

# Meta-analysis of oral antibiotics, in combination with preoperative intravenous antibiotics and mechanical bowel preparation the day before surgery, compared with intravenous antibiotics and mechanical bowel preparation alone to reduce surgical-site infections in elective colorectal surgery

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**Background:** Surgical-site infection (SSI) is a potentially serious complication following colorectal surgery. The present systematic review and meta-analysis aimed to investigate the effect of preoperative oral antibiotics and mechanical bowel preparation (MBP) on SSI rates.

**Methods:** A systematic review of PubMed, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials was performed using appropriate keywords. Included were RCTs and observational studies reporting rates of SSI following elective colorectal surgery, in patients given preoperative oral antibiotic prophylaxis, in combination with intravenous (i.v.) antibiotic prophylaxis and MBP, compared with patients given only i.v. antibiotic prophylaxis with MBP. A meta-analysis was undertaken.

**Results:** Twenty-two studies (57 207 patients) were included, of which 14 were RCTs and eight observational studies. Preoperative oral antibiotics, in combination with i.v. antibiotics and MBP, were associated with significantly lower rates of SSI than combined i.v. antibiotics and MBP in RCTs (odds ratio (OR) 0.45, 95 per cent c.i. 0.34 to 0.59;  $P < 0.001$ ) and cohort studies (OR 0.47, 0.44 to 0.50;  $P < 0.001$ ). There was a similarly significant effect on SSI with use of a combination of preoperative oral aminoglycoside and erythromycin (OR 0.40, 0.25 to 0.64;  $P < 0.001$ ), or preoperative oral aminoglycoside and metronidazole (OR 0.51, 0.39 to 0.68;  $P < 0.001$ ). Preoperative oral antibiotics were significantly associated with reduced postoperative rates of anastomotic leak, ileus, reoperation, readmission and mortality in the cohort studies.

**Conclusion:** Oral antibiotic prophylaxis, in combination with MBP and i.v. antibiotics, is superior to MBP and i.v. antibiotic prophylaxis alone in reducing SSI in elective colorectal surgery.

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## Introduction

Surgical-site infection (SSI) is a challenging problem following colorectal surgery. SSI can be separated into superficial and deep components, and is reported routinely until 30 days after surgery. SSI represents not only a costly expense to health services, but more importantly influences patient recovery and survival<sup>1</sup>.

Various strategies have been adopted in attempts to reduce postoperative SSI rates. Mechanical bowel preparation (MBP) alone has been shown in large data sets to have

no influence on SSI<sup>2</sup>. The value of i.v. antibiotics in the immediate preoperative period is clearly established and they are currently used worldwide, with or without MBP<sup>3</sup>. Advocates of preoperative antibiotics believe that cleansing of intestinal flora influences rates of subsequent infection. Controversy remains regarding the use of short-course oral antibiotics in the preoperative setting; although use of oral antibiotics in combination with MBP is a strategy employed widely in North America<sup>4</sup>, it remains much less common across Europe. The reasons for avoidance of

MBP in Europe are multifactorial, but the trend towards enhanced recovery after surgery (ERAS) protocols that exclude routine MBP is probably a significant contributor<sup>5</sup>. Concerns regarding hospital-acquired infections including *Clostridium difficile* are relevant only when patients are exposed to extended bowel-cleansing protocols<sup>6</sup>. The aim of this review was to assess only trials that included 1 day of preoperative antibiotics, and all trials assessing longer periods of preoperative antibiotic exposure were excluded.

Although the evidence for and against MBP can be debated, guidelines clearly state that there is no strong evidence for its use alone<sup>7</sup>. Evidence exists that suggests that its use in addition to oral antibiotics as part of a bowel-cleansing protocol is beneficial with respect to SSI<sup>4</sup>. The impact of the use of oral antibiotics in the absence of MBP with regard to SSI has not been established. Antibiotics are thought to have little influence in this context because of the faecal content present.

The value of employing different regimens of oral antibiotics has also not been clearly established. Most trials have used the combination of an aminoglycoside (neomycin or kanamycin) with a macrolide such as erythromycin or with metronidazole.

The aim of the present study was to examine the impact of oral antibiotics and MBP given on the day before operation, in combination with i.v. antibiotic prophylaxis at induction of anaesthesia, on rates of SSI following elective colorectal surgery. Secondary outcome measures included anastomotic leak, reoperation, duration of hospital stay, readmission and mortality. RCTs and observational studies that have assessed the role of preoperative oral antibiotics in the reduction of SSI in colorectal surgery were considered for inclusion, with the aim of determining the value of employing this preoperative strategy and to assess the best antibiotic combination available.

## Methods

The systematic review and meta-analysis was performed and reported in accordance with the PRISMA statement<sup>8</sup>.

## Outcomes of interest

The primary outcome was the impact of preoperative oral antibiotic prophylaxis given the day before surgery, in combination with i.v. antibiotic prophylaxis and MBP, compared with that in patients given only i.v. antibiotic prophylaxis with MBP, on rates of SSI following elective colorectal surgery. Secondary outcomes included: the impact of preoperative antibiotic prophylaxis on organ space SSI, anastomotic leak, postoperative ileus, unplanned return to the

operating theatre, readmission and mortality. Postoperative SSI, anastomotic leak, ileus, return to theatre, readmission and mortality were recorded as categorized by the authors of the included studies.

## Literature search and study selection

A systematic literature review was undertaken of PubMed, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials from inception to March 2017 inclusive. Combinations of the following search terms were used; [title/abstract]: (colorectal OR colon OR rectal OR colonic OR rectum) AND (surgery OR operation) AND (antibiotic OR antimicrobial). Abstracts were screened for relevance. Animal or preclinical studies, studies not published in English and review articles were excluded. Included were RCTs and observational studies reporting rates of SSI following elective colorectal surgery in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, compared with those in patients given only i.v. antibiotic prophylaxis with MBP. Studies reporting prolonged preoperative oral antibiotic regimens, without the use of MBP in both groups, without i.v. antibiotic prophylaxis in both groups, and including patients undergoing emergency surgery, were excluded. Relevant full-text articles were then appraised. Reference lists of included studies were hand-searched for further relevant studies. Two authors performed study selection and data extraction, and any uncertainties were resolved by consensus discussion with the senior author.

## Data extraction and meta-analysis

Data were extracted and analysis performed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Odds ratios (ORs) and 95 per cent confidence intervals were calculated from the total number of patients and the number of events within each group. Meta-analysis of the impact of preoperative oral antibiotics on SSI, anastomotic leak, reoperation, readmission and mortality rates was carried out using the Mantel–Haenszel method. Meta-analysis of the impact of preoperative oral antibiotics on postoperative length of hospital stay was done by calculating the mean difference and 95 per cent confidence interval using the inverse-variance method. Where data other than means and standard deviations were reported, an attempt was made to calculate these values using published confidence intervals or *P* values, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>9</sup>, or by Wan and

colleagues<sup>10</sup>. A fixed-effects model was used unless there was significant evidence of heterogeneity when quantified using the  $I^2$  statistic, in which case a random-effects model was used. The significance of the overall effect was determined using the  $Z$  test.  $P \leq 0.050$  was considered statistically significant.

### Assessment of bias

Assessment of the risk of bias was carried out using the Cochrane Collaboration tool provided by Review Manager version 5.3. Data were assessed for heterogeneity using the  $I^2$  statistic, with guidance from the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>9</sup>. A prespecified sensitivity analysis was undertaken by estimating the treatment effect size only in double-blind RCTs, and comparing this with the overall results. Assessment of potential publication bias was carried out by visual inspection of funnel plots.

## Results

### Study selection

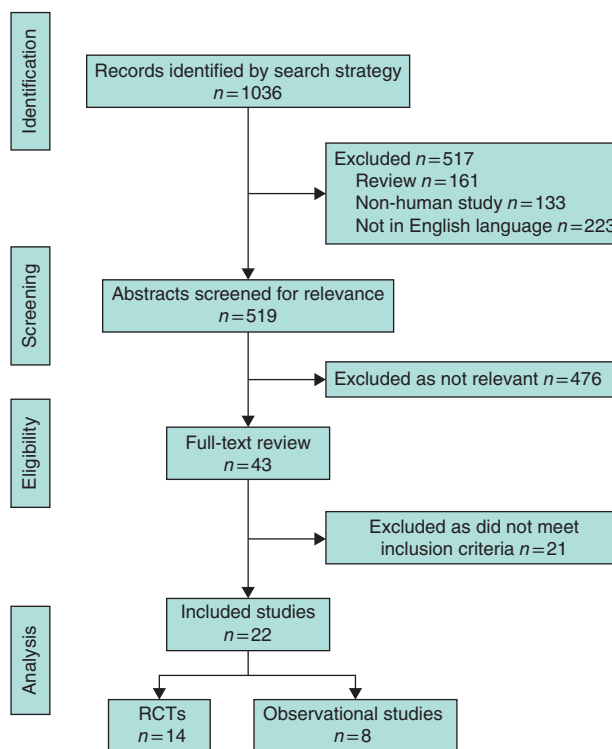
The study selection process is summarized in *Fig. 1*. Some 1036 abstracts were identified. At screening, 517 were excluded, of which 133 were animal or preclinical studies, 223 were not in the English language, 161 were review articles and 476 were not relevant to the review. After assessment of full-text articles of the remaining 43 studies, 18 studies were excluded owing to the lack of MBP, prolonged courses of preoperative oral antibiotics, or the inclusion of patients undergoing emergency or urgent surgery. A further three studies were excluded as they were duplicate publications using cohorts already included in the meta-analysis<sup>11–13</sup>. The remaining 22 studies were included in the review, of which 14 were RCTs<sup>14–27</sup>, and eight were observational cohorts<sup>2,4,28–33</sup> (*Table 1*; *Table S1*, supporting information). These studies included a total of 57 207 patients.

### Validity assessment

The risk of study bias is summarized in *Fig. S1* (supporting information). Of the included RCTs, five<sup>14,16,18,20,22</sup> were double-blinded, three<sup>15,17,23</sup> were single-blinded, and the remainder were unblinded. Most of the included cohort studies were at low risk of bias.

### Rates of all SSIs following colorectal surgery

In the 14 RCTs<sup>14–27</sup>, involving 3014 patients, rates of SSI in patients given preoperative oral antibiotic prophylaxis,



**Fig. 1** PRISMA flow chart showing selection of articles for review

in combination with i.v. antibiotic prophylaxis and MBP, were compared with those in patients who received only i.v. antibiotic prophylaxis with MBP (*Fig. 2*). There was minimal heterogeneity between studies ( $I^2 = 12$  per cent,  $P = 0.33$ ) and therefore a fixed-effect model was used. Preoperative oral antibiotics were significantly associated with lower rates of SSI (OR 0.45, 95 per cent c.i. 0.34 to 0.59;  $P < 0.001$ ).

Eight cohort studies<sup>2,4,28–33</sup>, including 54 193 patients, compared rates of SSI in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, with those in patients given only i.v. antibiotic prophylaxis with MBP (*Fig. 2*). There was moderate heterogeneity between studies ( $I^2 = 48$  per cent,  $P = 0.06$ ) and therefore a fixed-effect model was used. Preoperative oral antibiotics were significantly associated with lower rates of SSI (OR 0.47, 0.44 to 0.50;  $P < 0.001$ ).

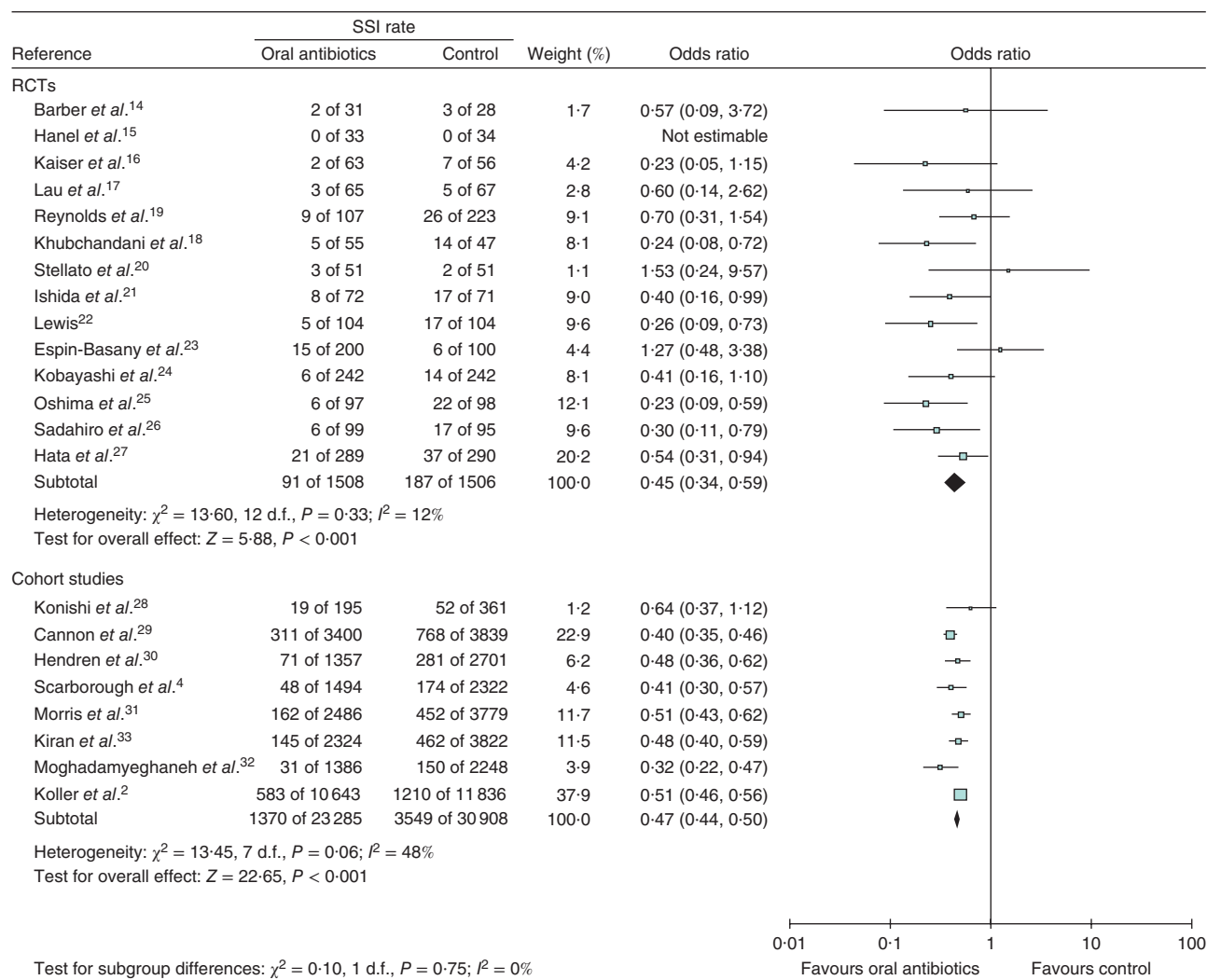
### Impact of oral antibiotic combination on overall SSI rates

Seven RCTs<sup>14,16–18,20,21,24</sup>, involving 1141 patients, examined rates of SSI in patients given a preoperative oral combination of an oral aminoglycoside (kanamycin or neomycin) and erythromycin, along with i.v. antibiotic

Table 1 Characteristics of included studies

Reference	Type of study	Placebo	Oral antibiotic combination	Intravenous antibiotic	MBP	SSI criteria	Secondary outcomes
Barber <i>et al.</i> <sup>14</sup>	RCT	Yes	Neomycin + erythromycin	Clindamycin + gentamicin	Magnesium citrate	Custom	–
Hanel <i>et al.</i> <sup>15</sup>	RCT	No	1 g neomycin × 6 + 200 mg metronidazole × 16	Clindamycin + cefazolin	Clear fluids for 4 days	Custom	–
Kaiser <i>et al.</i> <sup>16</sup>	RCT	Yes	1 g neomycin + 1 g erythromycin × 3	2 g cefoxitin or 1 g cefazolin × 1	Magnesium citrate	Custom	–
Lau <i>et al.</i> <sup>17</sup>	RCT	No	1 g neomycin + 1 g erythromycin × 3	500 mg metronidazole + 2 mg/kg gentamicin × 3	Bisacodyl + magnesium citrate	Lungqvist criteria	Organ space SSI, leak, LOS
Khubchandani <i>et al.</i> <sup>18</sup>	RCT	No	1 g neomycin + 1 g erythromycin × 3	1 g cefazolin + 1 g metronidazole × 3	Castor oil	Custom	Leak
Reynolds <i>et al.</i> <sup>19</sup>	RCT	No	Neomycin + metronidazole	n.r.	n.r.	Custom	–
Stellato <i>et al.</i> <sup>20</sup>	RCT	No	1 g neomycin + 1 g erythromycin × 1	2 g cefoxitin × 1	Magnesium citrate + sodium phosphate	Custom	–
Ishida <i>et al.</i> <sup>21</sup>	RCT	No	500 mg kanamycin + 400 mg erythromycin × 8	1 g cefotiam × 6	PEG	CDC	Organ space SSI, leak
Lewis <sup>22</sup>	RCT	Yes	2 g neomycin + 2 g metronidazole × 2	1 g amikacin + 1 g metronidazole × 1	Sodium phosphate	CDC	Organ space SSI, leak
Espin-Basany <i>et al.</i> <sup>23</sup>	RCT	No	1 g neomycin + 1 g metronidazole × 3	1 g cefoxitin × 3	Sodium phosphate	CDC	Organ space SSI, ileus
Kobayashi <i>et al.</i> <sup>24</sup>	RCT	No	1 g kanamycin + 400 mg erythromycin × 3	1 g cefmetazole × 1	PEG	CDC	–
Oshima <i>et al.</i> <sup>25</sup>	RCT	No	500 mg kanamycin + 500 mg metronidazole × 3	1 g flomoxef	Magnesium citrate	NNIS	Organ space SSI
Sadahiro <i>et al.</i> <sup>26</sup>	RCT	No	500 mg kanamycin + 500 mg metronidazole × 3	1 g flomoxef × 1	Sodium bicosulphate + PEG	Custom	Organ space SSI, leak
Hata <i>et al.</i> <sup>27</sup>	RCT	No	1 g kanamycin + 750 mg metronidazole × 2	1 g cefmetazole × 1	Sodium picosulphate + magnesium citrate	CDC	Organ space SSI, leak, ileus
Konishi <i>et al.</i> <sup>28</sup>	Cohort	n.a.	Kanamycin + metronidazole	Second-generation cephalosporin		NNIS	–
Cannon <i>et al.</i> <sup>29</sup>	Cohort	n.a.	n.r.	n.r.	PEG, sodium phosphate or magnesium citrate	VASQIP	–
Hendren <i>et al.</i> <sup>30</sup>	Cohort	n.a.	n.r.	n.r.	n.r.	ACS NSQIP	–
Morris <i>et al.</i> <sup>31</sup>	Cohort	n.a.	n.r.	n.r.	n.r.	Custom	Organ space SSI, leak, ileus, reoperation, LOS, readmission, mortality
Scarborough <i>et al.</i> <sup>4</sup>	Cohort	n.a.	n.r.	n.r.	n.r.	ACS NSQIP	Leak, LOS, readmission, mortality
Moghadamyeghaneh <i>et al.</i> <sup>32</sup>	Cohort	n.a.	n.r.	n.r.	n.r.	ICD-9	Organ space SSI, leak, reoperation, LOS, mortality
Kiran <i>et al.</i> <sup>33</sup>	Cohort	n.a.	n.r.	n.r.	n.r.	ACS NSQIP	Organ space SSI, leak, ileus, readmission, reoperation, mortality
Koller <i>et al.</i> <sup>2</sup>	Cohort	n.a.	n.r.	n.r.	n.r.	ACS NSQIP	Organ space SSI, leak, ileus, reoperation, LOS, readmission, mortality

MBP, mechanical bowel preparation; SSI, surgical-site infection; LOS, length of hospital stay; n.r., not recorded; PEG, polyethylene glycol; CDC, Centers for Disease Control and Prevention; NNIS, National Nosocomial Infections Surveillance system; n.a., not applicable; VASQIP, Veterans Affairs Surgical Quality Improvement Program; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program.



**Fig. 2** Forest plot of studies that used preoperative oral antibiotics the day before colorectal surgery to prevent surgical-site infection (SSI). A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

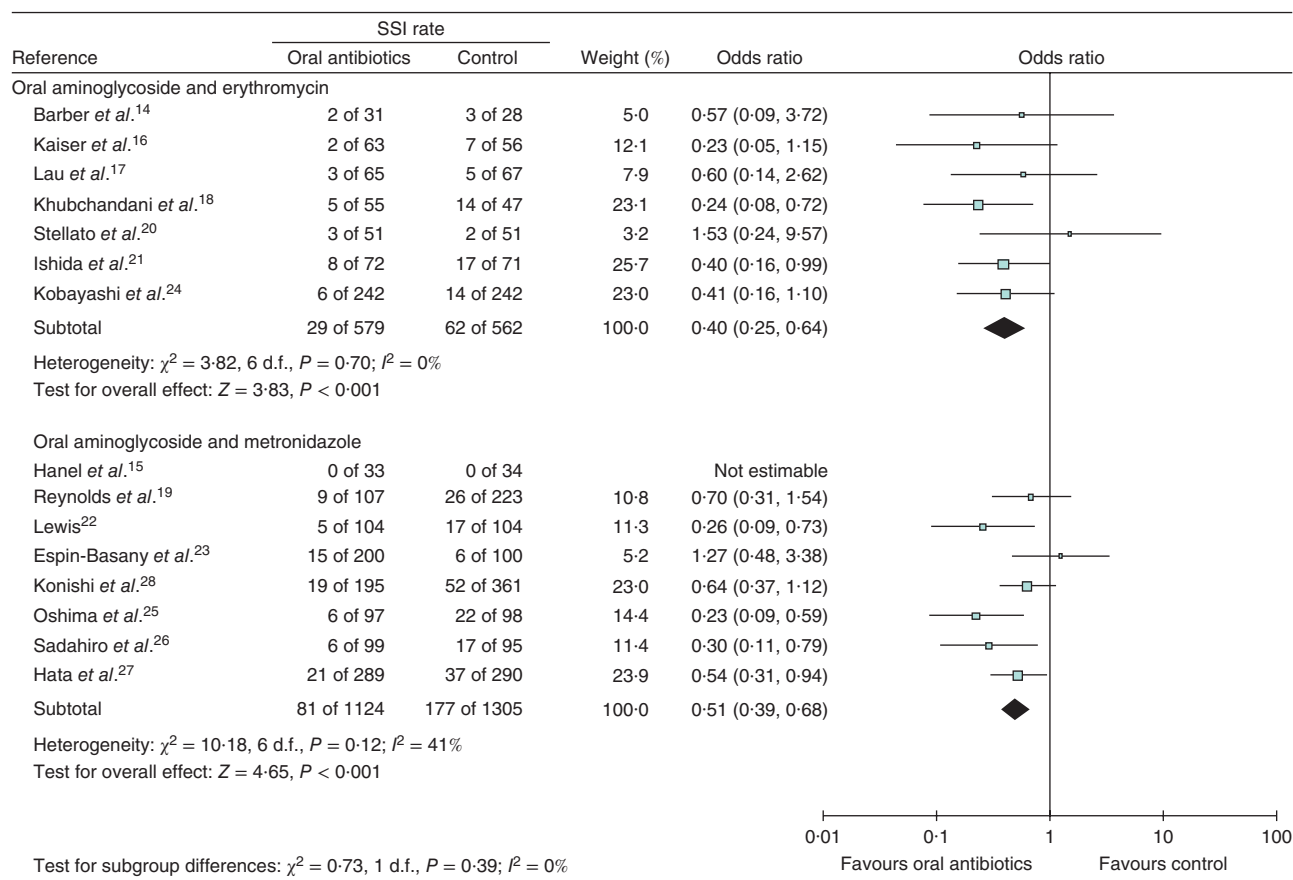
prophylaxis and MBP, in comparison with patients who received only i.v. antibiotic prophylaxis and MBP (Fig. 3). There was no heterogeneity between the studies ( $I^2 = 0$  per cent,  $P = 0.70$ ) so a fixed-effects model was used. The combination of preoperative oral aminoglycoside and erythromycin was associated with significantly lower rates of SSI (OR 0.40, 95 per cent c.i. 0.25 to 0.64;  $P < 0.001$ ).

Seven RCTs<sup>15,19,22,23,25–27</sup> and one cohort study<sup>28</sup>, involving 2429 patients, examined rates of SSI in patients who received a preoperative oral combination of an oral aminoglycoside (kanamycin or neomycin) and metronidazole, along with i.v. antibiotic prophylaxis and MBP, in comparison with patients given only i.v. antibiotic prophylaxis and MBP (Fig. 3). There was moderate heterogeneity between studies ( $I^2 = 41$  per cent,  $P = 0.12$ ) and therefore

a fixed-effects model was used. The combination of preoperative oral aminoglycoside and metronidazole was associated with significantly lower rates of SSI (OR 0.51, 0.39 to 0.68;  $P < 0.001$ ).

### Preoperative oral antibiotics and organ space SSI

Seven RCTs<sup>17,21–23,25–27</sup>, involving 1656 patients, examined rates of organ space SSI in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, compared with those in patients given only i.v. antibiotic prophylaxis with MBP. There was minimal heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 1.00$ ), so a fixed-effects model was used. There was no significant association between preoperative oral



**Fig. 3** Forest plot of studies that used preoperative oral aminoglycoside and either erythromycin or metronidazole the day before colorectal surgery to prevent surgical-site infection (SSI). A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

antibiotics and rates of organ space SSI (OR 0.76, 95 per cent c.i. 0.44 to 1.31;  $P = 0.32$ ).

Four cohort studies<sup>2,31–33</sup>, including 38 524 patients, compared rates of organ space SSI in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, with those in patients given only i.v. antibiotic prophylaxis and MBP. There was minimal heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.99$ ) so a fixed-effects model was used. Preoperative oral antibiotics were associated with significantly lower rates of organ space SSI (OR 0.58, 0.52 to 0.66;  $P < 0.001$ ).

### Preoperative oral antibiotics and anastomotic leak

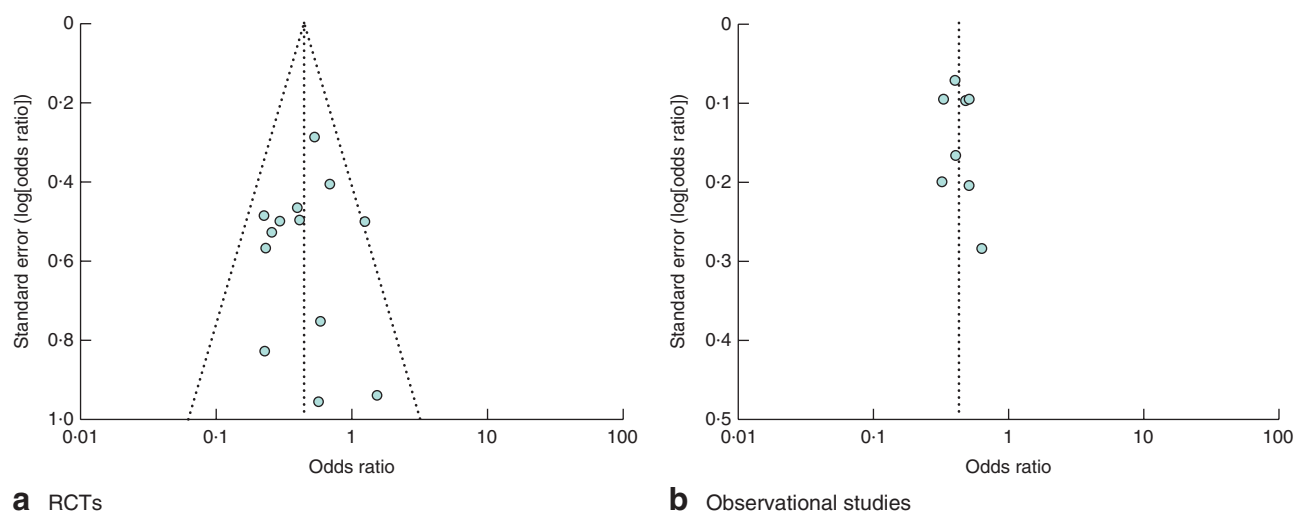
Six RCTs<sup>17,18,21,22,26,27</sup>, involving 1417 patients, examined rates of anastomotic leak in patients undergoing colorectal surgery who were given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, and in those who received only i.v. antibiotic prophylaxis with MBP. There was minimal heterogeneity

between studies ( $I^2 = 0$  per cent,  $P = 0.50$ ); therefore, a fixed-effects model was used. There was no significant association between preoperative oral antibiotics and anastomotic leak (OR 0.62, 95 per cent c.i. 0.30 to 1.28;  $P = 0.19$ ).

Five cohort studies<sup>2,4,31–33</sup> involving 42 329 patients, examined rates of anastomotic leak in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, compared with those in patients given only i.v. antibiotic prophylaxis with MBP. There was minimal heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.75$ ), so a fixed-effects model was used. Preoperative oral antibiotics were associated with significantly lower rates of anastomotic leak (OR 0.59, 0.53 to 0.67;  $P < 0.001$ ).

### Preoperative oral antibiotics and paralytic ileus

Two RCTs<sup>23,27</sup>, with 779 patients, examined rates of postoperative ileus in patients given preoperative oral antibiotic



**Fig. 4** Funnel plot of **a** all RCTs and **b** all cohort studies investigating use of oral antibiotics the day before colorectal surgery to prevent surgical-site infection

prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, and in those given only intravenous antibiotic prophylaxis with MBP. There was significant heterogeneity between studies ( $I^2 = 53$  per cent,  $P = 0.15$ ), so a random-effects model was used. There was no significant association between preoperative oral antibiotics and rates of paralytic ileus (OR 0.61, 95 per cent c.i. 0.11 to 3.38;  $P = 0.57$ ).

In three cohort studies<sup>2,31,33</sup>, involving 34 872 patients, rates of postoperative ileus in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, were compared with those in patients who received only intravenous antibiotic prophylaxis with MBP. There was minimal heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.63$ ); therefore, a fixed-effects model was used. Preoperative oral antibiotics were associated with a significantly lower rate of paralytic ileus (OR 0.78, 0.72 to 0.83;  $P < 0.001$ ).

### Preoperative oral antibiotics and unplanned reoperation

Four cohort studies<sup>2,31–33</sup>, including 38 524 patients, examined rates of unplanned reoperation in patients undergoing colorectal surgery who received preoperative oral antibiotic prophylaxis, in combination with intravenous antibiotic prophylaxis and MBP, compared with rates among patients given only i.v. antibiotic prophylaxis with MBP. There was no heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.89$ ), so a fixed-effects model was used. Preoperative oral antibiotics were associated with significantly lower rates of unplanned reoperation (OR 0.72, 95 per cent c.i. 0.65 to 0.80;  $P < 0.001$ ).

### Preoperative oral antibiotics and length of hospital stay following colorectal surgery

A single RCT<sup>17</sup> with 132 patients compared postoperative length of hospital stay in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, with that in patients who received only i.v. antibiotic prophylaxis with MBP. There was no significant association between preoperative oral antibiotics and length of stay: mean difference 0.3 (95 per cent c.i. –1.6 to 2.2) days ( $P = 0.76$ ).

Three cohort studies<sup>2,4,31</sup>, involving 32 662 patients, compared postoperative length of stay in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, with that among patients given only i.v. antibiotic prophylaxis with MBP. There was significant heterogeneity between studies ( $I^2 = 97$  per cent,  $P < 0.001$ ); therefore, a random-effects model was used. Preoperative oral antibiotics were associated with a significantly shorter hospital stay: mean difference –0.6 (–1.0 to –0.3) days ( $P = 0.001$ ). In addition, one cohort study<sup>32</sup> reported that a significantly lower proportion of patients receiving combination oral antibiotics and MBP had a hospital stay of more than 30 days compared with patients who received MBP alone.

### Preoperative oral antibiotics and readmission rates

Four cohort studies<sup>2,4,31,33</sup>, involving 38 808 patients, examined rates of unplanned readmission in patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, and among those

who received only i.v. antibiotic prophylaxis with MBP. There was no heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.78$ ), so a fixed-effects model was used. Preoperative oral antibiotics were associated with significantly lower rates of unplanned readmission (OR 0.87, 95 per cent c.i. 0.81 to 0.93;  $P < 0.001$ ).

### Preoperative oral antibiotics and mortality following colorectal surgery

Five cohort studies<sup>2,4,31–33</sup>, involving 42 341 patients, compared postoperative mortality rates between patients given preoperative oral antibiotic prophylaxis, in combination with i.v. antibiotic prophylaxis and MBP, and those given only i.v. antibiotic prophylaxis with MBP. There was no heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.78$ ), so a fixed-effects model was used. Preoperative oral antibiotics were associated with significantly lower postoperative mortality rates (OR 0.65, 95 per cent c.i. 0.50 to 0.83;  $P < 0.001$ ).

### Sensitivity analysis

A sensitivity analysis was undertaken, with only RCTs that employed double-blinding used in the meta-analysis<sup>14,16,18,20,22</sup>. There was minimal heterogeneity between studies ( $I^2 = 0$  per cent,  $P = 0.44$ ), and therefore a fixed-effect model was used. Preoperative oral antibiotics were significantly associated with lower rates of SSI, with an odds ratio similar to that of the earlier analysis of all included RCTs (OR 0.33, 95 per cent c.i. 0.18 to 0.59;  $P < 0.001$ ).

### Assessment of publication bias

Visual assessment of funnel plots of the included RCTs and cohort studies with regard to reporting of all SSIs suggested no evidence of publication bias (*Fig. 4*). No data point was generated for Hanel and colleagues<sup>15</sup> as no events occurred in either arm.

## Discussion

The present systematic review and meta-analysis suggest that preoperative oral antibiotic prophylaxis, in combination with mechanical bowel preparation and i.v. antibiotic prophylaxis, was associated with a significant reduction in rates of SSI in elective colorectal surgery. In addition, preoperative oral antibiotics were associated with lower rates of organ space SSI, anastomotic leak, paralytic ileus, unplanned reoperation, unplanned readmission and postoperative mortality when cohort studies were considered.

These findings are in keeping with a previous meta-analysis<sup>34</sup> investigating the impact of preoperative oral antibiotics on SSI in colorectal surgery, although it included patients who had received preoperative oral antibiotics for prolonged periods, patients who did not receive i.v. antibiotic prophylaxis, and those who did not receive MBP in combination with oral antibiotics. Koulouros and colleagues<sup>34</sup> also reported only on rates of postoperative SSI, whereas the present meta-analysis considered other outcomes of clinical significance whenever they were available, including anastomotic leak, unplanned reoperation and postoperative mortality.

At present, in the USA and Canada, around 40 per cent of patients are given oral antibiotics in combination with MBP<sup>6</sup>. The combination of oral neomycin and erythromycin has been recommended for use as preoperative antibiotic prophylaxis for colorectal surgery in an advisory statement from the Medicare National Surgical Infection Prevention Project<sup>35</sup>. Outside North America, this figure is much lower. Many centres in the UK and Europe have largely moved away from the routine use of MBP in elective colorectal surgery as ERAS and fast-track perioperative care protocols have become the standard of care. There are limited data on the value of using preoperative oral antibiotics in the unprepared colon, with one cohort study<sup>4</sup> finding no benefit, and a further two studies<sup>2,29</sup> reporting a reduction in SSI rates.

Based on the findings of the present meta-analysis, it appears that, as long as one drug in the preoperative combination is an aminoglycoside (kanamycin or neomycin), then combination with either metronidazole or erythromycin has equivalent efficacy in reducing SSI. There are some pharmacological considerations that suggest metronidazole should be the favoured agent in combination with an aminoglycoside in preoperative antibiotic protocols. Erythromycin is a cytochrome P450 inhibitor and the likelihood of drug interactions is greater. Furthermore, erythromycin may also prolong the QT interval and caution is advised regarding its routine use in patients with pre-existing cardiac disease.

The treatment effect size with regard to the reported postoperative outcomes was generally large. It is perhaps surprising that a single day of preoperative oral antibiotics has such a significant and wide-ranging impact. Other related factors may be relevant, including methodological issues, such as variations in systems used to define and record SSI in RCTs, diagnostic coding used to analyse large observational studies, as well as many clinical factors such as case mix, complexity, operative techniques, co-morbidities and compliance with preoperative preparation instructions. This effect size was, however, in keeping with the review of



Koullouros and colleagues<sup>34</sup>, which had less stringent entry criteria. An important limitation in the present analysis was variation in the exact type of MBP used, particularly in the cohort studies, which often did not report the exact nature or timing of bowel preparation. In addition, there were variations in the definition of SSI and other complications.

Oral antibiotic prophylaxis, in combination with MBP and i.v. antibiotics, was superior to MBP and i.v. antibiotic prophylaxis alone in reducing SSI after elective colorectal resections. This treatment approach was also associated with significantly lower rates of anastomotic leak, ileus, reoperation, length of stay, readmission and mortality. There was no association between the combination of antibiotics and outcome, as long as an aminoglycoside was included. Aminoglycosides administered orally reach very low levels in the circulation<sup>35</sup>, and toxicity is vanishingly rare. It is suggested that future ERAS protocols should factor in a combination of MBP and short-course oral antibiotic prophylaxis with an aminoglycoside and metronidazole, and i.v. antibiotic prophylaxis at induction of anaesthesia.

### Acknowledgements

This study was not preregistered in an independent institutional database.

*Disclosure:* The authors declare no conflict of interest.

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### Supporting information

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