f The retraction notice stated: large portions of text ... have been duplicated from another article previously published in *Annals of Surgery*. In fact, the text (but not the numerical data) in the two publications is identical (despite being conducted by different research teams based in different countries), raising concerns about the truthfulness of reporting in the second study.

Scabini, 2010 ⁷⁴ [20433721]	PEG / no OMBP	selective / selective	no / no	yes / yes
Watanabe, 2010 ⁸¹ [20799286]	MgCitrate / no OMBP	yes / no	no / no	yes / yes
Bertani, 2011 ³⁴ [21689356]	PEG / no OMBP	yes / yes	no / no	yes / yes
Sasaki, 2012 ⁷³ [22976604]	PEG + Na picosulfate / no OMBP	no / no	no / no	yes / yes

Comparisons of alternative OMBP strategies in adults

Matheson, 1978 ⁶² [359083]	MgSulphate / nutritional	yes / yes	yes / yes	no / no
Chung, 1979 ⁴² [365010]	MgCitrate / WGI with Ringer's	yes / no	no / no	yes / yes
Christensen, 1981 ⁴¹ [7318622]	WGI with NaCl, NaHCO ₃ , KCl / sodium salt solution	no / yes	no / no	yes / yes
Morris, 1983 ⁶⁴ [6190888]	senna / mannitol	no / no	no / no	yes / yes
Beck, 1985 ³³ [4017808]	senna + MgCitrate / PEG+bisacodyl	yes / no	no / no	yes / yes
Fleites, 1985 ⁴⁹ [3901374]	PEG / bisacodyl + MgCitrate	unclear / unclear	yes / yes	yes / yes
Panton, 1985 ⁶⁷ [3887955]	castor oil or MgSulfate / WGI with Ringer's	unclear / yes	no / no	yes / yes
Parker, 1985 ⁸⁹ [4037631]	MgSulphate / WGI with povidone-iodine + MgSulphate	yes / yes	no / no	yes / yes
Beck, 1986 ¹² [3095080]	PEG / mannitol	no / no	no / no	yes / yes
Dueholm, 1987 ⁴⁵ [3552504]	PEG / WGI with NaCl solution	no / no	no / no	yes / yes
Soballe, 1989 ⁷⁶ [2499830]	PEG / bisacodyl + MgCitrate	no / yes	yes / yes	no / no
Beck, 1991 ³² [2021332]	PEG / senna + MgCitrate	no / yes	no / no	yes / yes
Wolters, 1994 ⁸³ [8205446]	PEG / WGI with Ringer's / bisacodyl + NaP	no / no / no	no / no / no	no / no / no
Grundel, 1997 ⁵¹ [9369111]	PEG / PEG+bisacodyl+NaP	no / no	no / no	yes / yes
Oliveira, 1997 ⁶⁶ [9152189]	PEG / NaP	no / no	yes / yes	no / no
Makino, 1998 ⁶¹ [9496494]	senna + MgCitrate / PEG + senna	yes / no	yes / yes	no / no
Valverde, 1999 ⁷⁷ [10323423]	PEG / senna	yes / yes	no / no	yes / yes
Yoshioka, 2000 ⁸⁴ [10720834]	Na picosulphate / NaP	no / no	no / no	no / no
Koussidis, 2001 ⁵⁸ [11841079]	WGI with Ringer's / gastrografin	no / no	unclear / unclear	yes / yes
Reddy, 2007 ⁷¹ [17443852]	Na picosulphate + MgCitrate / Na picosulphate + MgCitrate / Na picosulphate + MgCitrate / nutritional	no / no / no / no	no / yes / yes / yes	no / no / no / no
Horvat, 2010 ⁵³ [20517667]	PEG + senna / nutritional / nutritional	no / no / no	unclear / unclear / unclear	unclear / unclear / unclear

Comparison of inpatient vs. outpatient OMBP

Frazer, 1992 ⁵⁰ [1740065]	PEG / PEG	yes / yes	yes / yes	yes / yes
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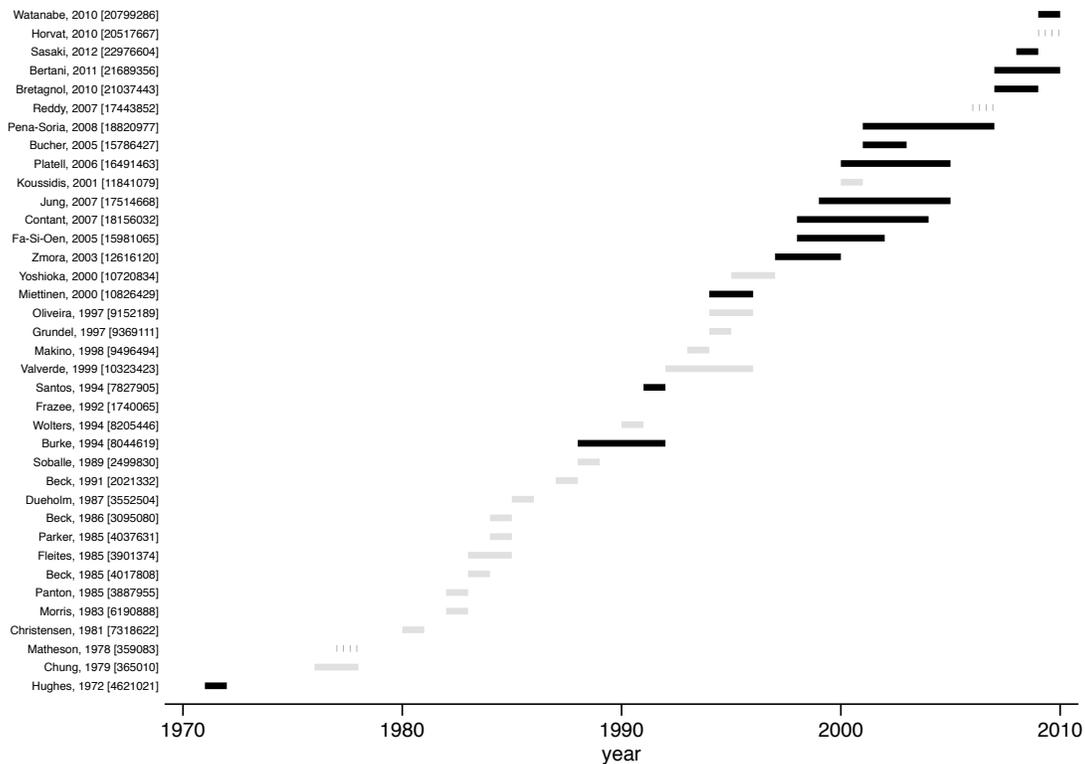
Comparisons of alternative OMBP strategies in children

Chattopadhyay, 2004 ⁴⁰ [14752676]	PEG / WGI with NaCl + KCl	no / no	no / no	yes / yes
Sinha, 2007 ⁷⁵ [17394002]	WGI with PEG / WGI with NaCl solution / WGI with Ringer's	no / no / no	no / no / no	yes / yes / yes

OMBP = oral mechanical bowel preparation; PMID = PubMed identification number; PEG = polyethylene glycol; WGI = whole gut irrigation.

We classified the remaining 37 RCTs into two mutually exclusive groups: trials comparing OMBP versus no OMBP (with or without enema) – active versus inactive comparison or Group 1; and trials comparing alternative active OMBP strategies – active versus active comparison or Group 2. Studies belonging to the latter group were conducted in earlier years (median year of enrollment start = 1987), followed by studies investigating the omission of OMBP (median year of enrollment start = 1999). **Figure 3** depicts this temporal pattern.

Figure 3: Enrollment Periods for RCTs Comparing OMBP versus no OMBP and alternative OMBP strategies



The information in the figure includes only RCTs conducted in adult patients. Horizontal lines denote the trial enrollment period (from enrollment start to end). Black lines denote trials comparing OMBP versus no OMBP; solid gray lines denote trials comparing alternative active OMBP preparations, and dashed gray lines denote nutritional preparation methods (prebiotics or symbiotics, with or without OMBP). Studies are plotted by year of enrollment start and then by year of publication. For studies not reporting the enrollment period we used the year of publication as the last year of enrollment and assumed a trial duration of one year.

The two groups of studies also differed with respect to the type, duration, and intensity of preparation, as well as the administered cointerventions (**Table 2**). For example, OMBP by whole gut irrigation with electrolyte solutions other than polyethylene glycol (PEG) was a comparator in 7 out of 46 OMBP-treated arms in Group 2 (older studies), but in none out of 15

OMBP-treated arms in Group 1 (more recent studies). (Whole gut irrigation is often done through a nasogastric tube, and is more invasive than oral administration; PEG is one of the most commonly used solutions nowadays.) Most importantly, perioperative intravenous or intramuscular antibiotics were used in all studies comparing OMBP versus no OMBP (Group 1) but only in 26 of the 46 OMBP-treated arms in trials comparing alternative active OMBP preparations (Group 2). The total duration of patient preparation for surgery also declined over time (**Figure 4**), indicating that older studies may have used more aggressive preoperative preparation strategies. Indeed, dietary modification of several days duration, repeated enemas, and multi-day OMBP regimens were more often or even exclusively used in the older studies (Group 2).

Further, studies conducted in recent years tended to be better designed, with more studies reporting the conduct of a prospective power calculation (8 of 14 versus 4 of 22). Reporting of randomization methods and allocation concealment was also better in recent studies.

Because of the aforementioned differences between studies in Group 1 (OMBP versus no OMBP, more recent studies) versus Group 2 (active versus active OMBP comparisons; older studies) with respect to design, interventions, and cointerventions, we review the findings separately by group.

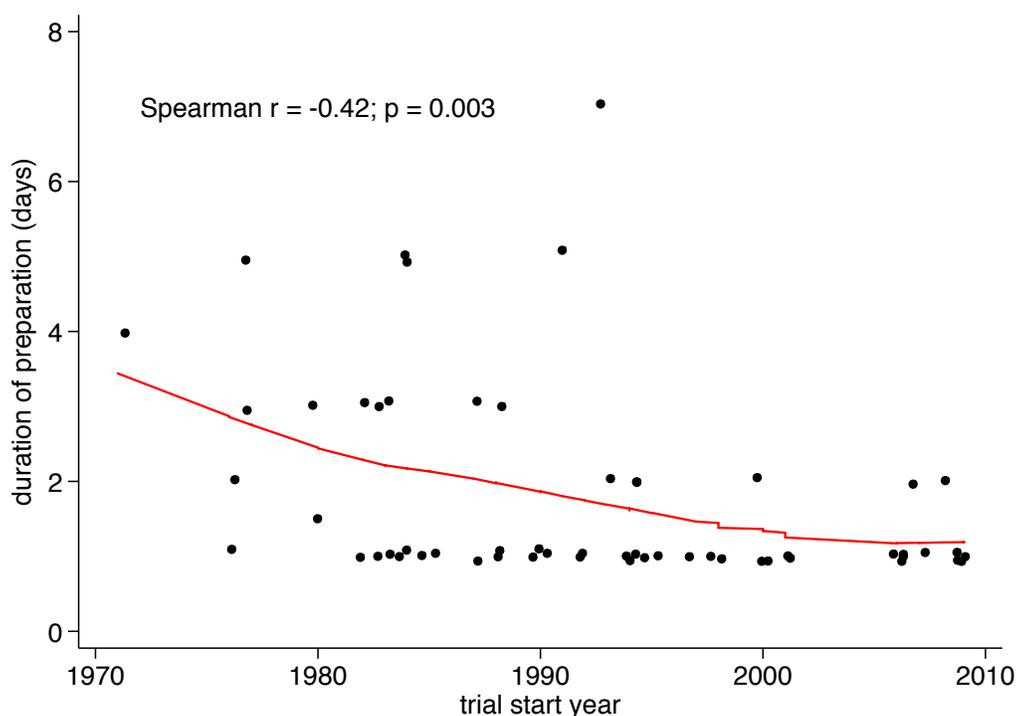
Table 2: Study Design Aspects and OMBP Methods Used in Included RCTs

Study characteristics		Trials comparing OMBP vs. no OMBP (15 trials with 15 OMBP-treated arms)	Trials comparing alternative active OMBP strategies (21 trials with 46 OMBP-treated arms)
Study design and surgical technique	Median Year Starting Enrollment	1999	1987
	Median Number of Included Patients	182	80
	Reported performing a power calculation	8 (53%)	4 (19%)
	Study conducted in the U.S.	0 (0%)	5 (24%)
	At least some patients treated with laparoscopic surgery	5 (33%)	2 (10%)
OMBP strategy (in OMBP-treated groups)	PEG	7 (47%)	9 (20%)
	Laxatives or cathartics	4 (27%)	17 (37%)
	PEG + laxatives/cathartics	1 (7%)	3 (7%)
	Hyperosmotic sodium solutions	0 (0%)	2 (4%)
	Whole gut irrigation	0 (0%)	7 (15%)
	Dietary modifications (symbiotics/prebiotics)	0 (0%)	4 (9%)
	Mixed/other	3 (20%)	4 (9%)
Planned administration through NG tube (in OMBP-treated groups)		0 (0%)	9 (20%)
Cointerventions (in OMBP-treated groups)	IV antibiotics	15 (100%)	26 (57%)
	Oral antibiotics	2 (13%)	13 (28%)
	Enema	6 (36%)	13 (28%)

Limited to studies of adult patients. Percentages have been rounded to the nearest integer.

IV = intravenous; NG = nasogastric; OMBP = oral mechanical bowel preparation; PEG = polyethylene glycol

Figure 4: Change in the Duration of Surgical Preparation Over Time



Limited to RCTs conducted in adult patients. Each dot represents an OMBP-treated arm. Markers have been jittered to make all OMBP-treated groups visible. A smoothed line is plotted to help visualize the association.

Ability to Evaluate the Effects of OMBP Separately By Anatomic Location

For Key Question 1 we planned to perform a detailed subgroup analysis of the effects of OMBP according to the anatomic location of the surgical procedures performed. Of the 40 included RCTs, one enrolled exclusively patients undergoing colonic surgery and one RCT enrolled exclusively patients undergoing rectal surgery. The remaining studies ($n = 38$) enrolled mixed populations of patients undergoing both colon and rectal surgery, or did not provide details regarding anatomic location. Studies of mixed populations (of rectal and colon surgery) rarely provided outcome information stratified by anatomic location (4 studies). When stratified results were reported, they pertained only to a single outcome (in all cases, anastomotic leakage) and the definitions of the anatomic locations used across trials were not always consistent. Thus, reporting patterns do not allow a meaningful subgroup analysis by anatomic location, based on data extracted from published papers. As mentioned in the Methods section, the EPC has asked the corresponding authors to provide the pertinent information. If adequate data are received, appropriate subgroup analyses will be incorporated in the Final Report.

Comparisons of OMBP Versus no OMBP

Fifteen RCTs and five NRCSs (reported in 26 publications) compared OMBP versus no use of mechanical preparation. One RCT was reported in two papers, but it was not possible to

deduce whether the two publications were in disjoint or overlapping sets of patients.^g To avoid double-counting, we did not use information from the publication reporting the smallest number of participants (50 patients).³⁶ Even if said publications describe disjoint groups of patients, it is unlikely that excluding the smaller group changes our results or conclusions (only four clinical events were reported in that group – 3 wound abscesses and 1 anastomotic leakage). We excluded from the main analysis a RCT described in a paper that was retracted because its text duplicated large portions from a previously published paper reporting the results of a different study, leaving a total of 15 RCTs and 5 NRCSs.

All but one study enrolled adult patients (or did not provide relevant information). A single RCT explicitly reported that the study population consisted of both adults and children, but did not report results by age group.⁷² Because children are probably the minority of the study sample, and for consistency with previous work, we included this study together with studies enrolling exclusively adults.¹ In sensitivity analyses, we assessed the robustness of our results by excluding this study.

Common indications for surgery were colorectal cancer and diverticular disease; five studies explicitly reported excluding patients with inflammatory bowel disease and three studies enrolled exclusively patients with colorectal cancer. Details on the surgical approach (e.g., operation types, anastomosis methods, open versus surgical surgery) were generally incompletely reported. One study enrolled only patients undergoing rectal surgery, and two studies enrolled only patients undergoing left-sided colorectal surgeries.

Four studies reported outcome information stratified by anatomic location (in all cases results were reported separately for patients undergoing colon and rectal surgery; left-sided and right-sided colon surgery were never considered separately). This information has been requested from the authors of the primary reports; any replies will be incorporated in the final version of this report.

Direct Comparisons of OMBP versus no OMBP in RCTs

Fifteen RCTs reported comparisons of OMBP strategies versus strategies omitting OMBP. In six studies all participants in OMBP-treated groups received enemas. In one study enemas were administered only to patients with rectal cancer, and eight studies did not administer enemas in the OMBP-treated groups. In their comparator groups, two studies used enemas for all participants, two studies administered enemas to patients undergoing rectal surgery, and 11 studies did not use any enema. In our main analyses, following previous work, we examined separately the comparisons of OMBP (with or without enema) versus enema, and OMBP versus no enema.

Studies used a variety of OMBP regimens: seven studies used PEG, four studies used other laxatives or cathartics, and four studies used other methods (including combinations of the aforementioned regimens). All studies reported using intravenous antibiotics in the perioperative period and two studies reported also using oral antibiotics.

^g We contacted the corresponding author of these two publications to obtain additional information, however we have received no response as of May 27, 2013.

The majority of RCTs were considered to be at moderate risk of bias. Overall, based on the number of items considered indicative of Low risk, five studies were considered to be at high risk of bias, nine to be at moderate risk of bias, and one to be at low risk of bias. Additional details on risk of bias of individual studies are provided in the relevant section, below.

Table 3 presents a summary of the results of our main analysis for outcomes where meta-analysis was possible. The following sections present detailed results for each outcome of interest, followed by the results of sensitivity analyses. Throughout this section, odds ratio (OR) values lower than 1 indicate benefit (i.e., decreased incidence of adverse events) in OMBP treated patients, as compared to controls.

Table 3: Summary of Meta-analysis Results for the Comparison of OMBP Versus Enema or No Preparation

Outcome	Comparison	N studies (N events / N patients, per group)	OR (95% CI); P value	Heterogeneity (P value; I ² %)
All-cause mortality	OMBP ± enema vs. no prep	9 (37 / 1973 vs. 39 / 1963)	0.94 (0.59, 1.48); P = 0.78	0.80; 0%
	OMBP ± enema vs. enema	4 (7 / 526 vs. 4 / 530)	1.67 (0.45, 6.13); P = 0.44	0.32; 0%
Anastomotic leakage	OMBP ± enema vs. no prep	9 (82 / 1968 vs. 93 / 1950)	0.88 (0.64, 1.20); P = 0.41	0.66; 0%
	OMBP ± enema vs. enema	4 (24 / 526 vs. 21 / 530)	1.16 (0.51, 2.64); P = 0.71	0.21; 34%
Wound Infection	OMBP ± enema vs. no prep	11 (206 / 2035 vs. 182 / 2022)	1.15 (0.93, 1.43); P = 0.19	0.67; 0%
	OMBP ± enema vs. enema	4 (48 / 526 vs. 49 / 530)	1.02 (0.53, 1.93); P = 0.96	0.11; 50%
Peritonitis	OMBP ± enema vs. no prep	8 (36 / 1756 vs. 60 / 1733)	0.58 (0.37, 0.89); P = 0.01	0.52; 0%
	OMBP ± enema vs. enema	4 (6 / 526 vs. 6 / 530)	1.00 (0.31, 3.24); P = 0.99	0.87; 0%
Reoperation	OMBP ± enema vs. no prep	5 (112 / 1691 vs. 108 / 1672)	1.02 (0.78, 1.35); P = 0.86	0.42; 0%
	OMBP ± enema vs. enema	2 (7 / 225 vs. 8 / 222)	0.61 (0.01, 32.65); P = 0.81	0.02; 83%
SSI	OMBP ± enema vs. no prep	4 (150 / 978 vs. 161 / 939)	0.90 (0.48, 1.70); P = 0.74	0.01; 75%
	OMBP ± enema vs. enema	2 (33 / 192 vs. 26 / 190)	1.51 (0.38, 6.06); P = 0.56	0.02; 81%

OR values lower than 1 indicate that events are less common among OMBP-treated groups (i.e., that OMBP is beneficial). CI = confidence interval; no prep = no OMBP and no enema; OMBP = oral mechanical bowel preparation (with or without enema); OR = odds ratio; SSI = surgical site infection.

All-Cause Mortality

OMBP Versus no Preparation

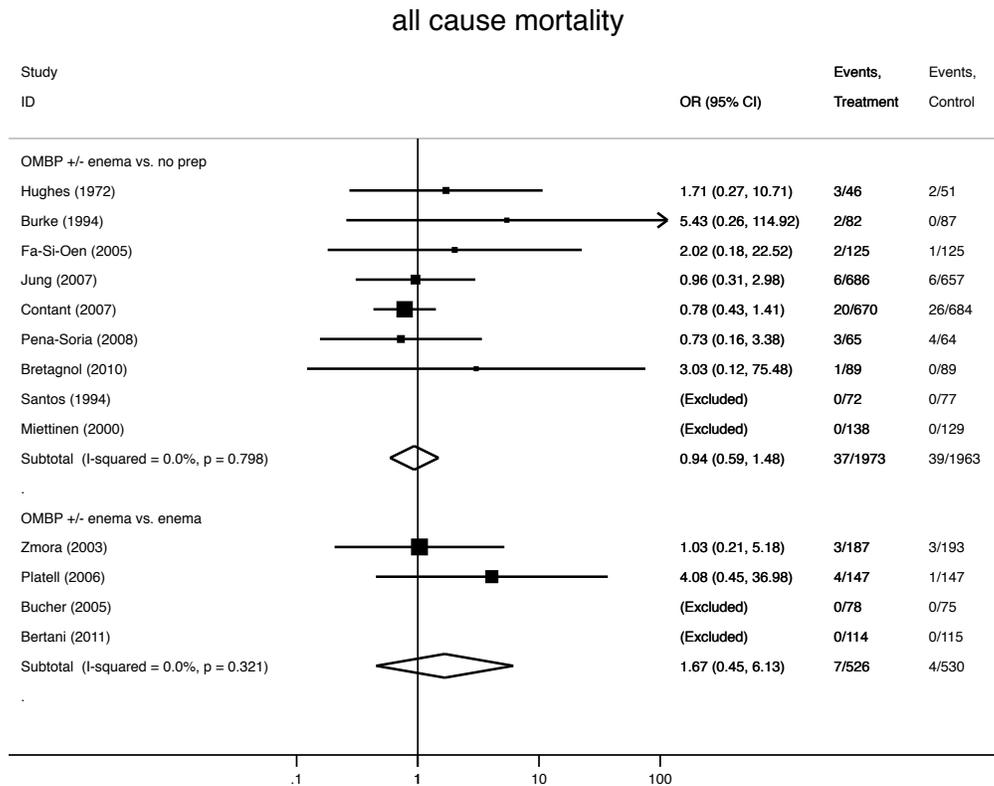
Nine RCTs comparing OMBP versus no preparation reported information on all cause mortality; seven of these reported the occurrence of at least one death. Study sizes ranged from

97 to 1354. Death was relatively rare (76 events in total across all nine studies). The summary OR for all-cause mortality for OMBP versus no preparation was 0.94 (95% CI 0.59 to 1.48) and the between-group difference was not statistically significant ($P = 0.78$). However, the estimate was imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the small number of observed events. There was little evidence of between-study heterogeneity ($P_Q = 0.80$; $I^2 = 0$ percent). **Figure 5** presents the meta-analysis results, along with study-specific event rates.

OMBP versus enema

Four RCTs comparing OMBP versus enema reported information on all-cause mortality (2 studies employed a strategy of selective enema use in patients undergoing elective colorectal surgery). Two of the four studies reported the occurrence of at least one outcome event. Studies were small (minimum = 153; maximum = 380) and reported a small number of outcome events (11 events total). The summary OR for all-cause mortality for OMBP versus enema was 1.67 (95% CI 0.45 to 6.13) and the between-group difference was not statistically significant ($P = 0.44$). However, the estimate was very imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the small number of observed events. Overall, there was little evidence of between-study heterogeneity ($P_Q = 0.32$; $I^2 = 0$ percent). **Figure 5** presents the meta-analysis results, along with study-specific event rates.

Figure 5: All-Cause Mortality Meta-analysis Results for Studies Comparing OMBP (With or Without Enema) Versus Enema or No preparation



CI = confidence interval; OMBP = oral mechanical bowel preparation; OR = odds ratio.

The solid squares (and horizontal lines) indicate the point estimate of the OR (and the corresponding 95% CI) for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. The numbers of events and the sample size of each treatment group are shown to the right of the plot. Diamonds depict the summary estimate for each group of studies and its corresponding CI. The solid line indicates an OR of 1.

Cause-specific Mortality

OMBP Versus no Preparation

Only two studies comparing OMBP versus no preparation reported information on mortality, stratified by cause of death.^{9, 54} The causes investigated included death due to chest infections, peritonitis, pulmonary embolism, and anastomotic leakage. Each study reported information on different causes of death. None of the comparisons were statistically significant and study-specific estimates of effect were very imprecise. Thus, no clinically meaningful conclusions could be reached.

OMBP Versus enema

Only two studies comparing OMBP versus enema reported information on mortality, stratified by cause of death.^{69, 87} The causes investigated included death due to infectious causes, anastomotic leakage, and cardiovascular causes (further stratified into deaths due to congestive heart failure, cardiac arrest, and acute myocardial infarction). Each study reported information on different causes of death. None of the comparisons were statistically significant and study-specific estimates of effect were very imprecise. Therefore, no clinically meaningful conclusions could be reached.

Anastomotic Leakage

OMBP Versus no Preparation

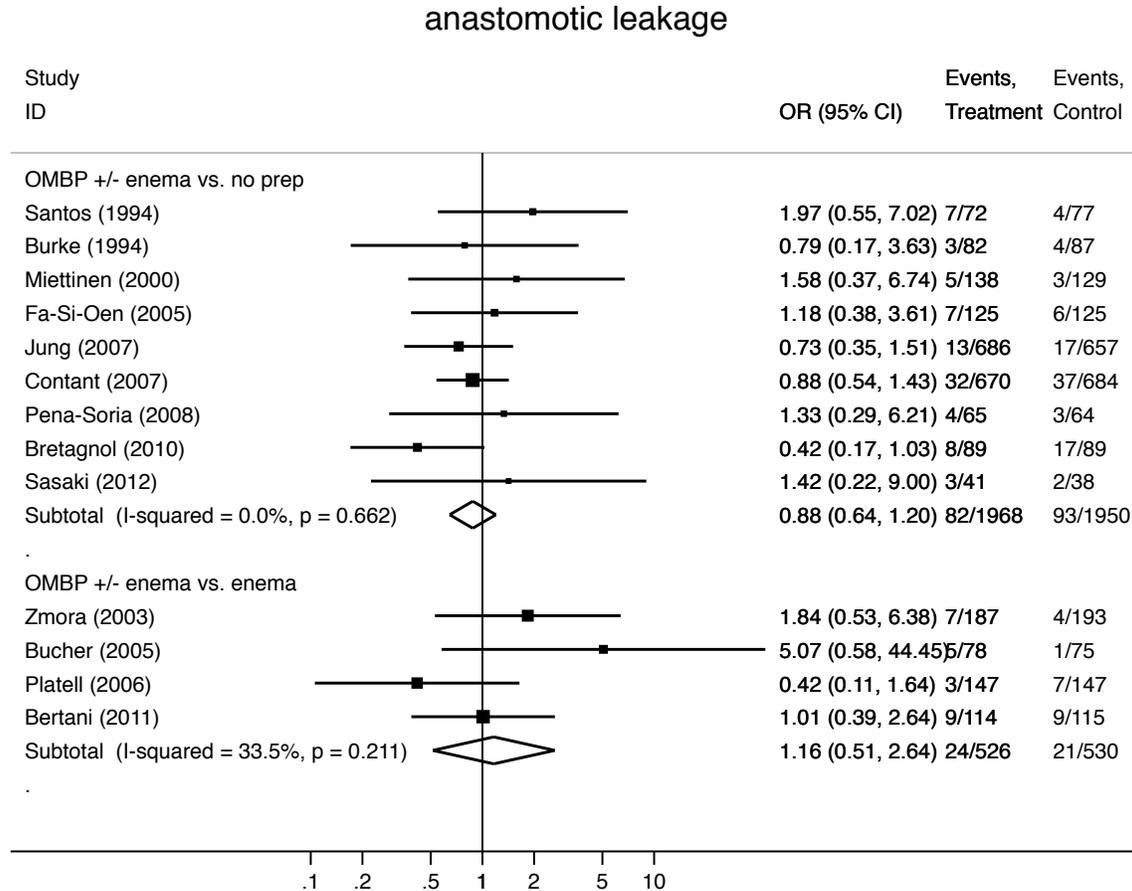
Thirteen RCTs comparing OMBP versus no preparation reported information on anastomotic leakage; all studies reported the occurrence of at least one outcome event. Study sample size ranged from 79 to 1354. The total number of outcome events across all 13 studies was 175, i.e., the events were relatively rare. The summary OR for anastomotic leakage in OMBP-treated patients versus controls was 0.88 (95% CI 0.64 to 1.20) and the between-group difference was not statistically significant ($P = 0.41$). However, the estimate was somewhat imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the small number of observed events. Overall, there was little evidence for between-study heterogeneity ($P_Q = 0.66$; $I^2 = 0$ percent). **Figure 6** presents the meta-analysis results, along with study-specific event rates.

OMBP Versus Enema

Four RCTs comparing OMBP versus enema reported information on anastomotic leakage (2 studies employed a strategy of selective enema use in patients undergoing elective colorectal surgery); all studies reported the occurrence of at least one outcome event. Studies were small (minimum = 153; maximum = 380) and reported a small number of outcome events (45 events total). The summary OR for all-cause mortality in OMBP-treated patients versus controls was 1.16 (95% CI 0.51 to 2.64) and the difference between groups was not statistically significant ($P = 0.72$). This estimate was imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the small number of observed events. Overall,

there was limited evidence of between-study heterogeneity ($P_Q = 0.21$; $I^2 = 34$ percent). **Figure 6** presents the meta-analysis results, along with study-specific event rates.

Figure 6: Anastomotic Leakage Meta-analysis Results for Studies Comparing OMBP (With or Without Enema) Versus Enema or No preparation



CI = confidence interval; OMBP = oral mechanical bowel preparation; OR = odds ratio. The solid squares (and horizontal lines) indicate the point estimate of the OR (and the corresponding 95% CI) for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. The numbers of events and the sample size of each treatment group are shown to the right of the plot. Diamonds depict the summary estimate for each group of studies and its corresponding CI. The solid line indicates an OR of 1.

Wound Infection

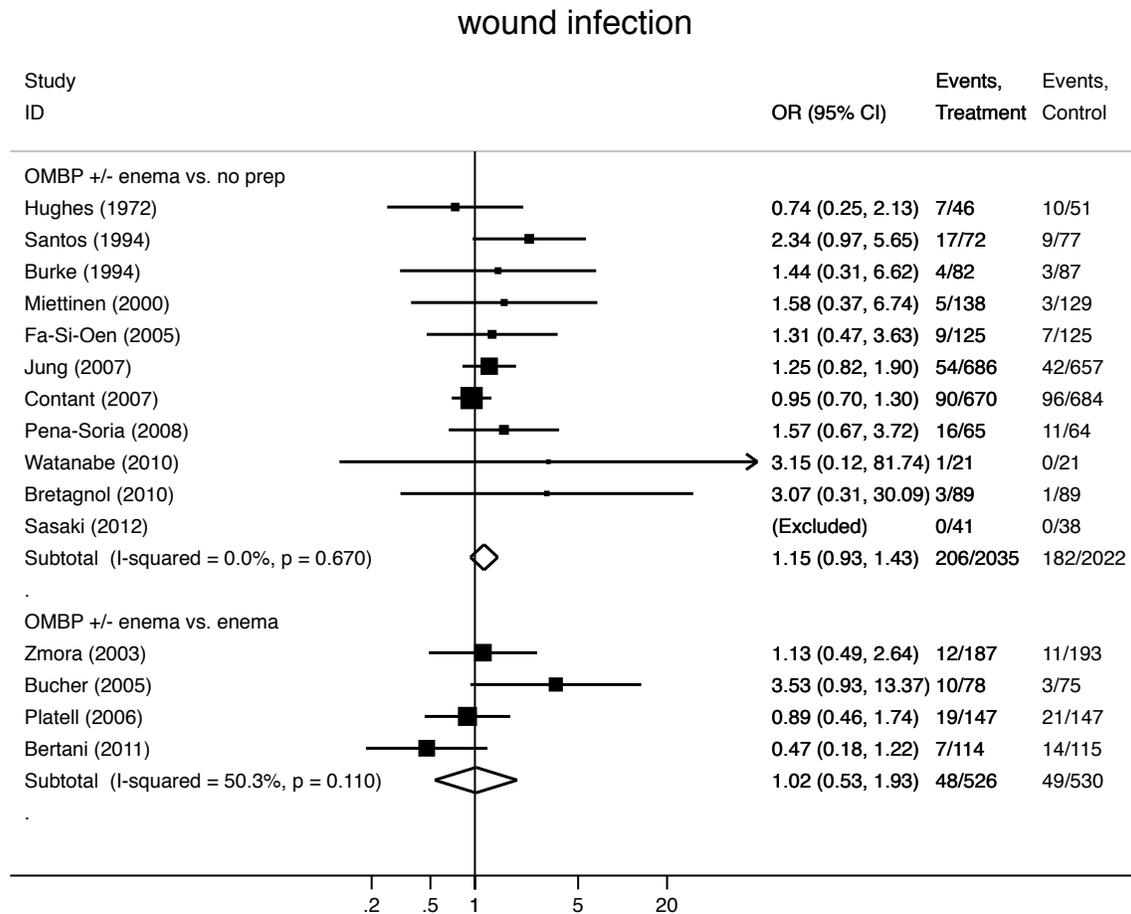
OMBP Versus no Preparation

Eleven RCTs comparing OMBP versus no preparation reported information on wound infection; nine studies reported the occurrence of at least one outcome event in either arm. Studies had varying sample sizes (minimum = 42; maximum = 1354) and reported a total of 388 outcome events. The summary OR for wound infection was 1.15 (95% CI 0.93 to 1.43) and the difference between the two groups was not statistically significant ($P = 0.19$). Overall, there was little evidence for between-study heterogeneity ($P_Q = 0.67$; $I^2 = 0$ percent). **Figure 7** presents the meta-analysis results, along with study-specific event rates.

OMBP Versus Enema

Four RCTs comparing OMBP versus enema reported information on wound infection (2 studies employed a strategy of selective enema use in patients undergoing elective colorectal surgery); all studies reported the occurrence of at least one outcome event. Studies were small (minimum sample size= 153; maximum = 380) and reported a total of 97 outcome events. The summary OR for wound infection was 1.02 (95% CI 0.53 to 1.93) and was not statistically significant ($P = 0.96$). However, the estimate was imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the moderate level of heterogeneity among studies ($P_Q = 0.11$; $I^2 = 50$ percent). **Figure 7** presents the meta-analysis results, along with study-specific event rates.

Figure 7: Wound Infection Meta-analysis Results for Studies Comparing OMBP (With or Without Enema) Versus Enema or No preparation



CI = confidence interval; OMBP = oral mechanical bowel preparation; OR = odds ratio.

The solid squares (and horizontal lines) indicate the point estimate of the OR (and the corresponding 95% CI) for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. The numbers of events and the sample size of each treatment group are shown to the right of the plot. Diamonds depict the summary estimate for each group of studies and its corresponding CI. The solid line indicates an OR of 1.

Peritonitis or Intra-Abdominal Abscess

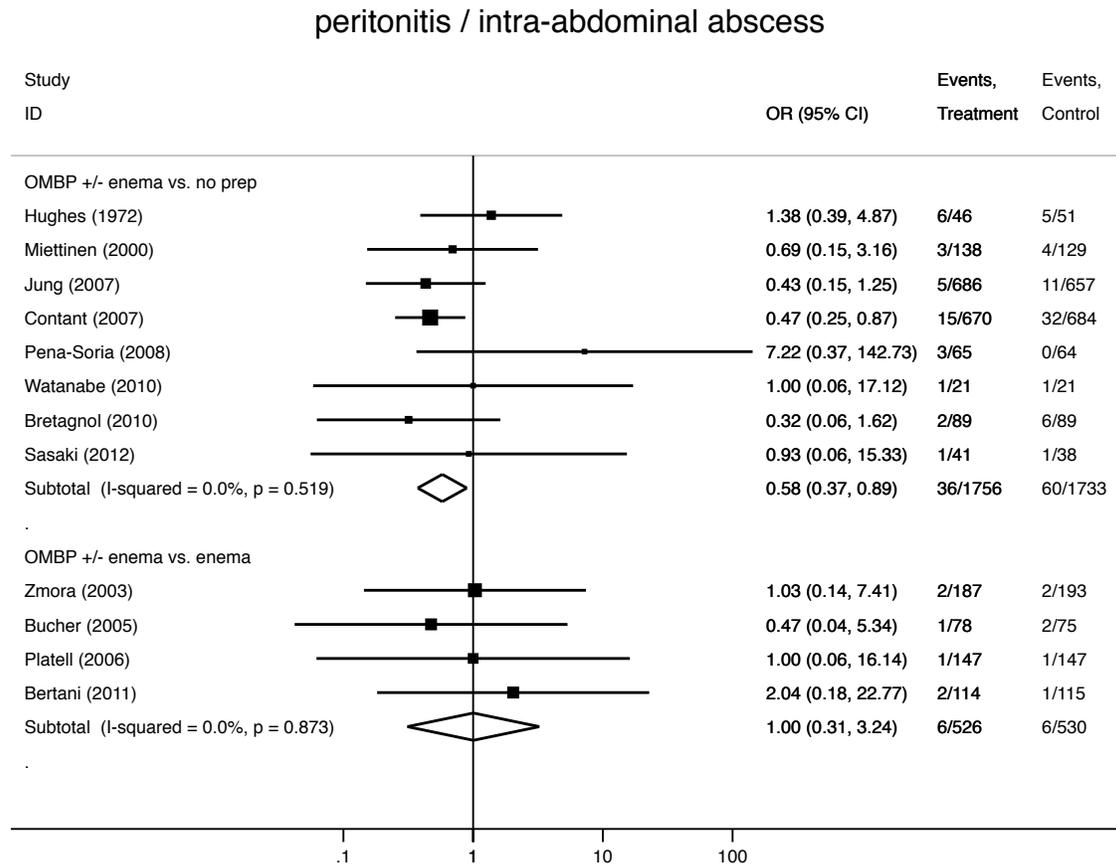
OMBP Versus no Preparation

Eight RCTs comparing OMBP versus no preparation reported information on peritonitis or intra-abdominal abscess development; all studies reported the occurrence of at least one outcome event. Studies had varying sample sizes (minimum = 42; maximum = 1354) and reported a small number of outcome events (96 events total). The summary OR for peritonitis or intra-abdominal abscess development was 0.58 (95% CI 0.37 to 0.89) and the difference was statistically significant ($P = 0.01$). However, the estimate was somewhat imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the small number of observed events. Overall, there was no evidence for between-study heterogeneity ($P_Q = 0.52$; $I^2 = 0$ percent). **Figure 8** presents the meta-analysis results, along with study-specific event rates.

OMBP Versus Enema

Four RCTs comparing OMBP versus enema reported information on peritonitis or intra-abdominal abscess development (2 studies employed a strategy of selective enema use in patients undergoing elective colorectal surgery); seven studies reported the occurrence of at least one outcome event. Studies were small (minimum = 153; maximum = 380) and reported a small number of outcome events (94 events total). The summary OR for peritonitis or intra-abdominal abscess development, comparing OMBP-treated patients versus controls was 1.00 (95% CI 0.31 to 3.24) and the difference was not statistically significant ($P = 0.995$). However, the estimate was very imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis and the small number of observed events. Overall, there was little between-study heterogeneity ($P_Q = 0.87$; $I^2 = 0$ percent). **Figure 8** presents the meta-analysis results, along with study-specific event rates.

Figure 8: Peritonitis/ Intra-Abdominal Abscess Meta-analysis Results for Studies Comparing OMBP (With or Without Enema) Versus Enema or No preparation



CI = confidence interval; OMBP = oral mechanical bowel preparation; OR = odds ratio.

The solid squares (and horizontal lines) indicate the point estimate of the OR (and the corresponding 95% CI) for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. The numbers of events and the sample size of each treatment group are shown to the right of the plot. Diamonds depict the summary estimate for each group of studies and its corresponding CI. The solid line indicates an OR of 1.

Reoperation

OMBP Versus no Preparation

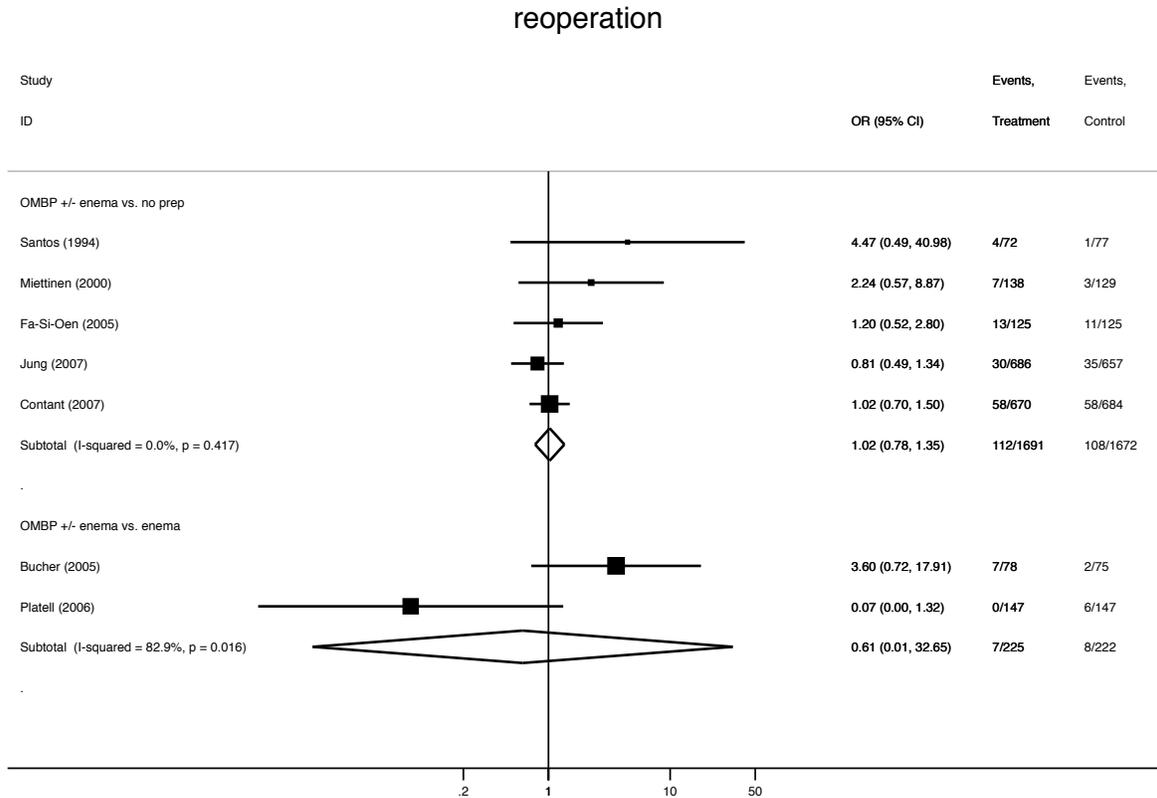
Five RCTs comparing OMBP versus no preparation reported information on reoperation; all studies reported the occurrence of at least one outcome event. Studies had varying sample sizes (minimum = 149; maximum = 1354) and reported a total of 220 events. The summary OR for reoperation was 1.02 (95% CI 0.78 to 1.35) and the difference was not statistically significant ($P = 0.86$). Overall, there was no between-study heterogeneity ($P_Q = 0.42$; $I^2 = 0$ percent). **Figure 10** presents the meta-analysis results, along with study-specific event rates.

OMBP Versus Enema

Two RCTs comparing OMBP versus enema reported information on reoperation; both studies reported the occurrence of at least one outcome event. Studies were relatively small (sample sizes were 154 and 294) and reported a small number of outcome events (15 events

total). The summary OR for reoperation was 0.61 (95% CI 0.01 to 32.65) and was not statistically significant ($P = 0.81$). However, the estimate was extremely imprecise, reflecting the small number of patients contributing information to the meta-analysis, the very small number of observed events, and the heterogeneity of the results of the two RCTs ($P_Q = 0.02$; $I^2 = 83$ percent). **Figure 10** presents the meta-analysis results, along with study-specific event rates.

Figure 10: Reoperation Meta-analysis Results for Studies Comparing OMBP (With or Without Enema) Versus Enema or No preparation



CI = confidence interval; OMBP = oral mechanical bowel preparation; OR = odds ratio. The solid squares (and horizontal lines) indicate the point estimate of the OR (and the corresponding 95% CI) for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. The numbers of events and the sample size of each treatment group are shown to the right of the plot. Diamonds depict the summary estimate for each group of studies and its corresponding CI. The solid line indicates an OR of 1.

Surgical Site Infections

OMBP Versus no Preparation

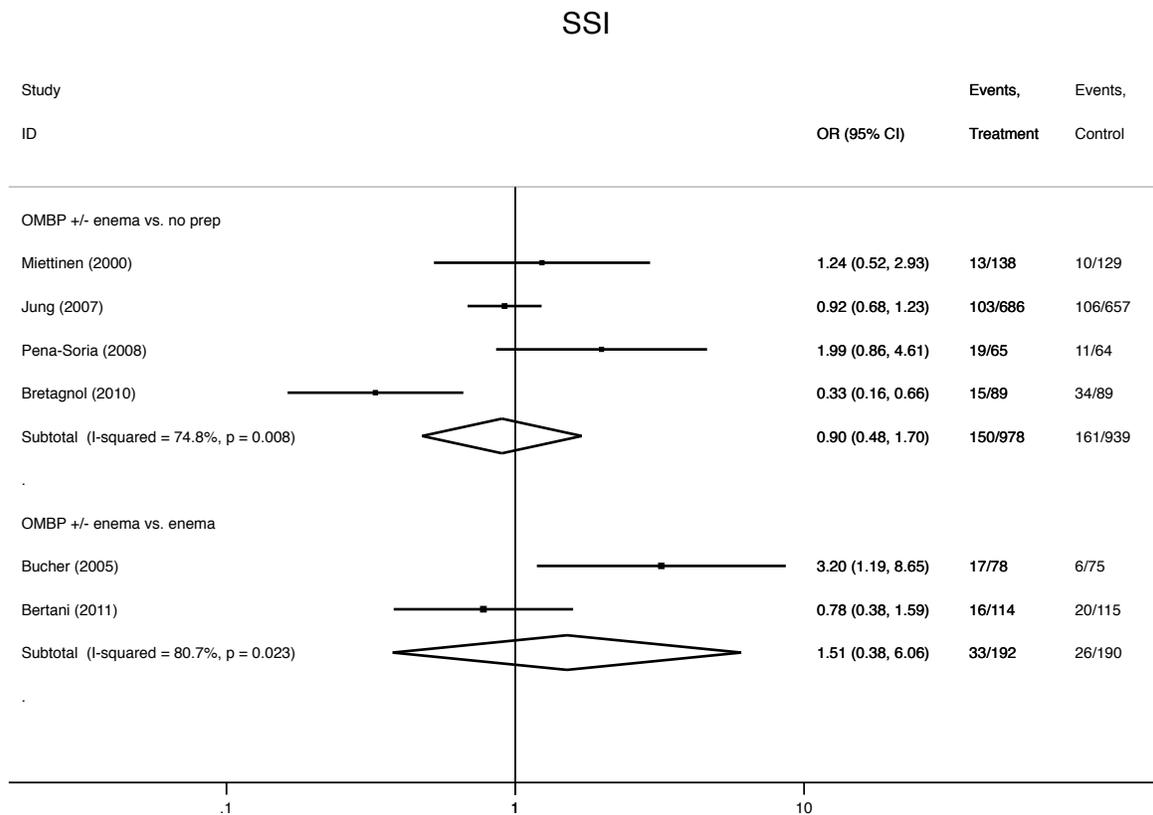
Four RCTs comparing OMBP versus no preparation reported information on infectious complications classified as surgical site infections; all studies reported the occurrence of at least one outcome event. Studies had varying sample sizes (minimum = 129; maximum = 1343) and reported a total of 311 events. The summary OR for SSI, comparing OMBP-treated patients versus controls was 0.90 (95% CI 0.48 to 1.70) and the difference was not statistically significant ($P = 0.74$). However, the estimate was somewhat imprecise, reflecting the relatively small number of studies contributing information to the meta-analysis and the large between-study

heterogeneity ($P_Q = 0.01$; $I^2 = 75$ percent). **Figure 9** presents the meta-analysis results, along with study-specific event rates.

OMBP Versus Enema

Two RCTs comparing OMBP versus enema reported information on surgical site infections. Studies were small (sample sizes of 153 and 229) and reported a small number of outcome events (59 events total). The summary OR for surgical site infections was 1.51 (95% CI 0.38 to 6.06) and the difference was not statistically significant ($P = 0.56$). However, the estimate was very imprecise, reflecting the relatively small number of patients contributing information to the meta-analysis, the small number of observed events, and the presence of substantial between-study heterogeneity ($P_Q = 0.02$; $I^2 = 81$ percent). **Figure 9** presents the meta-analysis results, along with study-specific event rates.

Figure 9: Peritonitis/Intra-abdominal Abscess Meta-analysis Results for Studies Comparing OMBP (With or Without Enema) Versus Enema or No preparation



CI = confidence interval; OMBP = oral mechanical bowel preparation; OR = odds ratio; SSI = surgical site infections.

The solid squares (and horizontal lines) indicate the point estimate of the OR (and the corresponding 95% CI) for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. The numbers of events and the sample size of each treatment group are shown to the right of the plot. Diamonds depict the summary estimate for each group of studies and its corresponding CI. The solid line indicates an OR of 1.

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

OMBP Versus no Preparation

Three studies comparing OMBP versus no preparation reported information on venous thromboembolic outcomes (1 study reported information on pulmonary embolism, 1 study on venous thrombosis, and 1 on both outcomes). None of the comparisons were statistically significant and study-specific estimates of effect were very imprecise. Thus, no clinically meaningful conclusions could be reached.

OMBP versus enema

No studies comparing OMBP versus enema reported information on venous thromboembolic outcomes.

Length of Hospital Stay

OMBP Versus no Preparation

Seven studies comparing OMBP versus no preparation reported information on mean or median length of hospital stay (5 studies on total and 2 studies on postoperative length of stay), but did not report information to enable statistical testing. The difference in mean or median length of stay between groups ranged from -0.2 days to 4.4 days and was positive in four studies, negative in one study, and (reported as) exactly zero in two studies (positive values indicate longer average length of stay for patients in the OMBP-treated group). Statistical comparisons of the duration of stay were possible only in three of the studies (2 reporting on total length of stay and 1 reporting on postoperative stay); differences were statistically non-significant in all cases.

OMBP versus enema

Three studies comparing OMBP versus enema reported information on mean or median total length of hospital stay (no studies reported information separately for the pre- and postoperative periods), but did not report information to enable statistical testing. The difference in mean or median length of stay ranged from 0.1 days to 0.9 days (and was positive in all studies).

Patient Satisfaction and Quality of Life

No studies reported information on patient satisfaction and quality of life using appropriate measurement scales. However, several studies assessed patient-relevant symptoms (e.g., nausea, discomfort, malaise, etc.) using ordinal scales. Findings from these studies have been summarized in Key Question 2.

Other Outcomes

No studies provided information on other prespecified effectiveness outcomes for this Key Question (unplanned ostomies, failed attempts to restore bowel continuity, readmissions after surgery, additional interventional procedures (other than surgery); admission to intensive care unit, admission to nursing care).

Sensitivity Analyses

For mortality, anastomotic leakage, and wound infection we reanalyzed the available data after (1) excluding one study⁷² that included both adults and children (and did not report results

separately by age group); (2) excluding one study⁵⁴ that was unclearly reported and had been presented as a conference paper published in a peer-reviewed journal (this study was also excluded from a recent Cochrane review on OMBP); (3) including the one study⁷⁴ that has been retracted; (4) excluding studies using selective enema strategies in their control groups^{37, 87} (i.e., studies using enemas for patients undergoing rectal surgery only). The complete results of these sensitivity analyses are presented in **Appendix C**. Overall, none of these analyses produced results that were qualitatively different from those discussed in the preceding sections.

Risk of Bias in RCTs comparing OMBP vs. no OMBP

Information on trial design needed to assess the risk of bias of individual studies was not fully reported. Among the 15 RCTs comparing OMBP versus no OMBP, information on the randomized sequence generation and allocation concealment was deemed Unclear in five and seven studies, respectively. Further, blinding of patients, care providers, and outcome assessors was unclear in 12, eight, and 10 of the studies, respectively. In contrast, information on withdrawals and dropouts was better reported. Of the studies reporting relevant information, only two reported a dropout rate of more than 10 percent (both only in their no-OMBP trial groups) and no study had evidence of differential dropout (defined as a greater than 10 percent difference in the dropout rate between treatment groups). Overall, based on the number of items considered indicative of Low risk, 5 studies were considered to be at high risk of bias, 9 to be at intermediate risk of bias, and 1 to be at low risk of bias. As always, aggregated risk of bias assessments need to be interpreted with caution, given our inability to fully distinguish inappropriate study design from poor reporting and lack of context-specific evidence that the risk items we assessed are indeed associated with bias.

Direct Comparisons of OMBP Versus no OMBP in NRCSs

Five NRCSs reported information on the comparison of OMBP versus omission of preparation. Because of heterogeneity in patient selection and outcomes reported, differences in study design, and concerns regarding risk for residual confounding we did not perform meta-analysis.

One study⁷⁰ reported an experimental^h nonrandomized comparison of OMBP (165 patients, all treated with sodium phosphate) versus no preparation (164 patients) in patients undergoing elective colorectal surgery in a single center. Assignment to treatments was based on patients' identification numbers, offering some protection from confounding bias. The study found no statistically significant difference between the two groups for the outcomes of all-cause mortality, wound dehiscence, wound infection, anastomotic leakage, thrombophlebitis, or the need for repeat laparotomy. Events were more common in the OMBP group for all outcomes except anastomotic leakage and thrombophlebitis. For all outcomes, estimates of effect were very imprecise and no between-group difference was statistically significant. The study was considered to be at moderate risk of bias because of lack of randomization, allocation concealment, or blinding of care providers and outcome assessors.

^h Experimental indicates that the investigators had control over treatment assignment (i.e., patients did not self-select into treatments). However, treatment assignment was deterministic (based on patient's identification numbers).

Another study⁵² reported an observational comparison of anastomotic leakage rates among patients treated at a single center before (1997-2002) and after (2002-2006) the implementation of a policy of omitting OMBP (in the first period patients were treated with bisacodyl and sodium phosphate). The authors noted that another change in treatment policy occurred during the study period: a replacement of ibuprofen by celecoxib (for the years between 2003 and 2004). The rates of anastomotic leakage were 3.5 percent (7 of 203 patients) versus 1.7 percent (3 of 180 patients) during the period of OMBP plus celecoxib and no OMBP no celecoxib preparation (P = 0.35). Results for the other treatment periods were not reported and the study was considered to be at high risk of bias because historical comparisons were unadjusted for potential confounding factors (particularly those that vary over time).

The third study⁵⁹ reported results from an observational analysis of 2263 patients undergoing nonemergent colectomy in 24 hospitals participating in the Michigan Surgical Quality Collaborative Colectomy project. A total of 1685 patients received OMBP (oral cathartics with or without enema; in 684 patients combined with oral antibiotics and in 1001 without), and 578 did not; the study outcome was the development of *Clostridium difficile* infection. The adjusted OR comparing OMBP-treated vs. not treated patients was 0.96 (95% CI 0.50 to 1.83) and was not-statistically significant. Among patients who received OMBP, the use of oral antibiotics was associated with a statistically nonsignificant reduction in the odds of *Clostridium difficile* infection (OR = 0.60; 95% CI 0.29 to 1.23). The study was considered to be at high risk of bias because of concerns about residual confounding (factors that differed between treated groups at baseline, and other potential confounders, may not have been included in the multivariable analysis because of the variable selection method employed).

The fourth study³⁹ reported results from an observational retrospective analysis of data from the Veterans Affairs Surgical Quality Improvement Program, using the Veterans Affairs Surgical Care Improvement Project and Pharmacy Benefits Management data to evaluate the impact of OMBP on surgical site infections within 30 days of elective colorectal surgery. The study included a total of 9940 patients (1978 received no preparation; 723 received oral antibiotics only; 3839 receive OMBP only; and 3400 received OMBP and oral antibiotics). OMBP strategies included polyethylene glycol, sodium phosphate, and magnesium citrate. In multivariable analyses (including 6070 patients), using the no preparation as the baseline, the OR for surgical site infection was 0.33 (95% CI 0.21 to 0.50); 0.99 (95% CI 0.80 to 1.22); and 0.43 (95% CI 0.34 to 0.55), for patients receiving oral antibiotics, OMBP without antibiotics, and OMBP plus oral antibiotics, respectively. The study was considered to be at moderate risk of bias because of concerns regarding residual confounding (a limited number of covariates were controlled in the analysis)

The fifth study⁶⁵ reported results using clinical audit data from the West of Scotland Colorectal Cancer Managed Clinical Network, and death records from the Scottish Cancer Registry and General Register Office of Scotland. The study included a total of 1730 patients (1460 received OMBP and 270 did not). In multivariable analyses, the OR for mortality comparing OMBP-treated versus non-treated patients was 0.85 (95% CI 0.67 to 1.10); P = 0.22; at a mean followup of 3.5 years. In unadjusted analyses of 30-day postsurgical outcomes, there was no statistically significant difference between groups for anastomotic leakage, intra-abdominal abscess, fistula, wound infection, deep venous thrombosis, pulmonary embolism, chest infection, or a composite of any postoperative complication. The study was considered to

be at moderate risk of bias on the basis of concerns about residual confounding and because some of the comparisons between treatment groups were not adjusted for potential confounders.

Overall, the NRCSs reported results consistent with those of RCTs and did not demonstrate significant differences between OMBP and no-OMBP strategies. However, studies were at substantial risk of bias, mostly due to confounding factors that had not been adequately controlled in the design or analysis of these investigations.

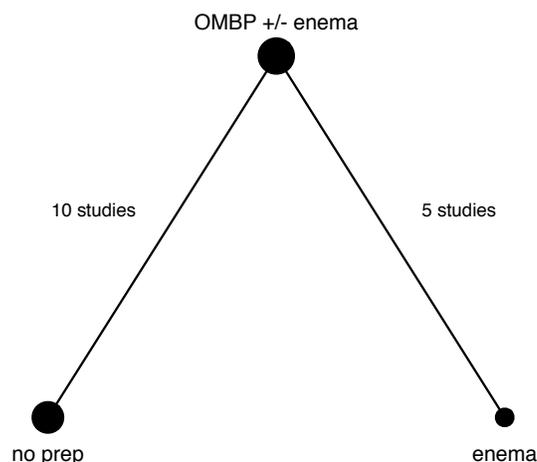
Network Meta-analysis (Including Indirect Comparisons)

To further explore the available data on the effectiveness of OMBP, as compared to enema or no preparation, we analyzed the data presented in the previous section using Bayesian network meta-analysis. Compared to the pairwise analyses presented in previous sections, this analysis better incorporates uncertainty regarding all model parameters. In addition, the model we used in the network analysis handles studies with zero or very low event rates appropriately (by using the binomial likelihood to model within study variability). Further, this methodology allows us to use data from direct comparisons of OMBP versus enema and OMBP versus no preparation to obtain an indirect estimate for the comparison between enema and no preparation. The underlying model respects the randomization procedure within each study and allows us to borrow strength across different direct comparisons when estimating between-study heterogeneity. See the Methods section for additional information on the network structure and details of the statistical analysis.

Comparative Effectiveness of OMBP, Enema, and No Preparation

Our main analysis used 3-node network structure (topology) comparing OMBP (with or without enema) versus enema alone and versus no preparation. **Figure 11** presents the structure of the network. Estimates of the comparative effectiveness of enema versus no preparation are only indirect (i.e., they are not informed by any trials directly comparing these two interventions).

Figure 11: 3-node network structure



Structure for the 3-node network meta-analysis comparing OMBP +/- enema vs. enema alone vs. no preparation. Nodes indicate the treatments compared and have size proportional to the total number of patients enrolled in the

corresponding trial groups. Connecting lines depict direct comparisons and are labeled with the total number of available studies (not all studies contributed data for all outcomes).

Table 4 summarizes the results of this analysis, for all the possible pairwise comparisons, for outcomes where enough studies were available. Generally, results are consistent with those of the direct comparisons reported in the preceding section except peritonitis: 95% credibility intervals do not exclude the null value for any outcome. Further, the Bayesian network analysis suggests that there is much greater uncertainty around the summary estimates, compared to what was indicated by (frequentist) pairwise methods. The larger uncertainty with the Bayesian analysis compared to the frequentist analyses is a well understood result. Frequentist approaches do not integrate over the whole distribution of the between-study heterogeneity, and therefore, they do not fully account for the uncertainty in the synthesis of the data. As expected, uncertainty is most striking for the indirectly estimated effect sizes (i.e., those comparing enema versus no preparation).

Table 4: Summary Estimates from the 3-Node Network Meta-analysis.

Outcome	Comparison	OR (95% CrI)
All-cause mortality	Enema vs. no preparation*	0.60 (0.09, 4.83)
	OMBP ± enema vs. no preparation	1.10 (0.55, 3.76)
	OMBP ± enema vs. enema	1.87 (0.37, 11.43)
Anastomotic leakage	Enema vs. no preparation*	0.76 (0.32, 1.80)
	OMBP ± enema vs. no preparation	0.90 (0.60, 1.46)
	OMBP ± enema vs. enema	1.19 (0.57, 2.57)
Wound infection	Enema vs. no preparation*	1.25 (0.66, 2.52)
	OMBP ± enema vs. no preparation	1.25 (0.91, 1.95)
	OMBP ± enema vs. enema	1.01 (0.58, 1.80)
Peritonitis/ Intra-abdominal abscess	Enema vs. no preparation*	0.65 (0.15, 3.28)
	OMBP ± enema vs. no preparation	0.64 (0.35, 1.47)
	OMBP ± enema vs. enema	0.99 (0.25, 3.89)

OR values lower than 1 indicate that events are less common among treatment groups receiving the first listed treatment for each comparison. CrI = credibility interval; OMBP = oral mechanical bowel preparation; OR = odds ratio.

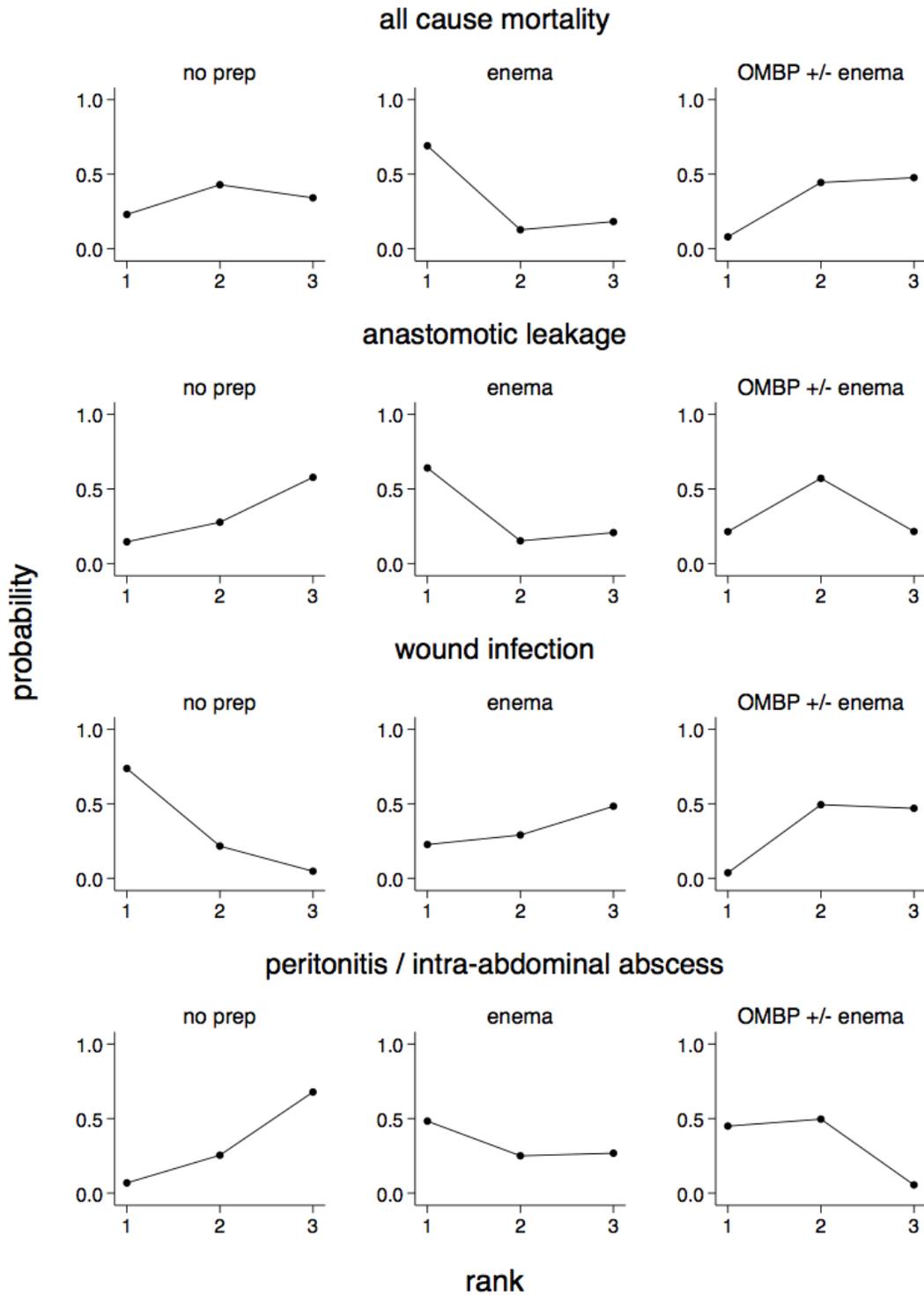
* Results based on an indirect comparison.

Rank Probabilities

Using the network structure presented in **Figure 11** we estimated the probability of a given treatment to be the best (i.e., to be associated with the lowest incidence of harmful events, rank = 1), second best (rank = 2), or last (rank = 3) with respect to each of four key outcomes of interest: all-cause mortality, anastomotic leakage, wound infection, and peritonitis or intra-abdominal abscess (**Figure 12**). The rank probabilities take into account the difference in the point estimates of the treatment effects and the uncertainty around them. However, they do not

readily convey the difference in the treatment effects and they have to be interpreted with caution. Overall, across outcomes, no one intervention appears to be uniformly better or worse than the others.

Figure 12: Ranking of Treatments Based on the 3-node Network Meta-Analysis



Each panel depicts the estimated probability that a given treatment is the best (rank = 1), second best (rank = 2), or last (rank = 3), for each of the outcomes of interest.

Probability of Differences Above Threshold Values

We also estimated the probability that the true (population) odds ratio comparing pairs of interventions was above or below some threshold. These results are summarized in **Table 5**. Note the substantial uncertainty around summary estimates: although very extreme odds ratio values (i.e. below 0.5 and above 2) are quite unlikely for all outcomes, values less than 0.8 or greater than 1.25, corresponding to a decrease of 20% or an increase of 25% in the odds of an event, are not unlikely for any outcome.

Table 5: Probability That the Treatment Effect is More Extreme Than Threshold Value, by Outcome

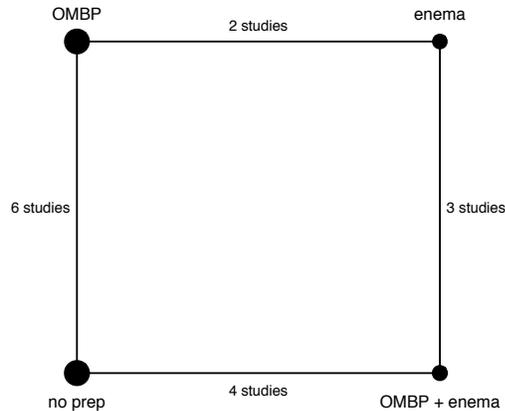
Outcome	Comparison	Probability, by threshold value (for the OR)												
		<0.2	<0.333	<0.5	<0.667	<0.80	<0.91	>1	>1.10	>1.25	>1.5	>2	>3	>5
All-cause mortality	Enema vs. no preparation	0.11	0.25	0.42	0.55	0.63	0.68	0.28	0.25	0.20	0.15	0.10	0.05	0.02
	OMBP vs.no preparation	0	0	0.02	0.07	0.17	0.29	0.61	0.51	0.38	0.24	0.11	0.04	0.01
	OMBP vs. enema	0.01	0.02	0.05	0.10	0.14	0.18	0.79	0.75	0.7	0.61	0.47	0.28	0.12
Anastomotic leakage	Enema vs. no preparation	0	0.03	0.15	0.37	0.55	0.66	0.26	0.19	0.12	0.06	0.02	0	0
	OMBP vs.no preparation	0	0	0	0.07	0.27	0.51	0.31	0.18	0.07	0.02	0	0	0
	OMBP vs. enema	0	0	0.01	0.06	0.13	0.23	0.68	0.58	0.44	0.26	0.08	0.01	0
Wound infection	Enema vs. no preparation	0	0	0.01	0.03	0.08	0.16	0.75	0.65	0.48	0.27	0.07	0.01	0
	OMBP vs.no preparation	0	0	0	0	0.01	0.03	0.91	0.77	0.47	0.15	0.02	0	0
	OMBP vs. enema	0	0	0.01	0.06	0.19	0.35	0.51	0.36	0.21	0.08	0.01	0	0
Peritonitis/ intra-abdominal abscess	Enema vs. no preparation	0.06	0.19	0.36	0.51	0.61	0.67	0.29	0.25	0.2	0.15	0.08	0.03	0.01
	OMBP vs.no preparation	0	0.02	0.21	0.55	0.74	0.83	0.12	0.08	0.05	0.03	0.01	0	0
	OMBP vs. enema	0.01	0.06	0.16	0.28	0.37	0.45	0.49	0.44	0.37	0.27	0.15	0.06	0.01

“0” should be interpreted as very low probability (because the probability cannot be exactly zero). OMBP = oral mechanical bowel preparation; OR =odds ratio.

Analysis of a Structural Variant of the Network

Figure 13 shows the topology of the structural variant of the network. Overall, the results of this sensitivity analysis are consistent with those based on the 3-node network model (Table 6) although there is even greater uncertainty regarding the comparative effectiveness of the available interventions than under the previous two models. This is particularly true for rare outcomes (e.g., mortality) and for comparisons without head to head data. Therefore the analysis did not lead to definitive conclusions regarding the effect of adding enema to OMBP.

Figure 13: 4-node Network Structure Used in Sensitivity Analysis



Structure for the 4-node network meta-analysis.

Table 6: Summary Estimates from the 4-Node Network Meta-analysis

Outcome	Comparison	OR (95% CrI)
All-cause mortality	Enema vs. no preparation*	0.23 (0.00, 16.70)
	OMBP vs. no preparation	1.13 (0.37, 10.84)
	OMBP + enema vs. no preparation	1.33 (0.23, 15.41)
	OMBP vs. enema	5.18 (0.18, 308.00)
	OMBP + enema vs. enema	5.95 (0.07, 645.60)
	OMBP + enema vs. OMBP*	1.13 (0.07, 12.97)
Anastomotic leakage	Enema vs. no preparation*	1.30 (0.44, 4.59)
	OMBP vs. no preparation	0.89 (0.53, 1.59)
	OMBP + enema vs. no preparation	0.95 (0.45, 2.26)
	OMBP vs. enema	0.69 (0.20, 2.08)
	OMBP + enema vs. enema*	0.73 (0.24, 2.13)
	OMBP + enema vs. OMBP	1.07 (0.45, 2.79)
Wound infection	Enema vs. no preparation*	1.84 (0.85, 4.60)
	OMBP vs. no preparation	1.19 (0.82, 2.01)
	OMBP + enema vs. no preparation	1.42 (0.81, 2.61)

	OMBP vs. enema	0.65 (0.29, 1.42)
	OMBP + enema vs. enema*	0.77 (0.31, 1.74)
	OMBP + enema vs. OMBP	1.18 (0.58, 2.30)
Peritonitis/ Intra-abdominal abscess	Enema vs. no preparation*	0.49 (0.04, 5.72)
	OMBP vs. no preparation	0.50 (0.19, 1.46)
	OMBP + enema vs. no preparation	1.12 (0.38, 4.26)
	OMBP vs. enema	1.03 (0.09, 13.21)
	OMBP + enema vs. enema*	2.31 (0.22, 31.05)
	OMBP + enema vs. OMBP	2.25 (0.53, 11.10)

*Based only on indirect data.

Comparisons of Alternative Active OMBP strategies

For the reasons outlined in the beginning of the Results chapter, studies comparing alternative active OMBP strategies were considered separately from those reporting on comparisons between OMBP and no OMBP strategies.

Twenty-three RCTs and two NRCs (reported in 25 publications) provided information on comparisons among active OMBP strategies for adult patients undergoing elective colorectal surgery. We first examine the findings of RCTs, followed by the findings of NRCs.

RCTs Comparing Alternative OMBP Strategies

Twenty-one of the 23 RCTs enrolled adult patients and two enrolled exclusively children. The most common indications for surgery were colorectal cancer and diverticular disease. Four studies enrolled only patients diagnosed with cancer. Six studies excluded patients with inflammatory bowel disease. Details on the surgical approach (e.g., operation types, anastomosis methods, open versus laparoscopic surgery) were generally not reported. Information on the breakdown of surgical sites into right colon, left colon and rectum was generally not reported. Most studies enrolled mixed populations of patients undergoing colon and rectal surgery, but none reported outcome data separately by anatomic location. One study enrolled exclusively patients undergoing left colon or rectal surgery. No study enrolled exclusively patients undergoing rectal surgery.

We grouped OMBP strategies in the active versus active studies into seven grand categories to facilitate synthesis and presentation, as described in the Methods section: PEG, hyperosmotic sodium solutions, other laxatives or cathartics, PEG and laxatives/cathartics, whole gut irrigation, mixed/other, and dietary interventions. The most common comparisons were between PEG- versus whole-gut-irrigation-based OMBP (examined in 5 RCTs) and PEG-based versus laxative/cathartic-based OMBP (3 RCTs). Note that we were lenient in the grouping of OMBP interventions in the seven categories, and that the actual interventions in RCTs that are grouped in the same category can be quite diverse.

The majority of RCTs (20 out of 23) had two treatment groups; three had three groups and one had four groups, for a total of 51 active OMBP groups and 35 possible pairwise contrasts. Studies compared diverse OMBP strategies: of the 51 groups, 11 received PEG solutions, 17

laxatives or cathartics (mainly, senna or bisacodyl), two hyperosmotic sodium solutions, three a combination of PEG with laxatives or cathartics, 10 whole gut irrigation with electrolyte solutions other than PEG (typically Ringer's lactate or normal saline), four combinations of these strategies or other OMBP drugs, and four nutritional interventions (prebiotics or symbiotics).

Many items necessary for detailed assessment of all risk of bias were unreported in most studies. Overall, based on the number of items considered indicative of low risk, 10 studies were considered to be at high risk of bias, 12 to be at intermediate risk of bias, and one to be at low risk of bias. Details on the risk of bias are given at the end of this subsection.

Summary of Findings from RCTs Comparing Active OMBP Strategies

We did not perform meta-analysis of findings from head-to-head (active versus active) studies of OMBP strategies, because of extensive diversity of the employed OMBP strategies, the heterogeneity in the assessed outcomes, and, of concerns regarding selective outcome reporting (and other risk of bias dimensions). Instead, we summarize the information extracted from studies in a series of graphs (**Figure 14**). The underlying data, together with additional extracted information are accessible online (at <http://srdhr.ahrq.gov/>).

We use the first page of **Figure 14** as an example. Each panel summarizes information on one outcome. The left upper panel shows information on overall mortality. Each outcome panel is a matrix of cells that represent contrasts between the strategies listed in the rows versus the strategies in the columns. Markers are plotted in a cell if an actual study compared the respective strategies. Marker color and shape is a key to whether the outcome was reported, and if so, to the direction and significance of the treatment effects:

- **Gray 'x' markers** denote that a study did not assess the predefined outcome, or if it did assess it, it did not report sufficient data for a meta-analysis.
- **Black hollow markers** denote that the effects in the first (row) versus the second (column) strategy were statistically not significant (2-tailed P-value ≥ 0.05).
 - **Black hollow circles** stand for studies where effects trend in favor of the row versus the column strategy
 - **Black hollow triangles** stand for studies where there is no effect (e.g., equal number of events in each arm)
 - **Black hollow squares** stand for studies where effects trend in favor of the column versus the row strategy
- **Red hollow markers** denote that the effects were statistically significant at the P < 0.05 level. The corresponding marker shapes (as for nonsignificant findings) denote the direction of the effects.

Consider the top left panel in the first page of **Figure 14**. For the outcome of all-cause mortality, a single grey 'x' marker in the cell intersected by hyperosmotic sodium solution-based strategy (4th column) with PEG (1st row) indicates that a single study compared these two OMBP protocols, but this study reported no analyzable results on all-cause mortality. Also, whole gut irrigation (WGI) was associated with reduced incidence of death compared to laxatives/cathartics, but the difference was not statistically significant at the 0.05 level.

Figure 14 allows us to make the following observations:

Only 14 out of the 28 cells (comparisons) have some empirical information, i.e., have at least one study (one marker). This density of observed versus possible comparisons is somewhat optimistic: we have been quite lenient in categorizing the individual active OMBP comparisons into the seven conceptual categories represented by rows and columns in each panel. If we used a more granular categorization, the matrix would be larger, and there would be fewer studies in each of the cell. Further, we have also been lenient in the categorization of outcomes. For example, we operationalized peritonitis (lower right panel in the first page in **Figure 14**) as a clinical diagnosis defined by the study authors as a condition (local or generalized) that warrants repeat surgery, or deep infection or abscess.

Outcomes are assessed or reported in sufficient detail in a minority of the conducted studies, perhaps with the exception of wound infection in **Figure 14**. Where two or more studies provided information for the same outcome (e.g., wound infection) no conclusions could be reached regarding the comparative effectiveness of interventions. **Some of the outcomes of interest to this review, such as surgical site infections, pulmonary embolism, and venous thrombosis were not reported in any study.**

Visually, most markers in each panel are grey x's, and just a handful are black or red. The empirical evidence that is available to a literature-based review is but a small fraction of what could have been available. This represents a lost opportunity. If the observed outcomes are missing at random (e.g., by design) or completely at random, the missingness is ignorable, and represents loss of precision in the estimates we get from these studies. If, however, information is censored for systematic reasons (e.g., because of selective outcome reporting^{91, 92}), then summaries of the published literature are likely misleading. We have no solid indications of outcome reporting bias in this set of studies. As discussed in the risk of bias subsection, however, one is left with the impression that a lot in their design, conduct and analysis could be done better.

The majority of the available studies are small, and probably underpowered to detect modest or small effect sizes, let alone relatively rare harms. Across all 74 analyzable results (outcome/comparison combinations) four were statistically significant –visually, in the three Figures the black markers far outnumber the red. This proportion (4.1%) is near the 5% that would be expected by chance if the null hypothesis of no association were true. Because the true distribution of effects in this body of literature is unknown, and because these analyses are not independent (per study, they are in the same patients), one cannot simply infer that all identified statistically significant findings are false. Nevertheless, this observation is congruent with the notion that very few, if any, genuine differences exist among active OMBP strategies in the included studies.

Figure 14: Summary of Findings from Studies Comparing Alternative Active OMBP Strategies

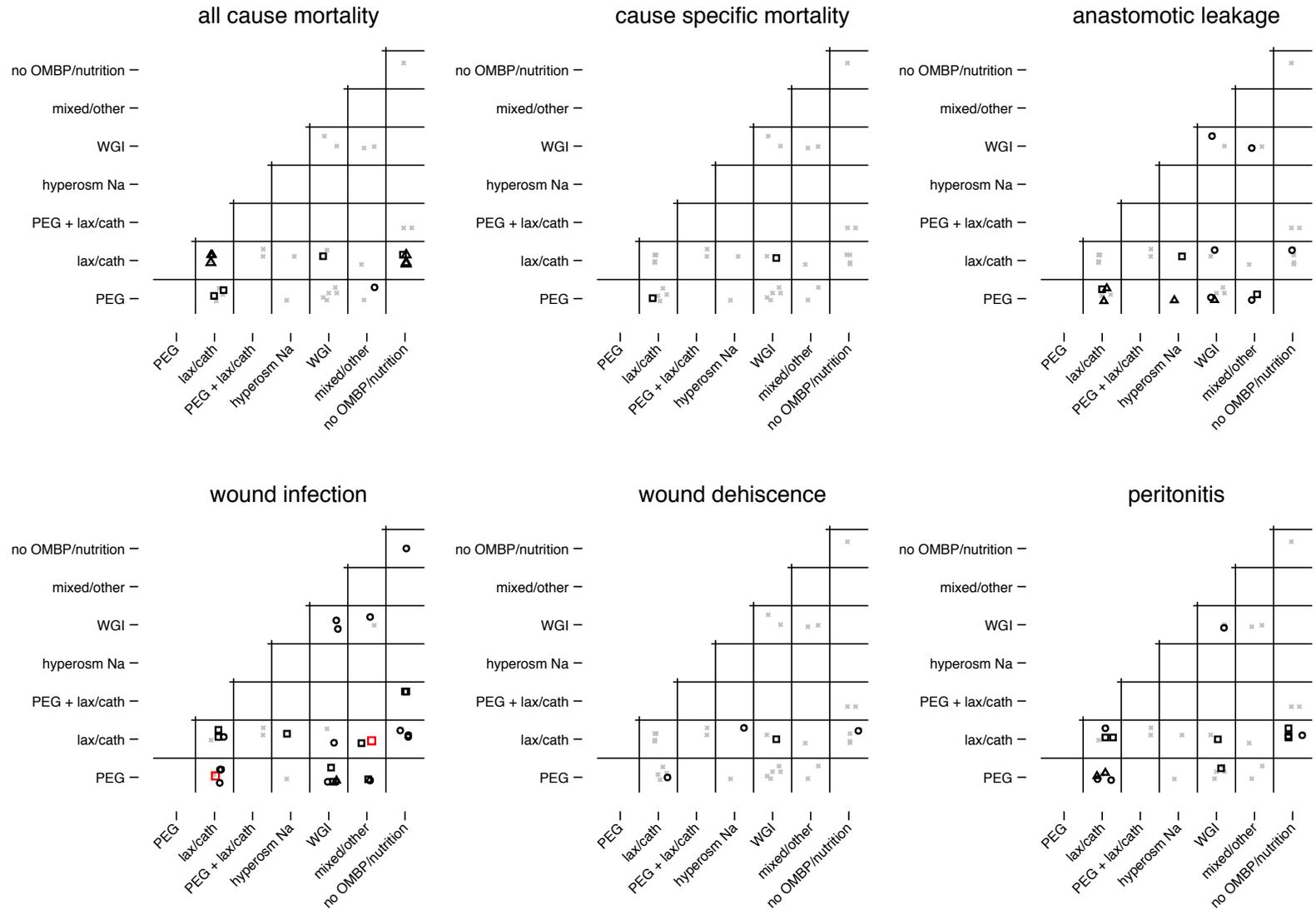
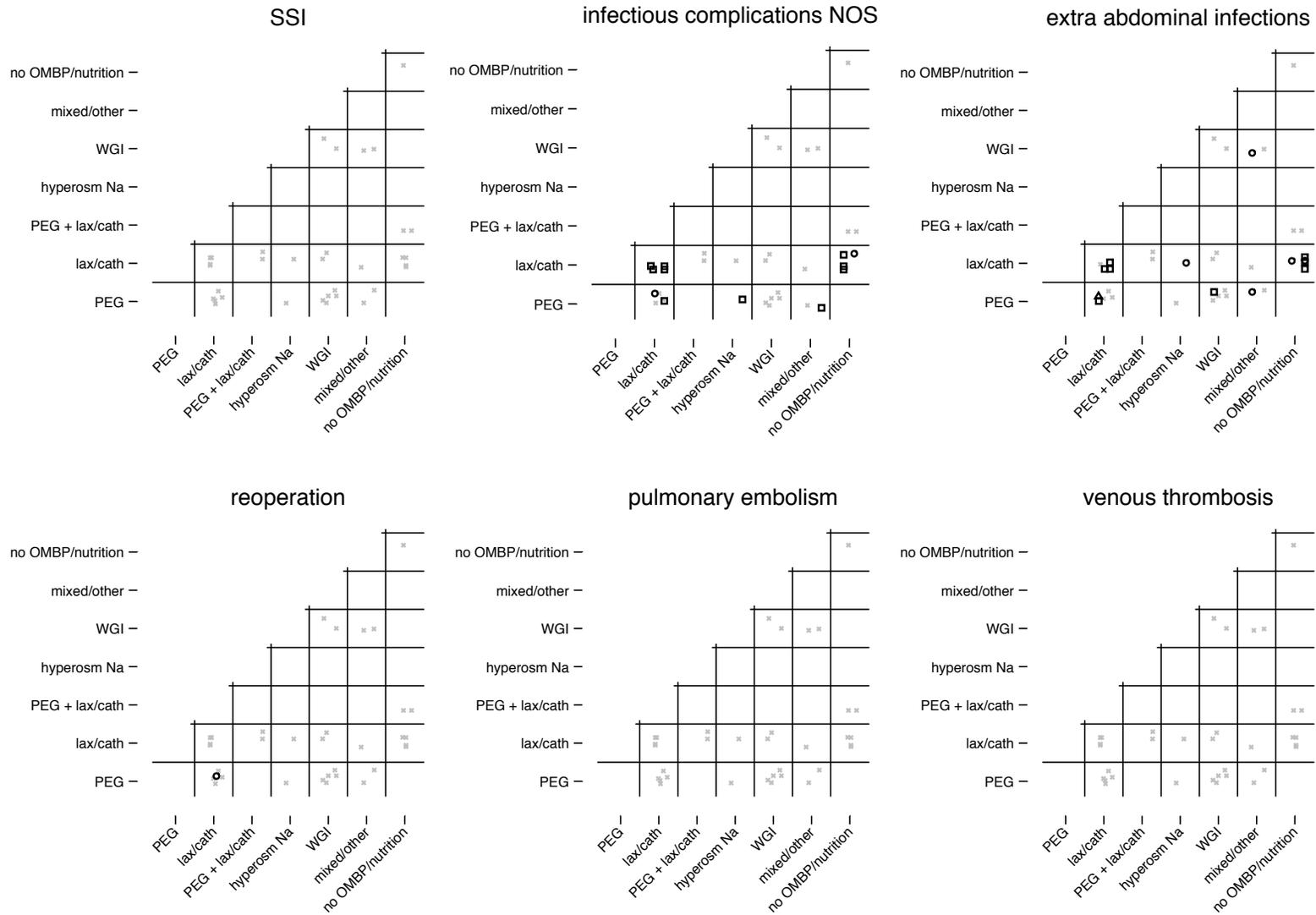


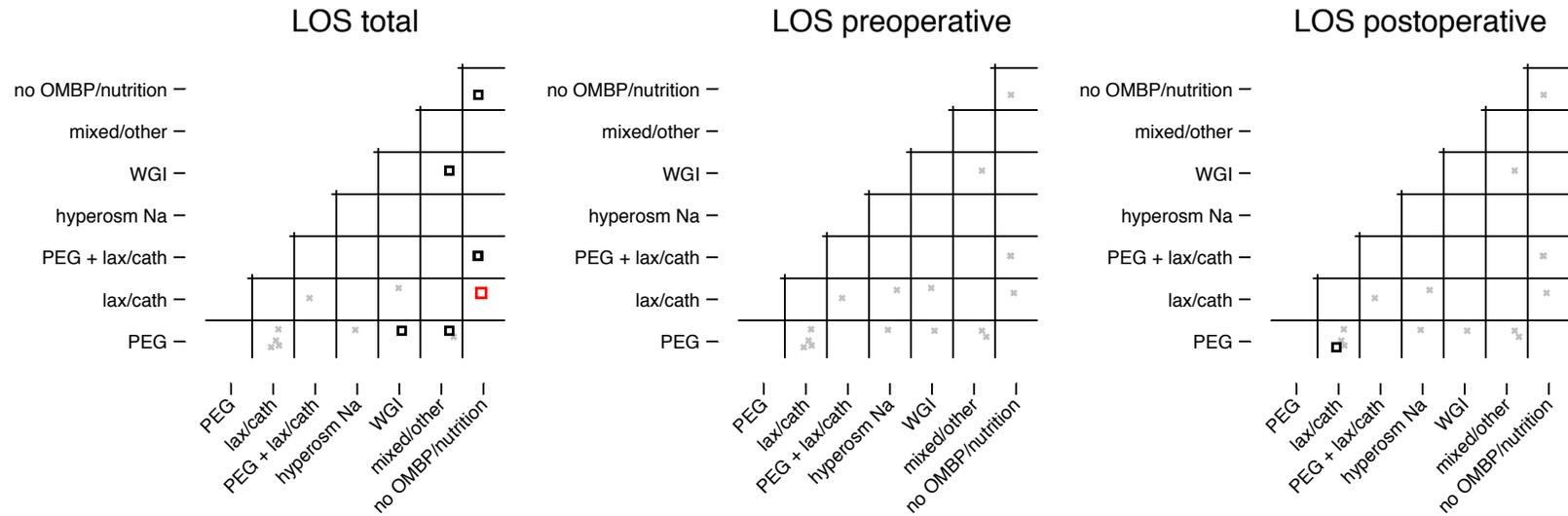
Figure 14: Summary of Findings from Studies Comparing Alternative Active OMBP Strategies (continued)



Comparisons of alternative active OMBP strategies. Please consult the main text of the report for details on how this graph should be interpreted.

The panel for extra-abdominal infections depicts more than one datapoint per study.

Figure 14: Summary of Findings from Studies Comparing Alternative Active OMBP Strategies (continued)



Comparisons of alternative active OMBP strategies. Please consult the main text of the report for details on how this graph should be interpreted.

Assessment of Risk of Bias for RCTs Comparing Alternative Active OMBP Strategies

Studies did not allow detailed assessment of the risk of bias for several important aspects of study design. For example, information on the randomized sequence generation and allocation concealment was deemed unclear in 13 and 19 of the 23 RCTs, respectively. Similarly, blinding of patients, physicians, and outcome assessors were deemed unclear in 19, 16, and 12 of the RCTs. In contrast, information on withdrawals and dropouts was generally well reported. Of the studies reporting relevant information, only two reported a dropout rate of more than 10% (one in both arms; one only in a single arm) and only one study had evidence of differential dropout (defined as a more than 10% difference in the dropout rate between arms). As shown in **Figure 14**, only few studies provided information on each of the outcomes of interest, raising some concerns about selective outcome reporting. Overall, based on the number of items considered indicative of low risk, 10 studies were considered to be at high risk of bias, 12 to be at intermediate risk of bias, and 1 to be at low risk of bias. As always, aggregated risk of bias assessments need to be interpreted with caution, given our inability to fully distinguish inappropriate study design from poor reporting and lack of context-specific evidence that the risk items we assessed are indeed associated with bias.

RCTs of Alternative Active OMBP Strategies in Children

Two studies, both conducted in India, compared alternative active OMBP strategies in children undergoing colorectal surgery (a minority of children underwent procedures for indications other than colorectal surgery in both studies). Both studies were considered to be at high risk of bias and provided limited information on the generation of the randomized sequence and allocation concealment.

The first study⁴⁰ enrolled 54 children and compared whole gut irrigation with normal saline with added potassium (26 patients) versus PEG (28 patients). Four patients developed a wound infection in the whole-gut irrigation group and three in the PEG group; the difference was not statistically significant ($P = 0.699$).

The second study⁷⁵ enrolled 126 children and compared whole gut irrigation with a NaCl solution (40 patients), PEG (55 patients), and Ringer's lactate (31 patients). Wound infections developed in two, three, and two patients in the NaCl, PEG, and Ringer's lactate treatment groups, respectively; the difference between groups was not statistically significant ($P > 0.99$).

NRCSS Comparing Active OMBP Strategies

Only two NRCSS reported information on the comparison of alternative active OMBP strategies. The first study⁸⁸ was a secondary analysis of a previously completed multicenter RCT of alternative antibiotic treatments (comparing ertapenem versus cefotetan) for patients undergoing elective colorectal surgery. Inclusion in the parent trial required patients to have undergone bowel preparation with PEG or sodium phosphate. Patients were followed up for SSI development for a period of 4 weeks. Of a total of 670 evaluable patients, 303 had OMBP with PEG and 367 with sodium phosphate. The overall rate of SSI was lower among patients who received sodium phosphate as compared with those who received PEG, however the difference was not statistically significant in multivariable analysis (OR = 0.69, 95% CI 0.46 to 1.02; $P = 0.07$). The study also reported a subgroup analysis by resection subtype, comparing PEG versus

sodium phosphate among patients who underwent resection of the rectum versus those who underwent other colorectal surgical procedures. The magnitude and direction of effects was similar in both groups [using data in the paper, we calculated the unadjusted OR to be 0.59 (95% CI 0.42 to 0.83) and 0.67 (95% CI 0.46 to 0.99), for patients undergoing and not undergoing rectal resection, respectively]. The test for interaction between resection type and preparation regimen was not statistically significant ($P = 0.64$). The study was considered to be at intermediate risk of bias, mainly due to concerns about confounding bias (some of the reported analyses were unadjusted).

The second study³¹ was a retrospective cohort comparing three groups: mannitol with ceftriaxone (150 patients), mannitol with ceftriaxone plus metronidazole (160 patients), and traditional preparation with purgatives and enemas, combined with neomycin and metronidazole (140 patients). Of note, 110 of the 140 patients in the traditional preparation group were not treated concurrently with the patients receiving mannitol (i.e., they were historical controls). A comparison across all three groups found statistically significant differences for the outcomes of peritonitis requiring reoperation and a composite outcome of all infectious complications ($P = 0.008$ and $P < 0.001$, respectively). Differences were not statistically significant for other outcomes assessed, including wound infection, intra-abdominal abscess necessitating reoperation, anastomotic insufficiency, death due to peritonitis, or all cause mortality. For all outcomes, event rates were higher in the traditional preparation group and lower in the two mannitol study groups. The study was considered to be at high risk of bias, on the basis of concerns regarding confounding bias (all comparisons between groups were unadjusted and patients in the traditional preparation group were not treated concurrently with those in the mannitol groups).

Comparisons of Inpatient Versus Outpatient OMBP

One RCT and one NRCS compared inpatient versus outpatient use of OMBP. The RCT⁵⁰ compared inpatient versus outpatient preparation using of PEG in 100 patients undergoing elective colorectal surgery (51 inpatient versus 49 outpatient). Overall, the study was considered to be at high risk of bias and provided limited information regarding blinding and allocation concealment. Two patients in each group developed a wound infection; the difference between groups was not statistically significant ($P > 0.99$). Information was not provided regarding the treatment received by patients experiencing two additional outcome events (1 intra-abdominal abscess and 1 enterocutaneous fistula). However, the difference between the two groups for these outcomes was also nonsignificant ($P > 0.99$).

The NRCS⁶⁰ retrospectively compared inpatient versus outpatient use of PEG in 319 patients who underwent colectomy with primary anastomosis (174 inpatient versus 145 outpatient). The study was considered to be at high risk of bias because of concerns regarding confounding bias (all comparisons were unadjusted). One death was observed in each study group ($P > 0.99$). Three patients who received inpatient OMBP and were discharged to a rehabilitation facility, no patients in the outpatient group required care in such a facility ($P = 0.25$). Length of hospitalization was 10.7^a days in the inpatient group and 9 days in the outpatient group and the

^a The number was reported as 107 (rather than 10.7), but based on the statistical analysis results reported in the study and the range of values (6-41 days) 10.7 appears to be the most likely correct value.

difference was not statistically significant (which the authors reported to be statistically nonsignificant).

Key Question 2. How does the use of OMBP, with or without cointerventions (e.g., antibiotics, rectal enema), compare with no OMBP or with OMBP plus different cointerventions with respect to presurgical and postsurgical adverse events?

a. What are the comparative adverse events of the various OMBP strategies?

In this section we summarize the evidence on the following predefined potential adverse events of OMBP: nausea, vomiting, dehydration, electrolyte imbalance, kidney damage, emergency admissions prior to surgery, cancelled, delayed, or rescheduled surgeries, allergic reactions, and seizures. Based on preliminary literature searches and discussions with TEP members, we expected that evidence on these outcomes would be sparse in comparative studies (both randomized and nonrandomized). We therefore also considered evidence from noncomparative (single group) cohort studies where all patients received OMBP.

The organization of the subsequent sections follows that of Key Question 1: we first discuss comparative studies of OMBP versus enema or no preparation, followed by comparative and noncomparative (single group) studies of alternative active OMBP strategies. The risk of bias assessment of comparative studies has already been presented in the section pertaining to Key Question 1. Thus, in the risk of bias subsection we provide assessments only for single-group cohorts.

Comparisons of OMBP versus no OMBP

RCTs Comparing OMBP Versus No Preparation

Of the 15 RCTs (also counting the single retracted publication) comparing OMBP with or without enema versus enema alone or no preparation, only two provided information pertaining to the prespecified adverse events (one for nausea and one for renal failure).

Nausea

In one study³⁴ patients were asked to rate their degree of nausea using a 1-to-5 ordinal scale (higher values indicated more severe symptoms). Of 233 randomized patients, 185 (95 OMBP-treated and 90 controls) replied to the questionnaire. The frequency of nonresponse to the questionnaire was not significantly different among OMBP-treated and untreated patients ($P = 0.40$). Nausea (the cut off on the scale was not reported) was reported by nine OMBP-treated patients and eight controls ($P = 0.77$).

Renal Failure

One study³⁵ comparing OMBP versus no preparation reported that three of 89 patients receiving OMBP versus one of 89 patients receiving no preparation experienced acute renal failure ($P = 0.62$).

Comparisons of OMBP Versus no OMBP in NRCSs

None of the five NRCSs comparing OMBP versus no preparation reported information on the prespecified adverse events.

Comparisons of Alternative Active OMBP strategies

RCTs Comparing Alternative OMBP Strategies in Adults

As discussed in the corresponding section of Key Question 1, studies of alternative active OMBP strategies used very diverse OMBP strategies, assessed heterogeneous outcomes, and, raised concerns of selective outcome reporting (and other risk of bias dimensions). Regarding the assessment of adverse events, studies utilized a diverse set of symptom scales to measure severity of patient reported adverse events (nausea, vomiting, fatigue, bloating, cramping, etc.). In most studies adverse event definitions were not clearly described, making it impossible to consistently compare outcomes across studies. Only a single study⁶⁶ provided a copy of the questionnaire that was administered to patients; no study described whether the validity of the questionnaires had been formally assessed.

For these reasons, we have used the same approach as in Key Question 1 and summarize findings using scatterplots that map the comparisons reported and the direction and statistical significance of effects (**Figures 15 and 16**). The underlying data, together with additional extracted information are accessible online (at <http://srdhr.ahrq.gov/>).

Based on **Figures 15 and 16** we make the following observations, which are in accordance with the corresponding descriptions in Key Question 1:

Only 10 out of the 28 cells (comparisons) have some empirical information, i.e., have at least one study (one marker). We have been quite lenient in categorizing the individual active OMBP comparisons into the seven conceptual categories represented by rows and columns in each panel; were we to use a more granular categorization, the matrix would be larger, and there would be fewer studies in each of the cell.

Outcomes are assessed or reported in sufficient detail in a minority of the conducted studies. Most reported data fall into the outcome category other patient-reported adverse events (**Figure 15**, first page, lower left panel), which is indicative of the nonstandardized reporting. Where two or more studies provided information for the same outcome (e.g., wound infection) no conclusions could be reached regarding the comparative effectiveness of interventions. Renal failure, an outcome considered important given that many OMBP strategies involve ingestion of large volumes of solutions, was not reported in any study. This nonstandardized and partial reporting of harms represents a lost opportunity, i.e., could have been averted by better planning of the conduct and reporting of said studies.

Finally, **the majority of the available studies are small, and probably underpowered to detect modest or small effect sizes, let alone relatively rare harms.** Across all 81 analyzable results (outcome/comparison combinations) 23 were statistically significant –visually, in the three Figures the black markers outnumber the red. However, there is no readily discernible pattern. Because the true distribution of effects in this body of literature is unknown, and because these analyses are not independent (per study, they are in the same patients), one cannot make

statements on whether the identified statistically significant findings are more than what would be expected by chance.

Figure 15: Summary of Findings from Studies Comparing Alternative Active OMBP Strategies (Results Reported As Binary Outcomes)

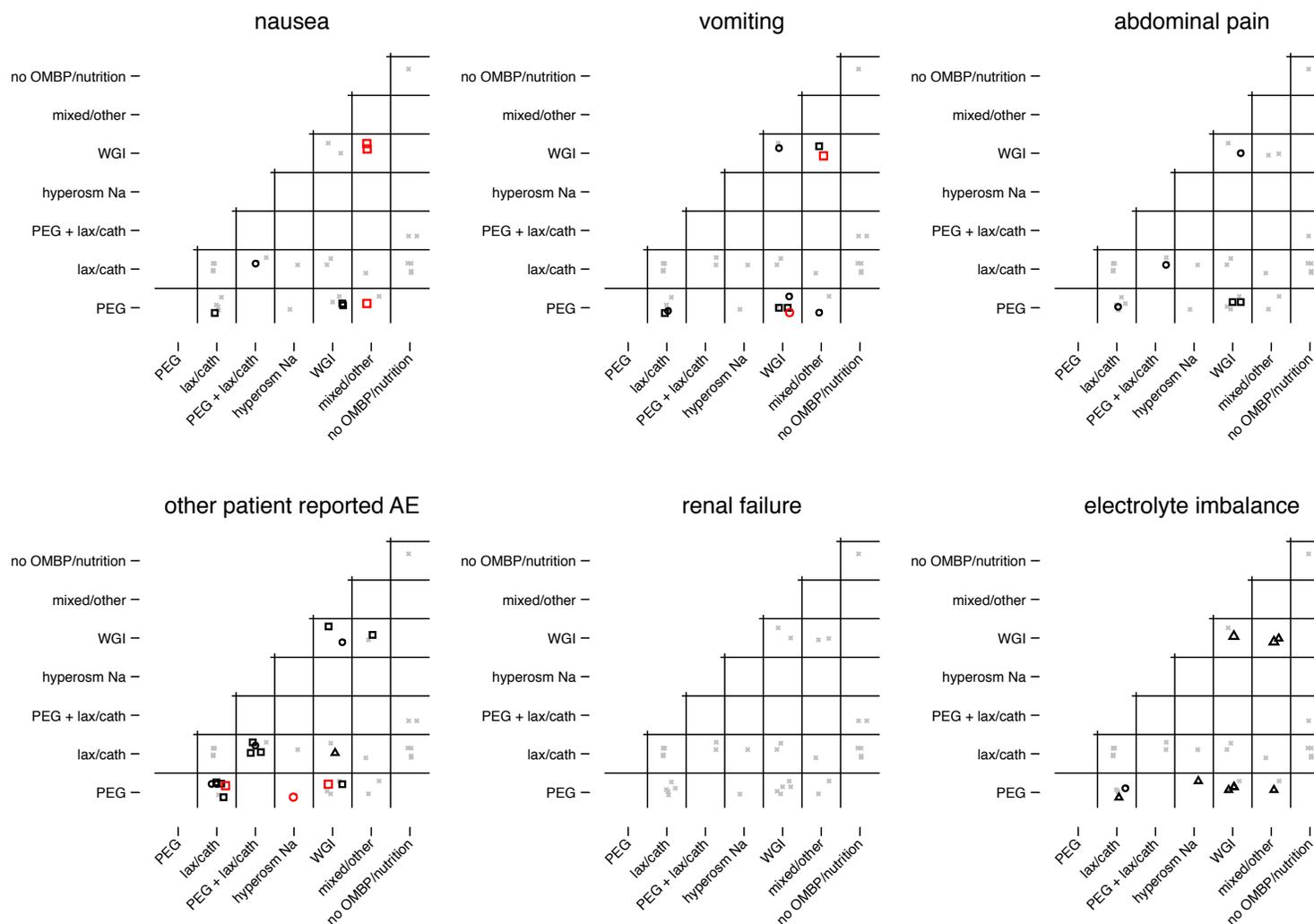
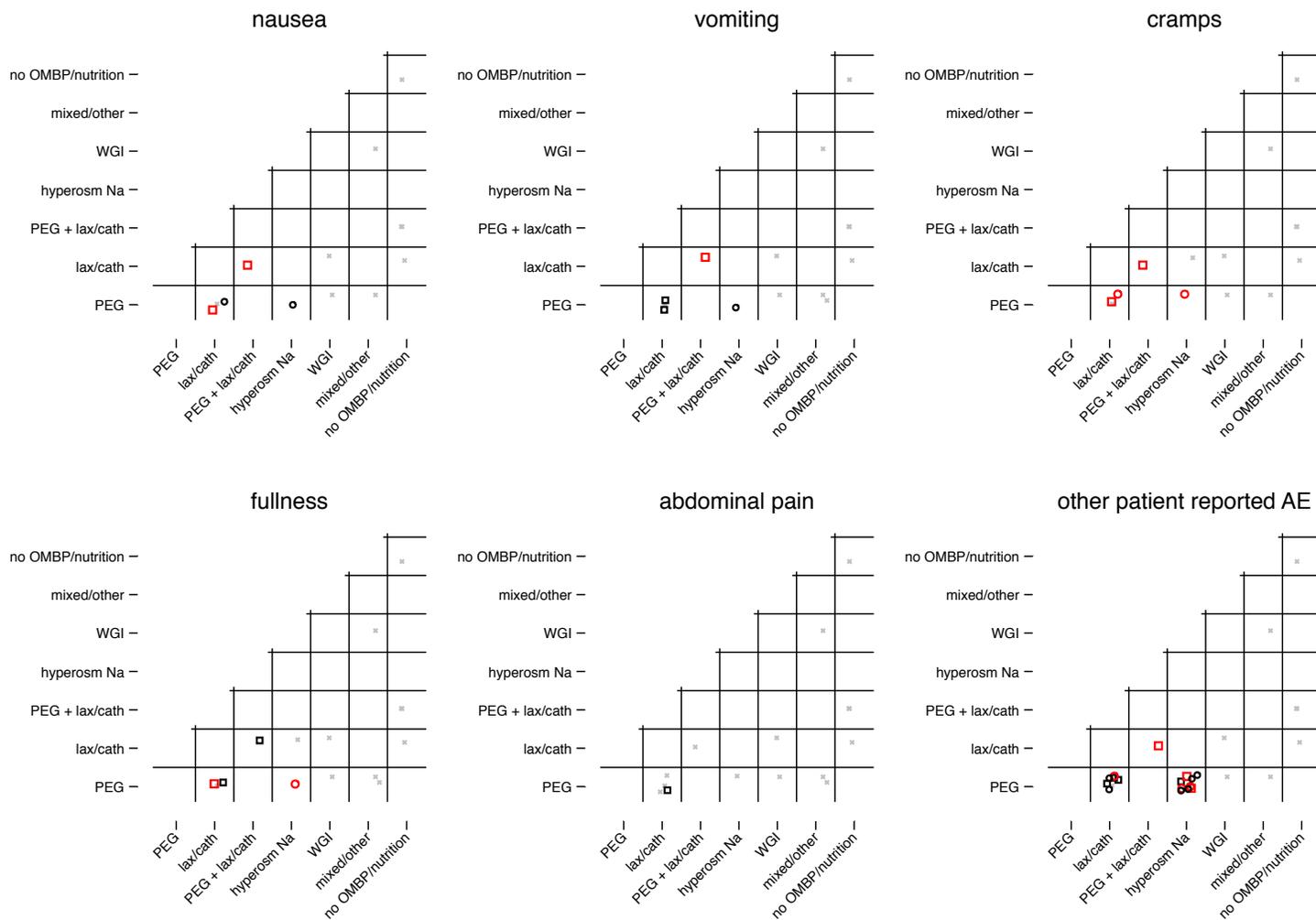


Figure 16: Summary of Findings from Studies Comparing Alternative Active OMBP Strategies (Results Reported As Continuous Outcomes)



Comparisons of alternative active OMBP strategies. Please consult the main text of the report for details on how this graph should be interpreted.

RCTs of Alternative Active OMBP Strategies in Children

Two studies reported information on the comparison of alternative OMBP strategies in children. The studies only reported information on vomiting and electrolyte imbalance.

Vomiting

Both studies reported information on vomiting. In the first study⁴⁰ 7 of 28 patients treated with whole gut irrigation with PEG experienced vomiting, compared to 13 of 23 patients treated with whole gut irrigation with normal saline and added potassium (P = 0.09). The second study⁷⁵ compared whole gut irrigation with PEG, Ringer's lactate and NaCl and reported that vomiting was experienced by 11 of 55 patients, 5 of 31 patients, and 2 of 40 patients, respectively (P = 0.10, across groups).

Electrolyte Imbalance

One study⁷⁵ reported that no clinically significant electrolyte imbalances were observed after OMBP in the three compared groups (whole gut irrigation with PEG, NaCl, or Ringer's lactate).

NRCs Comparing Alternative Active OMBP Strategies

None of the two NRCs comparing alternative active OMBP strategies versus no preparation reported information on the prespecified adverse events.

Single-group Cohorts of Active OMBP Strategies

Six studies met our inclusion criteria for single group cohorts and reported results on at least one of the prespecified adverse events of pertaining to Key Question 2. Of note all six studies were large comparative studies of antibiotic treatments (5 studies) or enema use (1 study) for patients with colorectal cancer. Because these studies used a uniform OMBP treatment for all patients – for the purposes of this report – they were treated as single group studies.

Vomiting

In one study⁴⁶ of OMBP with saline or mannitol the rate of vomiting was approximately 1.6 percent (5 of 308 patients). All patients were also receiving metronidazole and ceftriaxone. Vomiting was not attributed to the OMBP drugs by the authors. No vomiting was reported among 307 patients included in the same study and treated with the same OMBP regimen, plus metronidazole and cefepime instead of ceftriaxone.

In one study⁷⁸ of OMBP with senna the rate of vomiting was approximately 3.9 percent (20 of 517 patients; 277 received povidone-iodine and 240 sodium hypochlorite enema). Vomiting was not attributed to the OMBP drugs by the authors.

Finally, in one study⁴⁷ of OMBP with sodium phosphate the rate of vomiting was approximately 17 percent (51 of 300 patients; 100 received three doses of oral antibiotic, 100 received a single dose, and 100 received no oral antibiotics). Vomiting was not attributed to the OMBP drugs by the authors; the rate of vomiting was 31 percent among patients receiving three doses of oral antibiotics, 11 percent among those receiving a single dose, and 9 percent among those receiving no oral antibiotics (P < 0.001 for the comparison across groups).

Nausea

One study⁴⁶ of OMBP with saline or mannitol plus metronidazole and ceftriaxone reported nausea in approximately 1 percent of patients (3 of 308). Nausea was not attributed to the OMBP drugs by the authors. No nausea was reported among 307 patients included in the same study and treated with the same OMBP regimen plus metronidazole and cefepime (instead of ceftriaxone).

In one study⁴⁷ of OMBP with sodium phosphate the rate of nausea was approximately 25 percent (75 of 300 patients; 100 received three doses of oral antibiotic, 100 received a single dose, and 100 received no oral antibiotics). The authors did not attribute nausea to the OMBP drugs. The rate of nausea was 44 percent among patients receiving three doses of oral antibiotics, 18 percent among those receiving a single dose, and 13 percent among those receiving no oral antibiotics ($P < 0.001$ for the comparison across groups).

Vomiting and Nausea (Combined)

In one study⁵⁷ of OMBP with PEG, the rate of nausea and vomiting was approximately 2.2 percent (11 of 491 patients; 245 received intravenous antibiotics and 246 received both intravenous and oral antibiotics). The authors did not attribute these events to the OMBP drugs (they considered them probably related to the antibiotics).

Allergic Reactions

In one study⁴⁶ of OMBP with enemas and laxatives the rate of allergic reactions (maculopapular rash) was 2.7 percent (7 events among 263 patients). However, all patients were also receiving cephalosporin antibiotics. The authors did not attribute the allergic reactions to the OMBP drugs.

In a study⁸⁵ of OMBP with saline or mannitol the rate of allergic reactions was approximately 1 percent (3 of 308 patients). All patients were also receiving ceftriaxone plus metronidazole antibiotics. The authors did not attribute the allergic reactions to the OMBP drugs.

In a third study⁵⁷ of OMBP with PEG, no hypersensitivity reactions were observed (0 of 491 patients; 245 received intravenous antibiotics and 246 received both intravenous and oral antibiotics).

In a fourth study⁴⁴ of OMBP with sodium phosphate and enemas the rate of urticaria was less than 1 percent (1 of 241 patients; 121 treated with cefoxitin and 120 treated without parenteral antibiotics). The authors did not attribute the allergic reaction to the OMBP drugs (urticaria developed in a patient in the cefoxitin group).

Risk of Bias in Single Group Cohort Studies

(Please refer to the corresponding section of Key Question 1 for a description of the risk of bias of the comparative studies.)

We assessed the risk of bias of these studies using a set of items based on the Newcastle-Ottawa scale. Briefly, we examined whether there was risk of selection bias, the methods of exposure ascertainment, whether patients were outcome-free at baseline, whether rates of events were adjusted for key patient characteristics (e.g., whether incidence rates were standardized or stratified by age or sex), the methods for outcome assessment, and the adequacy of followup.

These studies were prospective (and were designed to provide information on the use of antibiotics or enemas). There was low risk that patients had the adverse events at baseline. Exposure was protocol-determined in all cases. Four of six studies explicitly reported enrolling consecutive patients, thus reducing the risk of selection bias. However, no study reported adjustment or standardization of event rates by key patient characteristics. Methods for outcome ascertainment were unclear in six studies, performed by an independent observer in one study, and based on a combination of self-report and care provider observation in two cases.

Comparisons of Inpatient Versus Outpatient OMBP

The two studies (1 RCT⁵⁰ and 1 NRCS⁶⁰) comparing inpatient versus outpatient administration of OMBP did not report information on the prespecified adverse events of interest.

Key Question 2. How does the use of OMBP, with or without cointerventions (e.g., antibiotics, rectal enema), compare with no OMBP or with OMBP plus different cointerventions with respect to presurgical and postsurgical adverse events?

- b. What are the comparative adverse events of OMBP in subgroups of patients especially susceptible to the potential adverse events?**

We sought information on adverse events of OMBP when used by patients who may be particularly susceptible to adverse events. Specifically, we aimed to identify evidence on the impact of OMBP on adults and children with cardiovascular or pulmonary disease, patients at the extremes of age, patients who have undergone adjuvant chemotherapy or radiotherapy, and patients with diabetes, kidney disease, or compromised immune function (including drug-induced immunosuppression) who undergo elective colorectal surgery.

No study in this report provided such information. Studies often excluded individuals who would be at particular high risk of adverse events following the use of OMBP. For example, several studies reported excluding patients with severe renal failure or hypertension at diagnosis. Among studies that did not report such exclusions (including a minority that explicitly stated including individuals belonging to the susceptible groups of interest to this Key Question), none reported outcome information limited to the populations of interest. Because of the sparseness of the evidence on these subgroups of patients, we considered the strength of the evidence to be insufficient.

Discussion

Key Findings

We reviewed more than 50 studies spanning 40 years of empirical data on the benefits and harms of alternative OMBP strategies for elective colorectal surgery. For a wide range of outcomes including clinical outcomes, we found no evidence that OMBP with or without enema differs from enemas or no preparation beyond what is expected by chance. For most outcomes, the uncertainty accompanying the treatment effects is large. Based on the boundaries of the confidence intervals, for many outcomes one cannot exclude a modest (e.g., 30 to 50 percent) change in odds in either direction. Most included studies were relatively small, especially considering that key clinical events such as mortality, anastomotic leakage, reoperation, and severe infection are relatively rare. Further, data for important subgroups, including by anatomic location (right colon versus left colon versus rectum) and type of surgery (laparoscopic versus open), were sparsely reported in the published literature.

Using Bayesian network meta-analysis methods we found that the evidence on the comparison of OMBP, enema alone, and no preparation was relatively weak. We also found that the evidence on the comparative effectiveness and safety of alternative preparation strategies was insufficient and probably not very applicable to current clinical practice. Information on the safety of OMBP prior to colorectal surgery was not consistently reported. It is unclear whether adverse events are more common with inpatient or with outpatient administration of OMBP. It is also unclear whether the type or frequency of adverse events of OMBP differ across patient subgroups, e.g., in patients with cardiac, pulmonary, or renal disease; cancer; suppressed immune function; or patients receiving chemotherapy, radiotherapy or immunosuppression.

We observed that the early trials explored comparisons among alternative active OMBP strategies, with later published and recent studies evaluating the more fundamental question of using versus not using OMBP. This reflects an apparent shift in the prevailing opinions about the role of OMBP prior to elective colorectal surgery. Since the early 1970's OMBP was widely considered highly desirable, presumably on the basis of pathophysiological and practical rationales but without serious concomitant empirical support.^{5, 14} The clinical equipoise was presumably between alternative OMBP strategies; today, it is probably fair to state that the question is between using versus not using OMBP (and, in fact, using relatively simple versions thereof, and of short duration).

Strengths and Limitations of This Review

This is a comprehensive review of OMBP strategies for elective colorectal surgery. We reviewed a large number of clinically-relevant prespecified outcomes, and considered comparisons between OMBP and no OMBP strategies, as well as comparisons among active OMBP strategies. Compared to a recent Cochrane Review of OMBP we have included a broader spectrum of study designs (including NRCSs and single group cohorts) and have performed more extensive data analyses using state-of-the art methods. Our interpretation of the evidence base is more conservative than that of the Cochrane review¹ and other recent meta-analyses.⁹³⁻⁹⁶ Compared to other meta-analyses, we performed analyses that more fully account for the uncertainties in the synthesis of evidence.⁹⁷ While our results are consistent with no difference

between using and not using OMBP, the confidence or credibility intervals cannot exclude a modest difference in either direction, and deem that a conservative interpretation of the findings is warranted. The OMBP strategies that are in current clinical use are cheap to implement, and the discomfort that patients experience is a rather short-lived one. In the future research section we argue that settling this question for good is entirely possible.

Nonetheless, several limitations need to be considered when interpreting our results. First, our conclusions, to a large extent, reflect limitations of the underlying evidence base. Our ability to perform subgroup analyses to explore the impact of patient-, disease-, or system-level characteristics on the effectiveness of OMBP is limited by the incomplete reporting of relevant information in the published papers. Second, we excluded studies not published in English. Previous work that included non-English language studies identified only three publications with small sample sizes (totaling 219 patients). Third, we have relied mainly on electronic database searches and perusal of reference lists to identify relevant studies. Unpublished relevant studies may have been missed. Fourth, indexing of nonrandomized studies – and single-group cohort studies in particular – is less complete than that of randomized trials and we may have failed to identify relevant studies. However, we did not use search filters that limit results to specific study designs, in order to increase the sensitivity of our searches.

Assessment of the Strength of Evidence

Table 7 presents a summary of the report's key findings for each Key Question. When appropriate, results are presented separately for each of the populations and outcomes of interest. Please see the Methods section for a detailed discussion of our approach to rating the strength of evidence.

Table 7. Summary Assessment of the Strength of Evidence

Population	Outcome	Comparison	Assessment of the strength of evidence	Key findings and comments*
KQ1: Adult patients undergoing colorectal surgery	All-cause mortality	OMBP versus no preparation	Insufficient	The OR in network meta-analysis of 9 studies was 1.10 (95% CrI 0.55 to 3.76), indicating substantial uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
		OMBP versus enema	Insufficient	The OR in network meta-analysis of 4 studies was 1.87 (95% CrI 0.37 to 11.43), indicating substantial uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
	Anastomotic leakage	OMBP versus no preparation	Low (for lack of difference)	The OR in network meta-analysis of 9 studies was 0.90 (95% CrI 0.60 to 1.46), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
		OMBP versus enema	Low (for lack of difference)	The OR in network meta-analysis of 4 studies was 1.19 (95% CrI 0.56 to 2.57), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
	Wound infection	OMBP versus no preparation	Low (for lack of difference)	The OR in network meta-analysis of 11 studies was 1.25 (95% CrI 0.91 to 1.95), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
		OMBP versus enema	Low (for lack of difference)	The OR in network meta-analysis of 4 studies was 1.01 (95% CrI 0.58 to 1.80), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was some evidence of inconsistency; the test for heterogeneity was not statistically significant (P = 0.11) but the I ² index was 50%
Peritonitis/Intra-		OMBP versus no	Low (for lack of	The OR in network meta-analysis of 8 studies was 0.64 (95% CrI 0.35 to 1.47), indicating moderate uncertainty in the summary estimate. Pairwise analysis indicated that OMBP was

abdominal infection	preparation	difference)	significantly associated with a reduction in peritonitis but that analysis does not fully reflect the statistical uncertainty of the data and therefore is less reliable. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
	OMBP versus enema	Low (for lack of difference)	The OR in network meta-analysis of 4 studies was 0.99 (95% CrI 0.25 to 3.89), indicating moderate uncertainty in the summary estimate. Pairwise analysis concurred. Studies were at low-moderate ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
Reoperation	OMBP versus no preparation	Low (for lack of difference)	No network analysis possible. The OR in pairwise meta-analysis of 5 studies was 0.78 (95% CI 0.78 to 1.35), indicating substantial uncertainty in the summary estimate Studies were at low-moderate ROB There was some concern regarding selective outcome reporting There was evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
	OMBP versus enema	Insufficient	No network analysis possible. The OR in pairwise meta-analysis of 2 studies was 0.61 (95% CI 0.01 to 32.65), indicating substantial uncertainty in the summary estimate. Studies were at low-moderate ROB There was some concern regarding selective outcome reporting There was statistical evidence of inconsistency; the test for heterogeneity was statistically significant (P=0.02) and the I ² index was 83%
All other effectiveness outcomes	OMBP versus no preparation	Insufficient	Few if any studies reported information; study-specific results were imprecise There was concern about selective outcome reporting
	OMBP versus enema	Insufficient	Few if any studies reported information; study-specific results were imprecise There was concern about selective outcome reporting
All outcomes	Alternative active OMBP strategies versus each other	Insufficient	Individual studies compared diverse interventions and reported outcomes heterogeneously, precluding synthesis Study specific results were imprecise Studies were at moderate-high ROB There was no indication of selective outcome reporting There was no statistical evidence of inconsistency; however, because there are only a few studies and most of them small statistical heterogeneity cannot be reliably detected
All outcomes	Inpatient vs. outpatient OMBP	Insufficient	Only two studies were available (1 RCT, at moderate ROB, and 1 NRCS, at high ROB) Study specific estimates were imprecise
KQ1: Children undergoing elective colorectal	All outcomes	All comparisons	Insufficient Only 2 studies provided evidence on children undergoing elective colorectal surgery Studies reported information only for wound infection (no other effectiveness outcomes were assessed) and produced imprecise results

surgery				
KQ1: Patients undergoing elective surgery for right-sided or left-sided colon, or rectal surgery	All outcomes	All comparisons	Insufficient	Only a small minority of studies provided anatomic location specific results (and only for a single outcome) There is concern regarding selective analysis reporting
KQ2: Patients undergoing elective colorectal surgery (unselected)	Adverse events	All comparisons	Insufficient	When interpreting the data available for this review results are insufficient: most prespecified adverse events of interest were evaluated by a small minority of studies or not examined at all; when reported study specific results did not lead to definitive conclusions due to imprecise results, and lack of validation of the measurement scales used (for patient symptom scores) However, the evolution of the preparation strategies used in trials (with most recent studies using PEG-based strategies, possibly in combination with laxatives) indicates that these preparations may be considered safest or more palatable for patients
KQ2: Patients undergoing elective surgery who may be at particular risk for adverse events	Adverse events	All comparisons	Insufficient	No relevant studies were identified

*Unless otherwise stated, summary estimates reported in this table are those from the network meta-analysis. We believe that these results better reflect statistical uncertainty.

CI = confidence interval; CrI = credibility interval; KQ = key question; NRCS = nonrandomized comparative study; OR = odds ratio; PEG = polyethylene glycol; RCT = randomized controlled trial; ROB = risk of bias.

Applicability

The existing evidence base comparing OMBP (with or without enema) versus enema or no preparation, appears to be applicable to U.S. settings. Studies enrolled patients with an age distribution similar to that of patients undergoing colorectal surgery in the U.S., and for indications that represent the most prevalent indications in U.S. clinical practice. However, none of these studies has been conducted in the U.S., raising some concern that system-level differences may render findings less applicable to surgical practice. Findings may be most applicable to patients undergoing colon surgery; data on patients undergoing rectal surgery were sparse, and thus the applicability of findings to this population is at best unclear. Similarly, the applicability of our findings to patients undergoing laparoscopic colorectal surgery is unclear, because few studies reported relevant information.

Preparation of the bowel is only one of many supportive interventions used prior to colorectal surgery with the goal of attaining better surgical outcomes and earlier postoperative recovery. Other pertinent interventions include preoperative (counseling, feeding, etc.), perioperative (avoiding hypothermia, using epidural analgesia, etc.), and postoperative (e.g., avoiding nasogastric tubes and drains, encouraging early mobilization and oral feeding) aspects of care.⁹⁸ Often such interventions are “bundled” in “Early Recovery After Surgery” (ERAS) programs that aim to reduce the length of stay and improve clinical outcomes. Although existing trials of ERAS programs include, among other things, the omission of OMBP as an intervention component, it is not clear how our findings apply in settings where additional ERAS components are implemented.

Regarding studies comparing alternative active OMBP strategies, applicability appears to be limited, because they examined OMBP regimens that have fallen out of use in modern practice, such as whole gut irrigation with non-PEG electrolyte solutions, and mannitol. Overall, the reviewed studies of active versus active OMBP strategies provide little information on comparative effectiveness and safety that is applicable to current clinical use. Further, there is reemerging interest in the use of oral antibiotics agents in bowel preparation. The majority of the included studies did not use oral antibiotics, but we deemed that this did not limit their applicability.

Limitations of the Evidence

On the basis of the reviewed studies, we believe that the evidence regarding OMBP for colorectal surgery is limited in the following ways:

- Most *studies enrolled small numbers of patients and reported low event rates for major clinical events* during followup. This led to imprecise study-specific results; for many outcomes substantial imprecision remained after combining evidence from most available published trials.
- Studies *did not report results for important clinical subgroups*, particularly those defined by anatomic location of surgery (colon versus rectal surgery) and the type of surgical procedure performed (e.g., open versus laparoscopic surgery).
- The *literature comparing alternative active OMBP strategies for colorectal strategy was fragmented* because studies used a large number of diverse preparation regimes and reported results for heterogeneous, often poorly defined, outcomes. It is not clear how

most of these map to current standard definitions of outcomes (e.g., CDC definitions for wound infections).

- *Nonrandomized trials, and particularly observational studies, could not effectively supplement the results of randomized trials* because exposure ascertainment was often not done in detail, analyses were not adjusted for or stratified by important patient-, disease-, or system-level characteristics, and methods to adequately control confounding bias were not consistently used.
- Studies, particularly those conducted in earlier years, typically did not report adequate information to *judge whether the outcome definitions of reported events matched currently recommended definitions* (e.g., those proposed by the Center’s for Disease Control and Prevention).

Ongoing Research

A search on May 15, 2013, in the ClinicalTrials.gov registry identified 11 potentially relevant records. After full text review, 6 records of studies that are expected to provide information relevant to the Key Questions of this report were identified. **Appendix D** summarizes information from these studies. None of these studies provided results in the ClinicalTrials.gov database at the time of this search.

Evidence Gaps

Table 8 summarizes the evidence gaps with regards to the two Key Questions of this systematic review.

Table 8: Evidence gaps

Key Question	Category	Evidence Gap
Comparative effectiveness of OMBP strategies	General	<ul style="list-style-type: none"> • There was substantial uncertainty regarding the effectiveness of OMBP versus enema or no preparation for patients undergoing colorectal surgery.
	Population	<ul style="list-style-type: none"> • Limited and incomplete information was available for patients undergoing elective rectal surgery • Very limited information is available for patients undergoing laparoscopic surgery
	Interventions & Comparators	<ul style="list-style-type: none"> • The optimal preparation regimen for patients undergoing elective colorectal surgery remains unclear • Potential interactions between OMBP regimens and cointerventions (e.g., enema, oral antibiotics) have not been explored adequately
	Outcomes	<ul style="list-style-type: none"> • Studies did not always use consistent outcome definition or did not provide adequate details on outcome ascertainment to reliably assess whether outcomes were “similar enough” across studies • Studies often heterogeneously and incompletely reported key clinical results, representing a “lost opportunity” for synthesis across studies
Adverse events of OMBP strategies	General	<ul style="list-style-type: none"> • Limited information was available for key adverse events of interest • Many adverse events have not been evaluated in trials comparing alternative active OMBP strategies
	Outcomes	<ul style="list-style-type: none"> • Limited information for specified outcomes across all investigated study designs • Nonrandomized studies did not offer
Adverse events in susceptible groups	General	<ul style="list-style-type: none"> • No studies provided information on the adverse events of OMBP in patient groups that may particularly susceptible [adults and children with cardiovascular or pulmonary disease, extremes of age (young children and the elderly), patients

who have undergone adjuvant chemotherapy or radiotherapy, and patients with diabetes, kidney disease, or compromised immune function (including drug-induced immunosuppression) who undergo elective colorectal surgery]]

OMBP = oral mechanical bowel preparation.

Future Research

This review identified major gaps in the published evidence on the comparative effectiveness and safety of OMBP for elective colorectal surgery. We believe that the following evidence gaps can be fruitful areas for future research:

- *RCTs to evaluate the comparative effectiveness of OMBP*: Given the uncertainty in meta-analytic estimates for most key clinical outcomes, a large, pragmatic RCT could substantially reduce uncertainty and definitively settle the main question. Conducting such a trial appears to be quite feasible, given the large number of elective colorectal surgeries performed annually, the relatively low cost of the interventions to be compared (OMBP, enema, no preparation), and that only a short-term followup (e.g., 30 days) is sufficient to assess almost all postsurgical outcomes of interest. Conducting such a trial in the U.S. may facilitate uptake of the findings in this country by mitigating concerns about applicability. Consideration should be given to factorial designs that can provide evidence on the comparative effectiveness of multiple interventions of interest (e.g., OMBP × enema × oral antibiotics). The study should be powered to evaluate major clinical outcomes including mortality and surgical site infections (using the latest CDC guidelines^a: superficial, deep incisional, organ/space). Of note, a single primary study is unlikely to reliably address all decisionmaking uncertainties for all populations of interest in isolation from existing evidence; for this reason plans should be in place for a prospective meta-analysis to combine the results of a new study with previously completed trials (if possible using patient-level data).
- *Conducting an individual patient data meta-analysis of existing trials of OMBP*: a consortium of investigators could perform such an analysis at much lower cost compared to a new trial. While it is unlikely that a reanalysis would result in more precise estimates, it would allow the opportunity to explore effects on subgroups for which no information is currently available (e.g., by anatomic location). By pooling existing datasets, an effort could be made to standardize outcome definitions and perform joint analyses for important subgroups of patients (e.g., colon versus rectal surgery). The results of such individual-patient data meta-analyses could be used to inform the design of future primary trials.
- *Eliciting patient preferences, developing decision aids (decision support tools), and conducting decision analyses*: Given the current uncertainty regarding the optimal preparation methods, and while additional data are awaited, clinical decisionmaking should be informed by patient preferences and values. Studies to elicit patient preferences can be conducted relatively inexpensively. Further, given the uncertainty on whether OMBP affects outcomes and the fact that it is at least an inconvenience, it is reasonable that decisionmaking on OMBP for colorectal surgery be shared between providers and patients and their loved ones. To inform and facilitate shared decisionmaking it is reasonable to develop decision aids. These are tools

^a Available at: <http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscscscurrent.pdf>; last accessed May 30, 2013.

for helping patients understand that a choice can be made and what their options are, appreciate the likelihood of the outcomes they most care about, and make a choice that is congruent with their values and preferences.⁹⁹

Finally, we also see a role for decision analysis models. These can be useful in at least two ways: first, they can inform the construction of decision aids by synthesizing evidence on effectiveness and adverse events with patient preferences. Second, they can be used in the design of the next large trial by using them as the basis for value-of-information analyses.

- *Conducting observational studies for the comparative effectiveness and harms of OMBP:* observational studies can inform the comparative effectiveness of alternative OMBP strategies, particularly for susceptible groups (e.g., patients with compromised function of major systems) that have not been represented in the RCTs thus far. Such studies should have large sample sizes (to account for the low incidence of most outcome events) chosen on the basis of prospective power analyses, include patients representative of those seen in clinical practice, and use strong methods to address confounding bias (e.g., propensity score or instrumental variable methods). Further, exposure assessment should include the collection of details regarding the preparation strategy (i.e., the OMBP regimen and any cointerventions) and outcome ascertainment should be done using standardized definitions for all outcomes of interest. Quantitative bias analyses could be used to address concerns regarding unobserved confounding in nonrandomized studies. Although the use of observational data always requires additional assumptions for valid inference on treatment effects (compared to randomized designs), well designed observational studies can offer valuable information both regarding the effectiveness and adverse effects of OMBP.

Conclusions

In summary, we found limited evidence to support or refute the use of OMBP for elective colorectal surgery. Studies comparing OMBP versus enema or no preparation provided insufficient or weak evidence regarding the comparative effectiveness of these interventions. Although differences between them were not statistically significant, confidence (or credibility) intervals around summary estimates could not exclude clinically significant effects for most outcomes. The large body of literature on alternative active OMBP strategies was largely irrelevant to current surgical decisionmaking because of the large number of diverse preparation strategies that have been compared in small, underpowered trials, reporting heterogeneous, and often poorly defined outcomes, the importance of which have not been agreed upon in the surgical community. Future studies, including pooled reanalyses of existing data, new comparative studies, elicitation of patient preferences, and decision modeling should be considered for obtaining definitive answers.

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Appendix C. Sensitivity Analysis for Pairwise Contrasts

Sensitivity analysis	Outcome	Comparison	N studies (N events / N patients, per group)	OR (95% CI); P value	Heterogeneity (P value; I ² %)
include Scabini, 2012	all cause mortality	OMBP +/- enema vs. no prep	9 (37 / 1973 vs. 39 / 1963)	0.90 (0.59, 1.48); P = 0.7783	P _Q = 0.7985; I ² = 0
	all cause mortality	OMBP +/- enema vs. enema	5 (11 / 646 vs. 6 / 654)	1.80 (0.64, 5.12); P = 0.2596	P _Q = 0.5989; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. no prep	9 (82 / 1968 vs. 93 / 1950)	0.90 (0.64, 1.20); P = 0.4124	P _Q = 0.6623; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. enema	5 (31 / 646 vs. 26 / 654)	1.20 (0.65, 2.23); P = 0.5511	P _Q = 0.3229; I ² = 14
	wound infection	OMBP +/- enema vs. no prep	10 (205 / 2014 vs. 182 / 2001)	1.10 (0.93, 1.42); P = 0.2036	P _Q = 0.6121; I ² = 0
	wound infection	OMBP +/- enema vs. enema	5 (59 / 646 vs. 55 / 654)	1.10 (0.65, 2.03); P = 0.6446	P _Q = 0.1051; I ² = 48
exclude Hughes, 1972	all cause mortality	OMBP +/- enema vs. no prep	8 (34 / 1927 vs. 37 / 1912)	0.90 (0.56, 1.45); P = 0.6605	P _Q = 0.7550; I ² = 0
	all cause mortality	OMBP +/- enema vs. enema	4 (7 / 526 vs. 4 / 530)	1.70 (0.45, 6.13); P = 0.4408	P _Q = 0.3206; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. no prep	9 (82 / 1968 vs. 93 / 1950)	0.90 (0.64, 1.20); P = 0.4124	P _Q = 0.6623; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. enema	4 (24 / 526 vs. 21 / 530)	1.20 (0.51, 2.64); P = 0.7146	P _Q = 0.2111; I ² = 34
	wound infection	OMBP +/- enema vs. no prep	9 (198 / 1968 vs. 172 / 1950)	1.20 (0.94, 1.46); P = 0.1570	P _Q = 0.5864; I ² = 0
	wound infection	OMBP +/- enema vs. enema	4 (48 / 526 vs. 49 / 530)	1.00 (0.53, 1.93); P = 0.9604	P _Q = 0.1099; I ² = 50
Exclude studies using selective enema strategies	all cause mortality	OMBP +/- enema vs. no prep	9 (37 / 1973 vs. 39 / 1963)	0.90 (0.59, 1.48); P = 0.7783	P _Q = 0.7985; I ² = 0
	all cause mortality	OMBP +/- enema vs. enema	2 (4 / 261 vs. 1 / 262)	4.10 (0.45, 36.98); P = 0.2107	NA (one study reported zero events)
	anastomotic leakage	OMBP +/- enema vs. no prep	9 (82 / 1968 vs. 93 / 1950)	0.90 (0.64, 1.20); P = 0.4124	P _Q = 0.6623; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. enema	2 (12 / 261 vs. 16 / 262)	0.70 (0.33, 1.70); P = 0.4861	P _Q = 0.3003; I ² = 7
	wound infection	OMBP +/- enema vs. no prep	10 (205 / 2014 vs. 182 / 2001)	1.10 (0.93, 1.42); P = 0.2036	P _Q = 0.6121; I ² = 0
	wound infection	OMBP +/- enema vs. enema	2 (26 / 261 vs. 35 / 262)	0.70 (0.39, 1.29); P = 0.2619	P _Q = 0.2826; I ² = 13
exclude the study enrolling children and adults	all cause mortality	OMBP +/- enema vs. no prep	8 (37 / 1901 vs. 39 / 1886)	0.90 (0.59, 1.48); P = 0.7783	P _Q = 0.7985; I ² = 0
	all cause mortality	OMBP +/- enema vs. enema	4 (7 / 526 vs. 4 / 530)	1.70 (0.45, 6.13); P = 0.4408	P _Q = 0.3206; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. no prep	8 (75 / 1896 vs. 89 / 1873)	0.80 (0.61, 1.15); P = 0.2685	P _Q = 0.7527; I ² = 0
	anastomotic leakage	OMBP +/- enema vs. enema	4 (24 / 526 vs. 21 / 530)	1.20 (0.51, 2.64); P = 0.7146	P _Q = 0.2111; I ² = 34
	wound infection	OMBP +/- enema vs. no prep	9 (188 / 1942 vs. 173 / 1924)	1.10 (0.88, 1.37); P = 0.4017	P _Q = 0.8160; I ² = 0
	wound infection	OMBP +/- enema vs. enema	4 (48 / 526 vs. 49 / 530)	1.00 (0.53, 1.93); P = 0.9604	P _Q = 0.1099; I ² = 50

Appendix D. List of Ongoing Studies

Clinical Trial Identifier	Study name	Status as of May 15, 2013	Availability of results	Population	Comparison
NCT01797770	Trial on Mechanical Bowel Preparation in Laparoscopic Colorectal Surgery	Recruiting	NA	colon and rectal cancer	OMBP vs. no preparation
NCT00687570	Bowel Preparation Before Rectal Cancer Surgery	Recruiting	NA	rectal cancer	OMBP vs. nutritional
NCT00940030	Comparison of Mechanical Bowel Preparation Versus Enema for Candidates to Colorectal Resection for Adenocarcinoma	Recruiting	NA	colorectal cancer	OMBP vs. enema
NCT00554892	Rectal Cancer Surgery Without Mechanical Bowel Preparation	Completed	NA	rectal cancer	OMBP + enema vs. enema
NCT00643084	Bowel Prep vs. Non-Bowel Prep for Laparoscopic Colorectal Surgery	Not yet recruiting	NA	colorectal surgery	OMBP vs. no preparation
NCT00618930	Moviprep Versus Fleet Phospho-Soda (Golden Standard): A Study That Compared Two Laxatives on Patients Undergoing Colo-Rectal Cleansing Prior to an Abdominal Operation	Completed	NA	colorectal surgery	Comparison of two laxatives

NA = not available; OMBP = oral mechanical bowel preparation.

Appendix A. Search Strategy

The following search strategy was utilized in PubMed:

((surgic* OR surgery OR surgeri* OR operativ* OR operation OR operations OR preoper* OR pre-oper* OR preoperative OR "surgery"[Subheading] OR "surgical procedures, operative"[MeSH]))

AND

("colorectal"[all fields] OR colon OR coloni* OR colore* OR recta* OR rectu* OR "colo-rectal" OR ((large) AND (bowel* OR intestin*)) OR "Intestine, Large"[Mesh] OR colon[mesh] OR rectum[mesh])) OR ("Colorectal Surgery"[Mesh]))

AND

(prepara* OR enema* OR cathartics[MeSH] OR cathartic* OR polyethylene glycols[MeSH] OR (polyethylene AND (glycol OR glycols)) OR phosphates[MeSH] OR phosphate* OR "Laxatives"[MeSH] OR laxative* OR "Senna Extract"[Mesh] OR (senna AND extract*) OR "Bisacodyl"[Mesh] OR "bisacodyl"[all fields] OR "Cascara"[Mesh] OR "cascara"[all fields] OR "Enema"[Mesh] OR "PEG"[all fields] OR "miralax"[all fields] OR "golytely"[all fields] OR "nulytely"[all fields] OR "halflytely"[all fields] OR "fleet"[all fields] OR "dulcolax"[all fields] OR "pico salax"[all fields])

The search strategy was translated for use in the Cochrane Central Register Of Controlled Trials, EMBASE, and CINAHL. Searches in these databases only included years 2010 to 2012 (because earlier years had been covered by the Cochrane Review by Guenaga et al., 2010).

Appendix B. List of Excluded Studies by Reason for Exclusion

Irrelevant

- Aarts, MA, Okrainec, A, Glicksman, A, *et al.* Adoption of enhanced recovery after surgery (ERAS) strategies for colorectal surgery at academic teaching hospitals and impact on total length of hospital stay. *Surg Endosc* 2012 Feb; 26(2): 442-450.[PMID: 22011937]
- Alves, A, Panis, Y, Bouhnik, Y, *et al.* Factors that predict conversion in 69 consecutive patients undergoing laparoscopic ileocecal resection for Crohn's disease: a prospective study. *Dis Colon Rectum* 2005 Dec; 48(12): 2302-2308.[PMID: 16228824]
- Ameh, EA, Lukong, CS, Mshelbwala, PM, *et al.* One-day bowel preparation in children with colostomy using normal saline. *Afr J Paediatr Surg* 2011 Sep-Dec; 8(3): 291-293.[PMID: 22248892]
- Andersen, J, Christensen, H, Pachler, JH, *et al.* Effect of the laxative magnesium oxide on gastrointestinal functional recovery in fast-track colonic resection: a double-blind, placebo-controlled randomized study. *Colorectal Dis* 2012 Jun; 14(6): 776-782.[PMID: 21883811]
- Andersen, J, Thorup, J, & Wille-Jorgensen, P. Use of preoperative bowel preparation in elective colorectal surgery in Denmark remains high. *Dan Med Bull* 2011 Sep; 58(9): A4313.[PMID: 21893013]
- Anthony, T, Murray, BW, Sum-Ping, JT, *et al.* Evaluating an evidence-based bundle for preventing surgical site infection: a randomized trial. *Arch Surg* 2011 Mar; 146(3): 263-269.[PMID: 21079110]
- Bakker, IS, Morks, AN, Hoedemaker, HO, *et al.* The C-seal trial: colorectal anastomosis protected by a biodegradable drain fixed to the anastomosis by a circular stapler, a multi-center randomized controlled trial. *BMC Surg* 2012; 12: 23.[PMID: 23153188]
- Barbuscia, M, Melita, G, Trovato, M, *et al.* Nosocomial infections in colo-rectal surgery of the old patient. *Acta Biomed* 2005; 76 Suppl 1: 16-20.[PMID: 16450501]
- Barisic, G, Krivokapic, Z, Markovic, V, *et al.* The role of overlapping sphincteroplasty in traumatic fecal incontinence. *Acta Chir Iugosl* 2000; 47(4 Suppl 1): 37-41.[PMID: 11432241]
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