National Institute for Health and Care Excellence

Final

Diverticular disease: diagnosis and management

[D] Evidence review for management of diverticular disease

NICE guideline NG147

Intervention evidence review

November 2019

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the most clinically and cost-effective treatment for diverticular disease?

1.2 Introduction

This review evaluates the evidence for treatment options for diverticular disease. These treatment options could be non-pharmacological treatments such as dietary advice or lifestyle changes or could include pharmacological treatment such as analgesia, aminosalicylates and antibiotics. The aim of these treatments would be to reduce the symptoms of diverticular disease.

Patients with diverticular disease are generally given dietary advice to increase fibre intake, maintain an adequate fluid intake and maybe avoid certain types of food. The aim of this question was to evaluate the evidence behind these common recommendations. There are currently no medicines routinely used to treat diverticular disease other than potentially recommending bulk forming laxatives if a high fibre diet is insufficient symptom control. Symptoms of diverticular disease often include abdominal pain and analgesia such as paracetamol may be recommended. Generally patients with diverticular disease are advised to avoid nonsteroidal anti-inflammatories and opioid based pain killers. This question also aimed to determine if there is any evidence for any pharmacological treatments in the management of diverticular disease.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults aged18 years and over with diverticular disease
Interventions	• High fibre diet (soluble and insoluble fibre) • Low fibre diet • Any dietary advice • Laxatives • Oral fluids • Antibiotics • Analgesia (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], opiates, nefopam) • Antispasmodics • Aminosalicylates • Probiotics and prebiotics
Comparisons	• Each other • No treatment • Placebo • Dosing studies

Outcomes	Critical outcomes:
	• Progression of disease
	  ○ Acute diverticulitis
	  ○ Hospitalisation
	  ○ Need for surgery
	  ○ Complications (infections, abscesses, perforation)

	• Symptom control (pain relief, bowel habit) • Quality of life Important outcomes: • Mortality • Side effects of: ○ Antibiotics: nausea and vomiting, diarrhoea, infections related to antibiotics ○ Analgesics: nausea and vomiting, constipation
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies Confounders: • Age • Gender

1.4 Clinical evidence

1.4.1 Included studies

Fourteen studies were included in the review[1,4,10,11,20,23,24,26,28,32,36,37,43,56]; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix H.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Annibale 2011[1]	**Symbiotic (1 sachet).** Twice daily 1 sachet of the symbiotic preparation for the first 14 days each month. n=18 **Symbiotic (2 sachets).** Twice daily 2 sachets of the symbiotic preparation for the first 14 days each month. n=16 **Control group.** Control group received no symbiotic. n=16	Outpatients with a well-established diagnosis of SUDD, defined as the presence of colonic diverticula associated with abdominal symptoms (pain and/or bloating) for at least 6 months before recruitment. Mean age: 65.2±8.1 Italy	• Symptoms (pain) Followed up at: 12 months	All patients were encouraged to follow a high-fibre diet containing at least a daily intake of 30 g diet fibre as well as a daily water intake of at least 1.5 L.

Study	Intervention and comparison	Population	Outcomes	Comments
Brodribb 1977[4]	**High fibre diet.** Bran crispbread supplying 6.7g of dietary fibre. n=9 **Placebo**. Wheat crispbread supplying 0.6g of dietary fibre. n=9	People referred from a gastroenterological clinic with large bowel symptoms and the radiological changes of diverticular disease. Mean age: NA UK	• Symptoms (total) • Symptoms (pain) • Symptoms (bowel dysfunction) Followed up at: • 3 months	
Colecchia 2007[10]	**Fibre supplement + antibiotic**. Rifaximin (400 mg twice a day for 7 d every month) plus dietary fibre supplementation (at least 20 gr/d). n=184 **Fibre supplement.** Dietary fibre supplementation (at least 20 gr/d). n=123	People with endoscopic or radiological evidence of diverticular disease of the sigmoid and/or descending colon, reporting the presence of symptoms attributable to diverticular disease of the colon. Mean age: 62.2±12.1 Italy	• Diverticulitis • Symptoms (total) • Symptoms (rectal bleeding) • Side effects Followed up at: 24 months	
Comparato 2007[11]	**Antibiotics (200mg).** Rifaximin, 200mg bd for 10 days every month. n=66 **Antibiotics (400mg).** Rifaximin, 400mg bd for 10 days every month. n=66 **Aminosalicylates (400mg).** Mesalazine, 400mg bd for 10 days every month. n=66 **Aminosalicylates (800mg).** Mesalazine, 800mg bd for 10 days	Outpatients with uncomplicated diverticular disease of the colon, diagnosed by double contrast barium enema and/or colonoscopy. Mean age: 66.1 (31-81) Italy	• Symptoms (total) Followed up at: 12 months	All participants were recommended to maintain a high-fibre diet. Same patients as Mario 2005[32], but outcomes reported at different time points (Mario 2005[32] at 3 months; Comparato 2007[11] at 12 months)

Study	Intervention and comparison	Population	Outcomes	Comments
	every month. n=66			
Hodgson 1977[20]	**Laxatives.** Methylcellulose B.P. 500 mg, two tablets daily. n=16 **Placebo**. Two tablets daily. n=11	Patients referred by GP to hospital for confirmation of diverticular disease – confirmed by symptoms, signs and barium enema results. Mean age: 67.3 (30-85) UK	• Symptoms (total) Followed up at: 3 months	
Kruis 2013[23]	**Aminosalicylates.** Salofalk granules, 1000mg t.i.d. n=56 **Placebo.** Placebo, 1000mg t.i.d. n=61	Diagnosis of diverticular disease with symptoms, acute pain, and without serious complications. Mean age: 62.5±8.6 Germany	• Mortality • Symptoms (lower abdominal pain) Followed up at: 6 weeks	All patients were instructed to follow high fibre diet and adequate intake of liquids. 12 of 56 patients in the mesalazine group arm used concomitant analgesics or spasmolytics. 21 of 61 patients in the placebo arm used concomitant analgesics or spasmolytics.
Kvasnovsky 2017[24]	**Probiotics.** Symprove (contains four strains of bacteria) in a water-based suspension of barley extract. To be taken at 1mL/kg each morning. n=71 **Placebo.** Placebo drink matched for appearance and taste. To be taken every morning. n=72	Patients presenting with persistent abdominal symptoms with an established diagnosis of uncomplicated diverticulosis. Mean age: 62.5±8.6 UK	• Symptoms (abdominal pain) • Symptoms (constipation) • Symptoms (diarrhoea) • Symptoms (rectum bleeding) Followed up at: 3 months	
Lahner 2012[26]	**High fibre diet + pre/probiotic**. High-fibre diet containing at least	Well-established diagnosis of symptomatic uncomplicated	• Symptoms (abdominal pain)	Rescue medication was not allowed during the study period.

Study	Intervention and comparison	Population	Outcomes	Comments
	30 g daily intake of dietary fibre. Flortec; a natural symbiotic agent, consisting a combination of Lactobacillus paracasei and arabinogalactan/xyl ooligosaccharides (prebiotic component).7 g sachet preparation in 100 mL of water once daily. n=184 **Fibre supplement.** High-fibre diet containing at least 30 g daily intake of dietary fibre. n=123	diverticular disease. Mean age: 62.5±8.6 Italy	Followed up at: 6 months	
Latella 2003[28]	**Fibre supplement + antibiotic**. Glucomannan 4g/day + rifaximin 400mg twice daily for 7 days every month. n=595 **Fibre supplement.** Glucomannan 4 g/day. n=373	People with endoscopic or radiological evidence of diverticular disease of the sigmoid and/or descending colon, reporting the presence of symptoms attributable to diverticular disease of the colon. Mean age: 62.5±8.6 Italy	• Diverticulitis • Symptoms (total) • Symptoms (rectal bleeding) • Side effects Followed up at: 12 months	
Di Mario 2005[32]	**Antibiotics (200mg).** Rifaximin, 200mg bd for 10 days every month. n=39 **Antibiotics (400mg).** Rifaximin, 400mg bd for 10 days every month. n=43 **Aminosalicylates (400mg).**	People with endoscopic and/or radiologic evidence of diverticular disease of the left colon. Mean age: 66.5±9.2 Italy	• Symptoms (total) Followed up at: 3 months	Same patients as Comparato 2007[11], but outcomes reported at different time points (Mario 2005[32] at 3 months; Comparato 2007[11] at 12 months)

Study	Intervention and comparison	Population	Outcomes	Comments
	Mesalazine, 400mg bd for 10 days every month. n=40 **Aminosalicylates (800mg).** Mesalazine, 800mg bd for 10 days every month. n=48			
Papi 1992[36]	**Fibre supplement + antibiotic**. Glucomannan 2g/day + rifaximin 400mg twice daily for 7 days every month. n=107 **Fibre supplement.** Glucomannan 2g/day. n=110	People with uncomplicated diverticular disease. Mean age: 65±10.7 Italy	• Symptoms (total) • Symptoms (frequency) Followed up at: 12 months	
Papi 1995[37]	**Fibre supplement + antibiotic**. Glucomannan 2g/day + rifaximin 400mg twice daily for 7 days every month. n=107 **Fibre supplement.** Glucomannan 2g/day. n=110	Outpatients with symptomatic uncomplicated diverticular disease of the colon, diagnosed by double contrast barium enema and/or colonoscopy. Mean age: 61.9 (40-84) Italy	• Symptoms (total) • Symptoms (severity) Followed up at: 12 months	
Smits 1990[43]	**Laxatives.** Lactulose: 15ml bd, to be reduced to 10ml bd if appropriate. n=22 **High fibre diet**. Patients received dietetic supervision throughout the study. Diet provided an intake of 30-40g of fibre daily. n=21	People with symptomatic, proven diverticular disease. Mean age: 65±10.7 UK	• Symptoms (abdominal pain) Followed up at: 12 weeks	
Tursi 2013[56]	**Aminosalicylates + probiotics.** Active Pentacol 800, 2 tablets/day + Active Enterolactis Plus, 1 sachet/day	Diverticulosis showed by colonoscopy no more than 6 months prior to study entry;	• Diverticulitis • Perforation Followed up at: 12 months	At enrolment, all patients were asymptomatic.

Study	Intervention and comparison	Population	Outcomes	Comments
	for 10 days/month. n=54 **Aminosalicylates.** Active Pentacol 800, 2 tablets/day for 10 days/month + Enterolactis Plus placebo, 1 sachet/ day for 10 days/month. n=51 **Probiotics.** Active Enterolactis Plus 1 sachet/day for 10 days/month + Pentacol 800 placebo, 2 tablets/day for 10 days/month. n=55 **Placebo**. Pentacol 800 placebo, 2 tablets/day and Enterolactis Plus placebo, 1 sachet/day for 10 days/month	symptomatic episode of uncomplicated diverticular disease no more than 4 weeks prior to study entry. Mean age: 67.5 (51-83) Italy		

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Brodribb 1977[4]	High fibre diet vs placebo.	Bowel dysfunction score Scale is unclear, high score is poor outcome.	Baseline mean vs 3 months: 11.7 to 3.3 (-8.4)	9	Baseline mean vs 3 months: 14.9 to 13.3 (-1.6)	9	Very high
			Change score of intervention vs control was not statistically significant. p>0.05				
Kruis 2013[23]	Mesalazine vs placebo.	Differences in lower abdominal pain intensity from baseline to week 4 Scale: 1-5, high score is poor outcome.	Median (range): -37 (-95-25)	56	Median (range): -33 (-78-24)	61	High
Annibale 2011[1]	Symbiotic (2 sachets) vs no intervention	Pain lasting <24 hours (VAS score) Scale: 0-10, high score is poor outcome.	Baseline mean vs 6 months: 2.2±2.1 vs 0.6±0.9	16	No change was observed in the control group, values not provided.	16	Very high
	Symbiotic (1 sachet) vs no intervention	Pain lasting <24 hours (VAS score) Scale: 0-10, high score is poor outcome.	Baseline mean vs 6 months: 3.7±3.5 vs 1.9±2.2 (p=0.23)	18	No change was observed in the control group, values not provided.	16	Very high

Table 4: Clinical evidence summary: High fibre diet compared to control diet for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control diet	Risk difference with High fibre diet (95% CI)
Global symptom score Scale unclear, high score is poor outcome.	18 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean global symptom score in the control groups was -6.9	The mean global symptom score in the intervention groups was 19.3 lower (29.56 to 9.04 lower)
Pain score Scale unclear, high score is poor outcome.	18 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain score in the control groups was -2.5	The mean pain score in the intervention groups was 7.5 lower (13.19 to 1.81 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 5: Clinical evidence summary: High fibre diet + antibiotics compared to high fibre diet for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High fibre diet	Risk difference with High fibre diet + antibiotics (95% CI)
Side effects (nausea, headache, and asthenia)	1275 (2 studies) 12-24 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.12 (0.47 to 2.65)	Moderate	
				19 per 1000	2 more per 1000 (from 10 fewer to 31 more)
Progression of diseases (diverticulitis)	1275 (2 studies) 12-24 months	⨁⨁⨁⊖ MODERATE1 due to risk of bias	RR 0.34 (0.15 to 0.8)	Moderate	
				31 per 1000	20 fewer per 1000 (from 6 fewer to 26 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High fibre diet	Risk difference with High fibre diet + antibiotics (95% CI)
Complications (rectal bleeding)	1275 (2 studies) 12-24 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.29 (0.24 to 7.03)	Moderate	
				5 per 1000	1 more per 1000 (from 4 fewer to 30 more)
Global symptomatic score Scale from: 0 to 15.	1622 (4 studies) 12-24 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	Results shown as mean change between groups.		The mean global symptomatic score in the intervention groups was 1.07 lower (1.19 to 0.95 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 6: Clinical evidence summary: High fibre diet + symbiotic compared to high fibre diet for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High fibre diet	Risk difference with High fibre diet + symbiotic (95% CI)
Abdominal pain lasting <24h Scale from: 0 to 10, high is poor outcome.	52 (1 study) 6 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean abdominal pain lasting <24h in the control groups was 2	The mean abdominal pain lasting <24h in the intervention groups was 0.2 higher (0.64 lower to 1.04 higher)
Abdominal pain lasting >24h Scale from: 0 to 10, high is poor outcome.	52 (1 study) 6 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean abdominal pain lasting >24h in the control groups was 5.5	The mean abdominal pain lasting >24h in the intervention groups was 1 lower (2.64 lower to 0.64 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High fibre diet	Risk difference with High fibre diet + symbiotic (95% CI)
at very high risk of bias. 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 7: Clinical evidence summary: Antibiotic (400mg) compared to antibiotic (200mg) for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Antibiotic (200mg)	Risk difference with Antibiotic (400mg) (95% CI)
Global Symptomatic Score at 3 months Scale from: 0 to 33, high is poor outcome.	82 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean global symptomatic score at 3 months in the control groups was 7.6	The mean global symptomatic score at 3 months in the intervention groups was 1.7 lower (3.73 lower to 0.33 higher)
Global Symptomatic Score at 12 months Scale from: 0 to 33, high is poor outcome.	121 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean global symptomatic score at 12 months in the control groups was 7.5	The mean global symptomatic score at 12 months in the intervention groups was 0.4 lower (1.67 lower to 0.87 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 8: Clinical evidence summary: Aminosalicylate (800mg) compared to aminosalicylate (400mg) for diverticular disease

Outcomes	No of	Quality of the	Relativ	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	e effect (95% CI)	Risk with Aminosalicylate (400mg)	Risk difference with Aminosalicylate (800mg) (95% CI)
Global Symptomatic Score at 3 months Scale from: 0 to 33, high is poor outcome.	88 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean global symptomatic score at 3 months in the control groups was 6.7	The mean global symptomatic score at 3 months in the intervention groups was 1.8 lower (3.37 to 0.23 lower)
Global Symptomatic Score at 12 months Scale from: 0 to 33, high is poor outcome.	123 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean global symptomatic score at 12 months in the control groups was 3.61	The mean global symptomatic score at 12 months in the intervention groups was 0.9 lower (1.6 to 0.2 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: Antibiotic compared to aminosalicylate for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate	Risk difference with Antibiotic (95% CI)
Global Symptomatic Score at 3 months Scale from: 0 to 33, high is poor outcome.	170 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean global symptomatic score at 3 months in the control groups was 5.7	The mean global symptomatic score at 3 months in the intervention groups was 1 higher (0.19 lower to 2.19 higher)
Global Symptomatic Score at 12 months Scale from: 0 to 33, high is poor outcome.	244 (1 study) 12 months	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean global symptomatic score at 12 months in the control groups was 3.02	The mean global symptomatic score at 12 months in the intervention groups was 4.27 higher (3.55 to 4.99 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate	Risk difference with Antibiotic (95% CI)
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 10: Clinical evidence summary: Aminosalicylates + probiotics compared to Aminosalicylates for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylates	Risk difference with Aminosalicylates + probiotics (95% CI)
Acute diverticulitis	105 (1 study) 12 months	⨁⨁⨁⨁ HIGH	Not estimable 1	Moderate	
				0 per 1000	-
Perforation	105 (1 study) 12 months	⨁⨁⨁⨁ HIGH	Not estimable 1	Moderate	
				0 per 1000	-
1 Zero events in either arm					

Table 11: Clinical evidence summary: Aminosalicylates + probiotic compared to Probiotic for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Probiotic	Risk difference with Aminosalicylates + probiotic (95% CI)
Acute diverticulitis	109 (1 study) 12 months	⨁⨁⊖⊖ LOW1 due to imprecision	Peto OR 0.14 (0.00 to 6.95)	Moderate	
				26 per 1000	22 fewer per 1000 (from 26 fewer to 155 more)
Perforation	109 (1 study) 12 months	⨁⨁⨁⨁ HIGH	Not estimable 2	Moderate	
				0 per 1000	-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Probiotic	Risk difference with Aminosalicylates + probiotic (95% CI)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 2 Zero events in either arm					

Table 12: Clinical evidence summary: Aminosalicylate + probiotic compared to placebo for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate + probiotic (95% CI)
Acute diverticulitis	104 (1 study) 12 months	⨁⨁⨁⨀ MODERATE1 due to imprecision	Peto OR 0.11 (0.02 to 0.58)	Moderate	
				120 per 1000	107 fewer per 1000 (from 50 fewer to 96 fewer)
Perforation	104 (1 study) 12 months	⨁⨁⨀⨀ LOW1 due to imprecision	Peto OR 0.12 (0 to 6.31)	Moderate	
				20 per 1000	18 fewer per 1000 (from 20 fewer to 106 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 13: Clinical evidence summary: Aminosalicylates compared to Probiotic for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Probiotic	Risk difference with Aminosalicylates (95% CI)
Acute diverticulitis	106 (1 study) 12 months	⨁⨁⨀⨀ LOW1 due to risk of bias, imprecision	Peto OR 0.15 (0.00 to 7.36)	Moderate	
				26 per 1000	22 fewer per 1000 (from 26 fewer to 165 more)
Perforation	106 (1 study) 12 months	⨁⨁⨀⨀ LOW1 due to imprecision	Peto OR 0.14 (0.01 to 2.32)	Moderate	
				36 per 1000	31 fewer per 1000 (from 36 fewer to 48 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Probiotic	Risk difference with Aminosalicylates (95% CI)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 14: Clinical evidence summary: Aminosalicylate compared to placebo for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (95% CI)
Mortality	117 (1 study) 12 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias	Not estimable 3	Moderate	
				0 per 1000	-
Acute diverticulitis	101 (1 study) 12 months	⨁⨁⨀⨀ LOW2 due to imprecision	RR 0.08 (0 to 1.3)	Moderate	
				120 per 1000	110 fewer per 1000 (from 120 fewer to 36 more)
Perforation	101 (1 study) 12 months	⨁⨁⨀⨀ LOW2 due to imprecision	Peto OR 0.33 (0 to 6.69)	Moderate	
				20 per 1000	13 fewer per 1000 (from 20 fewer to 114 more)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Zero events in either arm					

Table 15: Clinical evidence summary: Probiotic compared to placebo for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Probiotic (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Probiotic (95% CI)
Abdominal pain Scale from: 0 to 28, high is poor outcome.	120 (1 study) 3 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias		Outcome reported as mean change	The mean abdominal pain in the intervention groups was 0.54 lower (2.4 lower to 1.3 higher)
Abdominal pain frequency Scale from: 0 to 6, high is poor outcome.	120 (1 study) 3 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias		The mean abdominal pain in the control groups was -0.5	The mean abdominal pain in the intervention groups was 0.2 lower (0.79 lower to 0.39 higher)
Constipation frequency Scale from: 0 to 6, high is poor outcome.	120 (1 study) 3 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean constipation in the control groups was -0.9	The mean constipation in the intervention groups was 0.5 higher (0.08 lower to 1.08 higher)
Diarrhoea frequency Scale from: 0 to 6, high is poor outcome.	120 (1 study) 3 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias		The mean diarrhoea in the control groups was -0.5	The mean diarrhoea in the intervention groups was 0.1 higher (0.42 lower to 0.62 higher)
Per rectum bleeding frequency Scale from: 0 to 6, high is poor outcome.	120 (1 study) 3 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean per rectum bleeding in the control groups was -0.4	The mean per rectum bleeding in the intervention groups was 0.38 higher (0.1 lower to 0.86 higher)
Abdominal pain (likelihood of daily frequency of symptom)	60 (1 study) 3 months	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.61 (0.25 to 1.49)	Results shown risk difference between groups.	
Constipation (likelihood of daily frequency of symptom)	60 (1 study) 3 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 0.36 (0.13 to 1)	Results shown risk difference between groups.	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Probiotic (95% CI)
Diarrhoea (likelihood of daily frequency of symptom)	60 (1 study) 3 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.49 (0.21 to 1.14)	Results shown risk difference between groups.	
Per rectum bleeding (likelihood of daily frequency of symptom)	60 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.3 (0.07 to 1.29)	Results shown risk difference between groups.	
Acute diverticulitis	105 (1 study) 12 months	⨁⨁⨁⊖ MODERATE2 due to imprecision	RR 0.15 (0.02 to 1.22)	Moderate	
				120 per 1000	102 fewer per 1000 (from 118 fewer to 26 more)
Perforation	105 (1 study) 12 months	⨁⨁⊖⊖ LOW2 due to imprecision	Peto OR 0.12 (0 to 6.2)	Moderate	
				20 per 1000	18 fewer per 1000 (from 20 fewer to 104 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence summary: Symbiotic (2 sachets) compared to Symbiotic (1 sachet) for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Symbiotic (1 sachet)	Risk difference with Symbiotic (2 sachets) (95% CI)
Pain Scale from: 0 to 10, high is poor outcome.	28 (1 study) 6 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain in the control groups was 1.9	The mean pain in the intervention groups was 1.3 lower (2.52 to 0.08 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Symbiotic (1 sachet)	Risk difference with Symbiotic (2 sachets) (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 17: Clinical evidence summary: Laxatives compared to placebo for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Laxatives (95% CI)
Symptoms score Scale from: 0 to 50, high is poor outcome.	27 (1 study) 3 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean symptoms score in the control groups was 16.7	The mean symptoms score in the intervention groups was 3.7 lower (9.29 lower to 1.89 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 18: Clinical evidence summary: Laxative compared to High fibre diet for diverticular disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High fibre diet	Risk difference with Laxative (95% CI)
Abdominal pain (frequency) Scale unclear, high is poor outcome	39 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean abdominal pain (frequency) in the control groups was -1.55 days	The mean abdominal pain (frequency) in the intervention groups was 1 lower (2.8 lower to 0.8 higher)
Abdominal pain (severity) Scale unclear, high is poor	39 (1 study)	⨁⊖⊖⊖ VERY LOW1,2		The mean abdominal pain (severity) in the control groups was	The mean abdominal pain (severity) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High fibre diet	Risk difference with Laxative (95% CI)
outcome	12 weeks	due to risk of bias, imprecision		4.26	0.8 lower (3.5 lower to 1.9 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

The unit costs below were presented to the committee, to aid consideration of cost effectiveness.

Table 19: UK costs of laxatives, antibiotics, analgesia, antispasmodics, aminosalicylates, probiotics and prebiotics

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Laxatives				
Isphagula husk 3.5g effervescent granules sachets	2 x 3.5g sachets [5-10g once daily]	£0.09	£5.52	NHS Drug Tariff
Methylcellulose 500mg	2 x 500mg tablets daily [3-6 x 500mg tablets twice daily]	£0.05	£2.89	NHS Drug Tariff
Sterculia 62% granules 7g sachets	2 x 7g sachets twice daily [1-2 sachets 1-2 times a day]	£0.11	£13.53	NHS Drug Tariff
Bisacodyl 5mg gastro-resistant tablets	2 x5mg tablets [5-10mg once daily increased if necessary up to 20mg once daily]	£0.21	£12.66	NHS Drug Tariff
Sodium picosulfate 5mg/5ml oral solution	2 x 5mg/ml solutions [5-10mg once daily]	£0.12	£7.20	NHS Drug Tariff
Senna 7.5mg tablets	2 x 7.5mg tablets [7.5-15mg daily (maximum dose 30 mg daily)]	£0.03	£1.67	NHS Drug Tariff
Lactulose 3.1g-3.7g/5ml oral solution	6 x 3.1g-3.7g/5ml oral solution [Initially 15ml twice daily, adjusted according to response]	£0.02	£4.13	NHS Drug Tariff
Macrogol 3350 oral powder 8.5g sachets	2 sachets [2 sachets once daily usually for up to 2 weeks]	£0.14	£3.89[c]	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Docusate sodium 100mg capsules (by mouth)	5 x 100mg capsules [Up to 500mg daily in divided doses, adjusted according to response]	£0.07	£10.60	NHS Drug Tariff
Glycerol (by rectum) 4g suppositories	1 x 4g suppository [4g, as required]	£0.10	£2.94	NHS Drug Tariff
Micralax (sodium citrate 90mg/ml) 5ml micro-enema	1 enema [1 enema per dose]	£0.41	£12.35	British National Formulary
Arachis oil 130ml enema	1 x 130ml enema [130ml, as required]	£47.50	£95[d]	NHS Drug Tariff
Antibiotics				
Rifaximin 200mg tablets	2 x 200mg tablets - 4 x 200mg tablets [200mg every 8 hours for 3 days]	£1.68	£33.67[e] - £67.33[e]	NHS Drug Tariff
Analgesia				
Paracetamol 500mg (by mouth)	2 x 500mg tablets every 6 hours [0.5-1g every 4-6 hours (maximum 4g per day)]	£0.02	£3.87	NHS Drug Tariff
Ibuprofen 400mg tablets	1 x 400mg tablet 4 times a day [Initially 300-400mg 3-4 times a day; increased if necessary to up to 600mg 4 times a day; maintenance 200-400mg 3 times a day, may be adequate]	£0.03	£3.25	NHS Drug Tariff
Dexibuprofen 400mg tablets	2 x 400mg tablets [600-900mg daily in up to 3 divided doses; increased if necessary up to 1.2g daily (maximum per dose 400mg)]	£0.16	£9.61	NHS Drug Tariff
Naproxen 250mg tablets	5 x 250mg tablets [Initially 500mg, then 250mg every 6-8 hours as required (maximum dose after the first day 1.25g daily)]	£0.03	£4.24	NHS Drug Tariff
Nefopam 30mg tablets	6 x 30mg tablets [Initially 60mg, 3 times a day, adjusted according to response; usual dose 30-90mg, 3 times a	£0.21	£38.90	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
	day]			
Antispasmodics				
Atropine sulfate 600 microgram tablets	2 x 600µg tablets [600-1200µg daily]	£1.89	£115.05	NHS Drug Tariff
Dicycloverine hydrochloride 20mg tablets	3 x 20mg tablets [10-25mg, 3 times a day]	£2.34	£213.81	NHS Drug Tariff
Propantheline bromide 15mg tablets	3 x 15mg tablets [15mg, 3 times a day (maximum 120mg per day)]	£0.19	£16.91	NHS Drug Tariff
Alverine citrate 60mg capsules	6 x 60mg capsules [60-120mg 1-3 times a day]	£0.05	£8.31	NHS Drug Tariff
Mebeverine hydrochloride 135mg tablets	3 x 135mg tablets [135mg-150mg 3 times a day]	£0.04	£4.01	NHS Drug Tariff
Peppermint oil 0.2ml gastro resistant capsules	6 x 0.2ml capsules [1-2 capsules 3 times a day for up to 2-3 months if necessary]	£0.08	£15.31	NHS Drug Tariff
Aminosalicylates				
Mesalazine (Octasa®) tablets 800mg gastro-resistant tablets	1 x 800mg tablet[d] -2 x 800mg tablets daily [2.4-4.8g daily]	£0.45	£4.49[e] - £27.31	NHS Drug Tariff
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets	1 x 4.4g sachet daily	£1.15	£34.86	BNF (NHS indicative price)

Sources: NHS Drug Tariff, February 2018; British National Formulary
(a) Dosages for adults, British National Formulary
(b) Depending on number of units taken
(c) Cost per 14 day course; not per month
(d) Cost per 2 days; not per month
(e) Cost when dose taken 10 days out of every month

Table 20: UK costs to people with diverticular disease for items not prescribed on the NHS

Drug	Assumed daily dose[a]	Cost per unit (£)	Cost per month (£)[b]	Source
Dietary Fibre				
Glucomannan 500mg capsules	4 x 500mg capsules-8 x 500mg capsules	£0.12	£14.18-£28.37	Not available in BNF; Retail price from stockist[d]
GG Scandinavian Bran Crispbread (4.26g dietary fibre)	6 crispbreads (4.26g dietary fibre per crispbread)	£0.13	£24.20	Not available in BNF; Retail price from stockist[d]
Probiotics and prebiotics				
VSL#3 Probiotic food	1 x 4.4g sachet daily	£2.35	£71.47	Retail price from

Drug	Assumed daily dose[a]	Cost per unit (£)	Cost per month (£)[b]	Source
supplement oral powder 4.4g sachets (non-prescribed)				stockist[e]
Vivomixx (450 billion live bacteria per sachet) 4.4g sachets	1 x 4.4g sachet daily	£1.48	£45.02	Retail price from stockist[e]
Lactobacillus casei: Probio 10 (containing *L. casei* 5x10^7 viable cells, among 10 different species of micro-organisms)	1 capsule daily	£0.08	£2.53	Not available in BNF; Retail price from stockist[d]
Symprove™	1ml/kg	£0.03/ml	£75.14[c]	Not available in BNF; Retail price from stockist[f]

Sources: Amazon.co.uk, Holland and Barrett, shop.symprove.com
(a) Dosages for adults
(b) Depending on number of units taken
(c) Cost exclusive of VAT for a weight of 75kg calculated from the average BMI (BMI 27.7) reported in Kvasnovsky 2017[24]
(d) Retail price obtained from Holland and Barrett
(e) Retail price obtained from Amazon.co.uk
(f) Retail price obtained from shop.symprove.com

1.6 Evidence statements

1.6.1 Clinical evidence statements

High fibre diet

One small study (n=18) reported a clinically important benefit of a high fibre diet in terms of pain (very low quality evidence) and symptom control (low quality evidence) when compared to a control diet in people with diverticular disease. There was no benefit seen for the addition of antibiotics to a high fibre diet when compared to a high fibre diet alone in 2 studies (n=1275) in terms of progression of diverticular disease to diverticulitis (moderate quality evidence), side effects (nausea, headache and asthenia), rectal bleeding and symptom control (very low quality evidence). There was also no benefit found for the addition of symbiotic to a high fibre diet compared to a high fibre diet alone in 1 study in terms of abdominal pain lasting less than or greater than 24 hours (n=52, low quality evidence).

Antibiotics

Two studies demonstrated no clinically important difference in antibiotic doses (rifaximin); 400 mg versus 200 mg, on symptom control at 3 months (n=82, very low quality data) or 12 months (n=121, very low quality data). However, a clinically important benefit of antibiotics was seen for this outcome when compared to aminosalicylate in 1 study (n=244, low quality evidence).

Aminosalicylates

Two studies found no clinically important difference in the effects of 400 mg aminosalicylate compared to 800 mg aminosalicylate on symptom control at 3 months (n=88, very low quality evidence) and 12 months (n=123, very low quality evidence).

Single studies comparing the addition of probiotics to aminosalicylate when compared to aminosalicylate alone (n=105, moderate to low quality evidence) or probiotic alone (n=109, low to high quality evidence) also demonstrated no clinically important difference in terms of disease progression to diverticulitis and perforation. Some benefit for aminosalicylate with probiotics was observed when compared to placebo on disease progression to diverticulitis but not perforation (single study, n=104, moderate to low quality evidence).

One study found a clinically important benefit of aminosalicylate in terms of disease progression to acute diverticulitis when compared to placebo (n=101, low quality evidence), but not when compared to probiotics (n=106, low quality evidence). There was no clinically important difference seen in either comparison for perforation (low quality evidence).

Probiotic versus placebo

One small study demonstrated clinically important benefit of probiotics on the clinical outcomes; abdominal pain, constipation, diarrhoea and per rectum bleeding (n=60, low to very low quality). However this was not supported by another study which found no clinically important difference between probiotics and placebo on these outcomes (n=120, low to moderate quality of evidence). Another study found a clinically important benefit of probiotics on disease progression to acute diverticulitis (n=150, moderate quality evidence) but not on perforation (n=105, low quality evidence).

Symbiotic

Clinically important benefit was seen in a small single study for 2 sachets of symbiotic compared to 1 sachet in terms of pain (n=27, low quality evidence).

Laxative

There was no clinically important difference observed for laxatives when compared to placebo in terms of symptom control (n=27, low risk of bias), or when compared to a high fibre diet in terms of abdominal pain frequency and severity (n=39, very low quality evidence).

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

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1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee identified quality of life, symptom control, and progression of disease into acute diverticulitis, hospitalisation, surgery or complications (infections, abscesses, perforation, stricture and fistula) as the critical outcomes. The following outcomes were identified as important for management of diverticulosis; mortality, and side effects of probiotics and laxatives: diarrhoea, bloating, abdominal pain, and analgesics: nausea and vomiting, constipation.

Mortality was only considered to be an important outcome as it is accepted that the outcome would be unlikely to occur as a result of diverticular disease.

No evidence was identified for the interventions of any dietary advice, oral fluids, analgesia (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], opiates, nefopam), or antispasmodics.

1.7.1.2 The quality of the evidence

The quality of evidence ranged from very low to high. The majority of the evidence was graded at low or very low quality. This was mostly due to selection and performance bias, resulting in a high risk of bias rating, and imprecision.

All evidence was obtained from randomised controlled trial studies. Observational studies were considered, although no studies were identified for comparisons not already addressed by RCTs.

1.7.1.3 Benefits and harms

The committee acknowledged the potential for the use of dietary fibre in managing the symptoms associated with diverticular disease, but it expressed concern about insoluble fibre as a source of dietary fibre, as it is not recommended for some gastro-intestinal conditions for example IBS. The committee also felt that the evidence identified in the clinical review relating to insoluble fibre crispbreads was old and involved a small number of patients (n=18).

The committee discussed the evidence on the use of antibiotics. The results from 2 studies showed the addition of rifaxamin to a high-fibre diet might reduce the risk of developing acute diverticulitis, although the observed difference was not clinically significant. No observed difference was seen for the outcomes of side effects, rectal bleeding or global symptoms score. There was also no clinical difference seen between dosing regimens reported in 2 studies. The committee also raised concerns about antibiotic stewardship. A statement on antibiotics was included in the Delphi survey.

The committee noted the evidence supporting a potential positive effect of aminosalicylates in the prevention of progression to diverticulitis; however, there was a lack of evidence that treatment with aminosalicylate would reduce symptoms associated with diverticular disease. There was no clinical difference seen between dosing regimens reported in 2 studies. The committee also highlighted that renal failure is a rare but important side effect of treatment with aminosalicylate.

The committee discussed the evidence on the use of probiotics and noted the potential benefits with prevention of progression of disease. The committee felt that the evidence to support the effect of probiotic use on symptom control was inconsistent and inconclusive. The committee also noted the range of different probiotics available to patients, highlighted by the varying probiotics utilised by the studies included in the review.

The committee agreed that there was no evidence of notable effect of laxatives on the management of symptoms of diverticular disease.

1.7.2 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of treatments for people with diverticular disease. In the absence of relevant economic evaluations, the committee considered the unit cost of sources of dietary fibre. The committee expressed concern about insoluble fibre as a source of dietary fibre, as it is not recommended for some gastro-intestinal conditions such as IBS. In addition, the committee felt that the evidence identified in the clinical review relating to insoluble fibre crispbreads was old and involved a small number of patients (n=18). The committee considered the unit cost to the patient of insoluble fibre crispbreads (£24.20 per person per month) and compared them with those of other sources of dietary fibre. Glucomannan capsules cost the

patient £14.18-£28.37 per person per month. The committee was concerned the clinical evidence did not differentiate between soluble and insoluble dietary fibre and felt that a research recommendation was appropriate.

The committee discussed the clinical evidence for the effectiveness of the broad spectrum antibiotic rifaximin alongside the unit cost (£33.67-£67.33 per person per month, when doses of 400mg-800mg daily are taken in 10 day cycles), which was felt to be more expensive than other antibiotics. It was flagged that other antibiotics such as metronidazole, co-amoxiclav and ciprofloxacin may be cheaper and equally effective, but that no clinical or economic evidence exists. Concerns were also raised about antibiotic stewardship. The committee therefore felt that a research recommendation was appropriate.

The committee considered the unit costs and clinical evidence for mesalazine. In addition to the cost of £6.54 per person per month when 800mg mesalazine is taken daily for 10 days per month, further downstream costs are likely to accrue which would likely impact the cost effectiveness of mesalazine in the treatment of diverticular disease. The committee noted that renal failure is a rare but important adverse event which would negatively impact quality of life. Further, this adverse event necessitates renal screening after three months then yearly for people taking mesalazine, which would result in additional costs. The committee noted that evidence in the clinical evidence found no difference between low and high doses of mesalazine for symptom relief, and so it considered that the low dose would attenuate the risk of renal failure. The committee felt that, due to the small study size, risks of renal failure and the associated costs, a research recommendation was appropriate.

The committee discussed the lack of clinical and economic evidence attesting to the benefits of a wide variety of probiotic products, noting that these products often pose a large expense to people with diverticular disease. In the absence of relevant economic evaluations, the committee considered the unit cost of the only prescribable probiotic food supplement: VSL#3, which costs £34.86 per person per month. However, VSL#3 is licensed for use in adults for the maintenance of remission of ileoanal pouchitis. VSL#3 is often recommended to people with diverticular disease, who bear the cost. The current retail price of VSL#3 is £71.47 per person per month. Other probiotics considered were Vivomixx, which the committee felt was comparable to VSL#3, while cheaper, at a current retail price of £45.02 per person per month. The committee highlighted that Symprove™ is widely purchased by individuals. The current retail price of Symprove™ is £75.14 per person per month.

The committee discussed the unit costs of other classes of drugs including laxatives, antispasmodics and analgesics.

In conclusion, the committee chose to recommend that further research be conducted on the effectiveness and cost effectiveness of treatments for diverticular disease, due to the lack of evidence of effectiveness in symptom relief, with positive findings only for the outcome of disease progression.

The clinical evidence was poor and inconclusive and there was no cost effectiveness evidence. Therefore, recommendations were made by a Delphi panel and minor edits made by the committee. The panel recommended dietary advice and consideration of laxatives, paracetamol and antispasmodics. The cost-effectiveness of these treatments is not known for this population. However, the unit costs are relatively small, treatment can be stopped when symptoms subside and the recommendations do not represent a move away from current practice.

1.7.3 Other factors the committee took into account

In the experience of the committee members, insoluble fibre (for example wheat bran) may be discouraged for some other functional gastrointestinal conditions because it causes bloating. Antimicrobial stewardship considerations informed the committee's decision not to recommend antibiotics in addition to the evidence base. The committee were aware of the

NICE guideline on Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15).

The committee discussed people who do not have control over their diet, for example people in care homes and prisons, and highlighted that they should have access to high fibre diets.

The committee emphasised the importance of not prescribing antibiotics for people with diverticular disease due to lack of effectiveness and the importance of antimicrobial stewardship. The committee acknowledged that current practice for the treatment of adults with diverticular disease is to recommend a high-fibre diet and improved lifestyle factors including weight loss and exercise. Often bulk-forming laxatives are effective as they help to soften the stool and can also help solidify loose stools. The aim of these is to improve general wellbeing and an understanding of gut health. The committee were aware of observational evidence which supports the recommendation of bulk-forming laxatives, however they did not meet the inclusion criteria of this review protocol. Paracetamol is indicated and used in current practice for the pain and is safe to do so. The committee highlighted the importance of avoiding non-steroidal anti-inflammatories and opioid analgesia due to the risk of diverticular perforation. Some people experience abdominal cramping and antispasmodics are indicated. The committee noted the importance of considering alternative causes and further investigations in people with persistent symptoms or who do not respond to treatment. Due to the limited or absence of evidence for the some of the interventions and critical outcomes listed in the review protocol, statements were included in the Delphi survey.

The statement on antibiotics did not reach consensus in round one with respondents indicating they would be used if there was infection. In the second round consensus was reached when a qualifying statement ‘in the absence of acute diverticulitis’ was added. The statement to reduce red meat intake was removed because the majority of respondents disagreed or strongly disagreed with the statement and neither the survey respondents nor the committee suggested any amendments. The statement to increase fibre intake was modified to make it specific to people experiencing constipation. The statement to consider using prebiotics and probiotics for abdominal pain was removed because the majority of respondents disagreed or strongly disagreed with the statement because there is no evidence and neither the survey respondents nor the committee suggested any amendments. The remaining statements reached consensus in the first round.

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Appendices

Appendix A: Review protocols

Table 21: Review protocol: Management of diverticular disease

Field	Content
Review question	What is the most clinically and cost-effective treatment for diverticular disease?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To find the most effective treatment for diverticular disease
Eligibility criteria – population / disease / condition / issue / domain	Adults 18 years and over with diverticular disease
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• High fibre diet (soluble and insoluble fibre) • Low fibre diet • Any dietary advice • Laxatives • Oral fluids • Antibiotics • Analgesia (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], opiates, nefopam) • Antispasmodics • Aminosalicylates • Probiotics and prebiotics
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Each other • No treatment • Placebo • Dosing studies

Outcomes and prioritisation	Critical outcomes:
	• Progression of disease
	  ○ Acute diverticulitis
	  ○ Hospitalisation
	  ○ Need for surgery
	  ○ Complications (infections, abscesses, perforation)
	• Symptom control (pain relief, bowel habit)
	• Quality of life
	
	Important outcomes:
	• Mortality
	• Side effects of:
	  ○ Antibiotics: nausea and vomiting, diarrhoea, infections related to antibiotics
	  ○ Analgesics: nausea and vomiting, constipation

Eligibility criteria – study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies

	Confounders: age, gender
Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger • Primary prevention
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups: • people of Asian family origin as they are known to develop right-sided diverticula • transplant patients/ immunocompromised • Age (<50 years and >50 years)
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Bibliographies, citations and study sifting managed using EndNote • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/conditions-and-diseases/digestive-tract-conditions/diverticular-disease
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or G (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report (Chapter R) for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.

Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by James Dalrymple in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 22: Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[34] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 11 of 12 CENTRAL to 2018 Issue 11 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Table 24: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	randomized controlled trial.pt.
23.	controlled clinical trial.pt.
24.	randomi#ed.ti,ab.
25.	placebo.ab.
26.	randomly.ti,ab.
27.	Clinical Trials as topic.sh.
28.	trial.ti.

29.	or/22-28
30.	Meta-Analysis/
31.	exp Meta-Analysis as Topic/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/50-59
41.	Epidemiologic studies/
42.	Observational study/
43.	exp Cohort studies/
44.	(cohort adj (study or studies or analys* or data)).ti,ab.
45.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
46.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
47.	Controlled Before-After Studies/
48.	Historically Controlled Study/
49.	Interrupted Time Series Analysis/
50.	(before adj2 after adj2 (study or studies or data)).ti,ab.
51.	or/30-39
52.	exp case control study/
53.	case control*.ti,ab.
54.	or/41-42
55.	40 or 43
56.	Cross-sectional studies/
57.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	or/45-46
59.	40 or 47
60.	40 or 43 or 47
61.	21 and (29 or 40 or 60)

Table 25: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7

9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	random*.ti,ab.
21.	factorial*.ti,ab.
22.	(crossover* or cross over*).ti,ab.
23.	((doubl* or singl*) adj blind*).ti,ab.
24.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
25.	crossover procedure/
26.	single blind procedure/
27.	randomized controlled trial/
28.	double blind procedure/
29.	or/20-28
30.	systematic review/
31.	meta-analysis/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/30-39
41.	Clinical study/
42.	Observational study/
43.	family study/
44.	longitudinal study/
45.	retrospective study/
46.	prospective study/
47.	cohort analysis/
48.	follow-up/
49.	cohort*.ti,ab.
50.	48 and 49
51.	(cohort adj (study or studies or analys* or data)).ti,ab.

52.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
53.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	(before adj2 after adj2 (study or studies or data)).ti,ab.
55.	or/41-47,50-54
56.	exp case control study/
57.	case control*.ti,ab.
58.	or/56-57
59.	55 or 58
60.	cross-sectional study/
61.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	or/60-61
63.	55 or 62
64.	55 or 58 or 62
65.	19 and (29 or 40 or 64)

Table 26: Cochrane Library (Wiley) search terms

#1.	diverticul*.mp.

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Diverticular Disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 27: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 November 2018 NHSEED - Inception to March 2015	None

Table 28: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language

3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	Economics/
23.	Value of life/
24.	exp "Costs and Cost Analysis"/
25.	exp Economics, Hospital/
26.	exp Economics, Medical/
27.	Economics, Nursing/
28.	Economics, Pharmaceutical/
29.	exp "Fees and Charges"/
30.	exp Budgets/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/22-37
39.	exp models, economic/
40.	*Models, Theoretical/
41.	markov chains/
42.	monte carlo method/
43.	exp Decision Theory/
44.	(markov* or monte carlo).ti,ab.
45.	econom* model*.ti,ab.

46.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
47.	Models, Organizational/
48.	*models, statistical/
49.	*logistic models/
50.	models, nursing/
51.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
52.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
53.	(SSM or SODA).ti,ab.
54.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
55.	soft systems method*.ti,ab.
56.	(Meta-heuristic* or Metaheuristic*).ti,ab.
57.	(dynamic* adj2 (model* or system*)).ti,ab.
58.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
59.	(microsimulation* or "micro* simulation*").ti,ab.
60.	((flow or core) adj2 model*).ti,ab.
61.	(data adj2 envelopment*).ti,ab.
62.	system* model*.ti,ab.
63.	or/41-64
64.	quality-adjusted life years/
65.	sickness impact profile/
66.	(quality adj2 (wellbeing or well being)).ti,ab.
67.	sickness impact profile.ti,ab.
68.	disability adjusted life.ti,ab.
69.	(qal* or qtime* or qwb* or daly*).ti,ab.
70.	(euroqol* or eq5d* or eq 5*).ti,ab.
71.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
72.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
73.	(hui or hui1 or hui2 or hui3).ti,ab.
74.	(health* year* equivalent* or hye or hyes).ti,ab.
75.	discrete choice*.ti,ab.
76.	rosser.ti,ab.
77.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
78.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
79.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
80.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
81.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
82.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
83.	or/22-40
84.	21 and (38 or 63 or 83)

Table 29: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/

4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	Economics/
21.	Value of life/
22.	exp "Costs and Cost Analysis"/
23.	exp Economics, Hospital/
24.	exp Economics, Medical/
25.	Economics, Nursing/
26.	Economics, Pharmaceutical/
27.	exp "Fees and Charges"/
28.	exp Budgets/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/20-35
37.	statistical model/
38.	*theoretical model/
39.	nonbiological model/
40.	stochastic model/
41.	decision theory/
42.	decision tree/
43.	exp nursing theory/

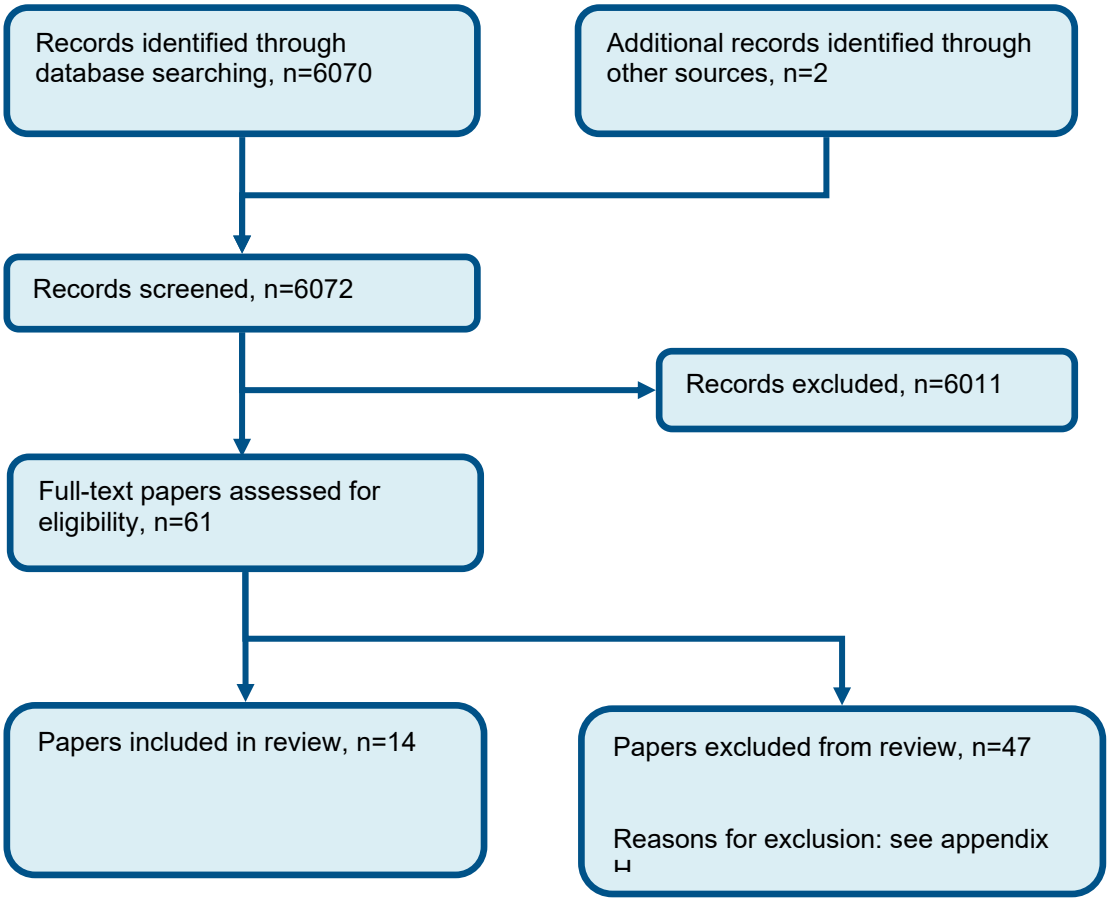
44.	monte carlo method/
45.	(markov* or monte carlo).ti,ab.
46.	econom* model*.ti,ab.
47.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
48.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
49.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
50.	(SSM or SODA).ti,ab.
51.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
52.	soft systems method*.ti,ab.
53.	(Meta-heuristic* or Metaheuristic*).ti,ab.
54.	(dynamic* adj2 (model* or system*)).ti,ab.
55.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
56.	(microsimulation* or "micro* simulation*").ti,ab.
57.	((flow or core) adj2 model*).ti,ab.
58.	(data adj2 envelopment*).ti,ab.
59.	system* model*.ti,ab.
60.	or/39-61
61.	quality adjusted life year/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.
66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.
69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/20-40
83.	19 and (36 or 60 or 82)

Table 30: NHS EED and HTA (CRD) search terms

#1.	diverticul*

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of management of diverticular disease.



Appendix D: Clinical evidence tables

Table 31: Clinical evidence tables

Study	Annibale 2011[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=59)
Countries and setting	Conducted in Italy; Setting: Three academic tertiary centres in Italy
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of SUDD, defined as the presence of colonic diverticula associated with abdominal symptoms (pain and/or bloating)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients with a well-established diagnosis of SUDD, defined as the presence of colonic diverticula associated with abdominal symptoms (pain and/or bloating) for at least 6 months before recruitment.
Exclusion criteria	Radiological evidence of less than five diverticula, recent history (<1 month) or actual clinical evidence of complicated DD (acute diverticulitis or colonic stricture, as diagnosed by the presence of fever, increased erythrocyte sedimentation rate, increased C-reactive protein, and/or increased leukocyte count, and/or by endoscopy and/or computerized tomography, as appropriate), previous colonic surgery, antibiotics, non-steroidal anti-inflammatory drug (NSAID) or laxative use during the 30 days before enrolment, coexisting inflammatory bowel diseases, diseases with possible small intestine bacterial overgrowth.
Recruitment/selection of patients	Outpatients recruited by gastroenterologists.
Age, gender and ethnicity	Age - Mean (SD): 65.2 (8.1). Gender (M:F): 28/32. Ethnicity: Not reported
Further population details	
Extra comments	All patients underwent a double contrast enema to localise and quantify the extent of colonic diverticulosis, and

	complete routine biochemistry (complete blood count, evaluate erythrocyte sedimentation rate, C-reactive protein, protein electrophoresis) in order to ascertain the presence of signs of acute inflammation.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Probiotics/prebiotics - Probiotics. Twice daily 2 sachets of the symbiotic preparation for the first 14 days each month. The symbiotic was a probiotic/prebiotic preparation, each 2.5 g sachet contains viable lyophilized Lactobacillus paracasei sub. paracasei F19. . Duration 6 months. Concurrent medication/care: All patients were encouraged to follow a high-fibre diet containing at least a daily intake of 30 g diet fibre as well as a daily water intake of at least 1.5 L. . Indirectness: No indirectness (n=18) Intervention 2: Probiotics/prebiotics - Probiotics. Twice daily 1 sachet of the symbiotic preparation for the first 14 days each month. The symbiotic was a probiotic/prebiotic preparation, each 2.5 g sachet contains viable lyophilized Lactobacillus paracasei sub. paracasei F19. . Duration 6 months. Concurrent medication/care: All patients were encouraged to follow a high-fibre diet containing at least a daily intake of 30 g diet fibre as well as a daily water intake of at least 1.5 L. Indirectness: No indirectness (n=16) Intervention 3: No intervention/placebo - No intervention. Control group received no symbiotic. High-fibre diet only. Duration 6 months. Concurrent medication/care: All patients were encouraged to follow a high-fibre diet containing at least a daily intake of 30 g diet fibre as well as a daily water intake of at least 1.5 L. Indirectness: No indirectness
Funding	Study funded by industry (Part supported by Siffra Farmaceutici)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYMBIOTICS (4 SACHETS/DAY) versus SMBIOTICS (2 SACHETS/DAY)

Protocol outcome 1: Symptom control (pain relief)
- Actual outcome: Pain lasting <24 hours (VAS score) at 6 months; Group 1: mean 0.6 (SD 0.9); n=13, Group 2: mean 1.9 (SD 2.2); n=15; VAS 0-10 Top=High is poor outcome; Comments: Baseline measures: 4 sachets: 2.2±2.1; 2 sachets: 3.7±3.5
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in baseline pain scores.; Group 1 Number missing: 3; Group 2 Number missing: 3
- Actual outcome: Bloating (VAS score) at 6 months; Group 1: mean 1.8 (SD 2.1); n=13, Group 2: mean 2.3 (SD 2); n=15; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in baseline pain scores.; Group 1 Number missing: 3; Group 2 Number missing: 3

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYMBIOTICS (4 SACHETS/DAY) versus NO INTERVENTION Protocol outcome 1: Symptom control (pain relief) - Actual outcome: Pain lasting <24 hours (VAS score) at 6 months; MD; , Comments: Baseline measures vs 6 months: 4 sachets: 2.2±2.1 vs 0.6±0.9. No change was observed in the control group, values not provided.; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in baseline pain scores.; Group 1 Number missing: 3; Group 2 Number missing: 1 - Actual outcome: Bloating (VAS score) at 6 months; MD; , Comments: Baseline measures vs 6 months: 4 sachets: 3.9±2.9 vs 1.8±2.1 (p<0.05). No change was observed in the control group, values not provided.; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in baseline pain scores.; Group 1 Number missing: 3; Group 2 Number missing: 1 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SMBIOTICS (2 SACHETS/DAY) versus NO INTERVENTION Protocol outcome 1: Symptom control (pain relief) - Actual outcome: Pain lasting <24 hours (VAS score) at 6 months; MD; , Comments: Baseline measures vs 6 months: 2 sachets: 3.7±3.5 vs 1.9±2.2 (p=0.23). No change was observed in the control group, values not provided.; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in baseline pain scores.; Group 1 Number missing: 3; Group 2 Number missing: 1 - Actual outcome: Bloating (VAS score) at 6 months; MD; , Comments: Baseline measures vs 6 months: 2 sachets: 4.6±2.6 vs 2.3±2.0 (p<0.05). No change was observed in the control group, values not provided.; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in baseline pain scores.; Group 1 Number missing: 3; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Brodribb 1977[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Large bowel symptoms and the radiological changes of diverticular disease
Exclusion criteria	Evidence of complications or other colonic disorders. Receiving treatment at the time of the study.
Recruitment/selection of patients	Referred from the general surgeons and the gastroenterological clinic.
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): 9/9. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: High fibre diet . Bran crispbread supplying 6.7g of dietary fibre. Dietary regimen not reported. Duration 3 months. Concurrent medication/care: No treatment. Indirectness: No indirectness (n=9) Intervention 2: No intervention/placebo - Placebo. Wheat crispbread supplying 0.6g of dietary fibre. Dietary regimen not reported. Duration 3 months. Concurrent medication/care: No treatment. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FIBRE DIET versus PLACEBO

Protocol outcome 1: Symptom control (pain relief)
- Actual outcome: Pain score at 3 months; MD; -7.5 (p value: 0.02) 0-15 Top=High is poor outcome, Comments: High fibre symptom change: from 11.1 to 1.1 (-10) Control symptom change: from 12.7 to 10.2 (-2.5);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Baseline details: Demographic data not reported; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Symptom control (bowel habit) - Actual outcome: Total symptom score at 3 months; MD; (p value: <0.002) 0-50 Top=High is poor outcome, Comments: High fibre symptom change: from 34.3 to 8.1 (-26.2) Control symptom change: from 42.0 to 35.1 (-6.9); Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Demographic data not reported; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Dyspeptic score at 3 months; Mean; -4.6 (p value : Not significant) Top=High is poor outcome, Comments: High fibre symptom change: from 11.4 to 3.7 (-7.7) Control symptom change: from 14.7 to 11.6 (-3.1); Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Demographic data not reported; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Bowel dysfunction score at 3 months; MD; -6.8 (p value: Not significant), Comments: High fibre symptom change: from 11.7 to 3.3 (-8.4) Control symptom change: from 14.9 to 13.3 (-1.6)); Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Demographic data not reported; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Colecchia 2007[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=307)
Countries and setting	Conducted in Italy; Setting:
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of diverticular disease was performed by colonoscopy in 46.2% of patients treated with Rifaximin and in 53.7% of patients treated with fibers, and by barium enema in 60.9% and 48.8% of patients, respectively
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 40 and 80 years, endoscopic or radiological evidence of diverticular disease of the sigmoid and/or descending colon, presence of symptoms attributable to the diverticular disease of the colon such as lower abdominal pain/discomfort, bloating, tenesmus, diarrhea and abdominal tenderness. Patients who referred the continuous presence of three, or more, of these symptoms for at least 1 month before the enrolment entered in the study.
Exclusion criteria	Presence of a solitary diverticulum of the right colon, signs of complicated diverticular disease, previous colonic surgery, neoplastic or haematological diseases, immunodeficiency, pregnancy and questionable ability to cooperate. Patients who assumed antibiotics in the previous 4 weeks were also excluded.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Rifaximin + fibre group: 63.6 (11.7); fibre group: 60.7 (12.5). Gender (M:F): 118/198. Ethnicity: Not stated
Further population details	
Extra comments	Five clinical variables (lower abdominal pain/discomfort, bloating, tenesmus, diarrhea and abdominal tenderness) were graded according to the following scale: 0 = no symptoms; 1 = mild symptoms, easily tolerated; 2 = moderate symptoms, sufficient to cause interference with normal daily activities; 3 = severe, incapacitating symptoms, with inability to perform normal daily activities. Consequently the global score could range from 0 (absence of symptoms) to 15 (presence of all symptoms with the higher degree of severity).
Indirectness of population	No indirectness

Interventions	(n=184) Intervention 1: Combination of interventions - Fibre supplement + antibiotic. Rifaximin (400 mg twice a day for 7 d every month) plus dietary fibre supplementation (at least 20 gr/d). Duration 24 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=123) Intervention 2: High fibre diet . Dietary fibre supplementation (at least 20 gr/d). Duration 24 months. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRE SUPPLEMENT + ANTIBIOTIC versus HIGH FIBRE DIET Protocol outcome 1: Progression of disease: acute diverticulitis (clinical examination) - Actual outcome: Diverticulitis at 24 months; Group 1: 2/184, Group 2: 4/123 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25; Group 2 Number missing: 23 Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation) - Actual outcome: Rectal bleeding at 24 months; Group 1: 2/184, Group 2: 1/123 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25; Group 2 Number missing: 23 Protocol outcome 3: Symptom control (pain relief) - Actual outcome: Symptom score at 24 months; Group 1: mean 1 (SD 0.7); n=184, Group 2: mean 2.4 (SD 1.7); n=123; Global score 0-15 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25; Group 2 Number missing: 23 Protocol outcome 4: Side effects of antibiotics: nausea and vomiting - Actual outcome: Side effects (mainly represented by nausea, headache and weakness) at 24 months; Group 1: 4/184, Group 2: 3/123 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25; Group 2 Number missing: 23	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: need for surgery ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: hospitalisation

Study	Comparato 2007[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=268)
Countries and setting	Conducted in Italy; Setting: Gastroenterological Unit
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by double contrast barium enema and/or colonoscopy.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged between 18 and 85 years; endoscopic and/or radiologic evidence of diverticular disease (with presence of more than five diverticula) of the left colon; and presence of symptoms attributable to diverticular disease of the colon such as upper and/or lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, nausea, emesis, fever, dysuria, and bleeding. Only patients who experienced two or more symptoms for at least 1 month before the enrollment were admitted to the study.
Exclusion criteria	Solitary diverticulum of the colon; signs of diverticulitis; previous colonic surgery; concomitant colonic or extracolonic cancer; use of antibiotics in the previous 4 weeks; chronic hematological and/or hepatic and/or renal diseases; immunodeficiency; pregnancy, or lactation; proven intolerance to rifaximin or mesalazine; and a questionable ability to cooperate.
Recruitment/selection of patients	Consecutive outpatients recruited from Gastroenterological Unit from January 2003 to December 2004
Age, gender and ethnicity	Age - Mean (range): 66.1 (31-81). Gender (M:F): 122/146. Ethnicity: Not reported
Further population details	
Extra comments	Outpatients with uncomplicated diverticular disease of the colon, diagnosed by double contrast barium enema and/or colonoscopy. Twelve clinical variables (upper abdominal pain/discomfort, lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria, bleeding were graded as 0 = no symptom; 1 = mild, symptoms easily tolerated; 2 = moderate, symptoms sufficient to cause interference with usual daily activities; and 3 = severe, incapacitating symptoms with inability to perform normal activities. Patients were invited to return for interim visits whenever they considered it necessary. The Global Symptomatic Score (GSS), calculated as the sum of each symptom score, was assigned to each patient at every clinical evaluation (maximum score = 36).

Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: Antibiotics - Rifaximin. Rifaximin, 200mg bid for 10 days every month. Duration 12 months. Concurrent medication/care: Usual care. No selective dietary regimen was prescribed at entry except the recommendation of a high-fiber diet. Indirectness: No indirectness (n=69) Intervention 2: Antibiotics - Rifaximin. Rifaximin, 400mg bid for 10 days every month. Duration 12 months. Concurrent medication/care: Usual care. No selective dietary regimen was prescribed at entry except the recommendation of a high-fiber diet. Indirectness: No indirectness (n=66) Intervention 3: Aminosalicylates - Mesalazine. Mesalazine, 400mg bid for 10 days every month. Duration 12 months. Concurrent medication/care: Usual care. No selective dietary regimen was prescribed at entry except the recommendation of a high-fiber diet. Indirectness: No indirectness (n=67) Intervention 4: Aminosalicylates - Mesalazine. Mesalazine, 400mg bid for 10 days every month. Duration 12 months. Concurrent medication/care: Usual care. No selective dietary regimen was prescribed at entry except the recommendation of a high-fiber diet. Indirectness: No indirectness (n=135) Intervention 5: Antibiotics - Rifaximin. Rifaximin, 200mg or 400mg bid for 10 days every month. Duration 12 months. Concurrent medication/care: Usual care. No selective dietary regimen was prescribed at entry except the recommendation of a high-fiber diet. Indirectness: No indirectness (n=133) Intervention 6: Aminosalicylates - Mesalazine. Mesalazine, 400mg or 800mg bid for 10 days every month. Duration 12 months. Concurrent medication/care: Usual care. No selective dietary regimen was prescribed at entry except the recommendation of a high-fiber diet. Indirectness: No indirectness
Funding	Academic or government funding (Roberto Farini Foundation for Gastroenterological Research.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN (LOW DOSE) versus RIFAXIMIN (HIGH DOSE)

Protocol outcome 1: Symptom control (bowel habit)
- Actual outcome: Global symptom score at 12 months; Group 1: mean 7.5 (SD 3.27); n=59,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Dropout (3), side effects (2), diverticulitis (2); Group 2 Number missing: 7, Reason: Dropout (3), side effects (3), diverticulitis (1)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE (LOW DOSE) versus MESALAZINE (HIGH DOSE)

Protocol outcome 1: Symptom control (bowel habit) - Actual outcome: Global symptom score at 12 months; Group 1: mean 3.61 (SD 1.89); n=61, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Dropout (3), side effects (1), diverticulitis (1); Group 2 Number missing: 5, Reason: Dropout (3), side effects (2), diverticulitis (0) RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus MESALAZINE Protocol outcome 1: Symptom control (bowel habit) - Actual outcome: Global symptom score at 12 months; Group 1: mean 7.3 (SD 3.51); n=121, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Dropout (6), side effects (5), diverticulitis (3); Group 2 Number missing: 10, Reason: Dropout (6), side effects (3), diverticulitis (1)	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (pain relief) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Hodgson 1977[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Barium enema
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Recruitment/selection of patients	Consecutive patients referred by GP to hospital for confirmation of diverticular disease
Age, gender and ethnicity	Age - Mean (range): Female: 63.8 (47-85); male: 56.8 (30-72). Gender (M:F): Define. Ethnicity: Not stated
Further population details	
Extra comments	A proforma containing 26 questions to include symptoms, signs and the barium enema results was used to standardize history taking and examination. Each question was subdivided to indicate differing degrees of severity, or the simple yes/no format was adopted and the resulting 88 items were given a score ranging from 0-6. Scoring was arranged so that the maximum score was 50, indicating that the patient had severe symptoms and signs.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Laxatives. Methylcellulose B.P. (Celevac) 500 mg, two tablets daily. Duration 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=11) Intervention 2: No intervention/placebo - Placebo. 2 tablets daily. Each tablets consisted of light magnesium carbonate, 100 mg; soluble (modified maize) starch 200 mg; maize starch, 50 mg; sucrose, 50 mg; acacia powder, 220 mg. Duration 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Study funded by industry (WB pharmaceutical provided placebo tablets, methylcellulose (Celevac) tablets and a grant for the trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LAXATIVES versus PLACEBO Protocol outcome 1: Symptom control (pain relief) - Actual outcome: Score (based on signs and symptoms) at 3 months; Group 1: mean 13 (SD 4.2); n=16, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Kruis 2013[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in Germany; Setting: Not stated
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	age 45–80 years; diagnosis of DD with acute pain without serious complications (e.g. peritonitis, abscess, fistula, visible blood on stool not originating from haemorrhoids, ileus, stenosis); lower abdominal pain of moderate or severe intensity on at least four of the previous 7 days before study inclusion; a minimum of four diverticula observed on endoscopy (at least flexible sigmoidoscopy) examination at baseline; and at least four of eight specified symptoms present for at least the previous 2 days before inclusion and still present at study inclusion (i.e. abdominal pain localised mainly in the lower left part of the abdomen; abdominal pain enhanced after meals; abdominal pain decreased after defaecation or wind; bloating; constipation defined as ?2 defaecations/week; diarrhoea, defined as >3 loose stools per day; a sensation of incomplete evacuation after defaecation; and painful lower left abdomen at palpation).
Exclusion criteria	chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis); fever (>38.0 °C by axillary measurement) or other signs of serious complications; a medical history of severe renal disease, defined as serum creatinine >1.5 mg/dL; known intolerance to the study medication; or a requirement for prohibited concomitant medication.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Mesalazine group: 62.8 (8.6); placebo group: 61.9 (8.6). Gender (M:F): 43/74. Ethnicity: Not stated
Further population details	
Extra comments	No concomitant administration of any other drugs for treatment of gastrointestinal tract disorders was permitted that could affect the results or interfere with the study medication, with the exception of short-acting spasmolytics (e.g. butylscopolaminiumbromide) and short-acting analgesics (e.g. paracetamol). Opioids were prohibited. Patient demographics were similar between treatment groups. Both treatment groups were comparable

	with respect to histological and sigmoidoscopic assessments of the diverticula, but there was a nonsignificant trend to a lower proportion of patients with diverticula in the descending colon in the mesalazine group (19.6% vs. 34.4% in the placebo arm, P = 0.073). The combined symptom score at baseline was approximately 10% higher in the mesalazine group vs. the placebo cohort (365.8 ? 115.4 vs. 330.8 ? 109.8, P = 0.091). The mean score for the straining scale (pressing on defaecation) was significantly higher in the mesalazine arm (Table 1). At least one of three inflammatory parameters [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or leucocytes] was elevated in 37.5% (21/56) of patients in the mesalazine group and in 41.0% (25/61) of patients in the placebo group (P = 0.700).
Indirectness of population	--
Interventions	(n=56) Intervention 1: Aminosalicylates - Mesalazine. 1000 mg t.d.s. Salofalk granules, Dr Falk Pharma GmbH. Duration 6 weeks. Concurrent medication/care: All patients were instructed to follow nutritional recommendations including consumption of meals rich in fibre and adequate intake of liquids (at least 2 L/day). 12 of 56 patients (21.4%) in the mesalazine group arm used concomitant analgesics or spasmolytics. Indirectness: No indirectness (n=61) Intervention 2: No intervention/placebo - Placebo. 1000 mg t.d.s. Duration 6 weeks. Concurrent medication/care: All patients were instructed to follow nutritional recommendations including consumption of meals rich in fibre and adequate intake of liquids (at least 2 L/day). 21 of 61 patients (34.4%) in the placebo arm used concomitant analgesics or spasmolytics. Indirectness: No indirectness
Funding	Study funded by industry (Dr Falk Pharma GmbH, Freiburg, Germany)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE versus PLACEBO Protocol outcome 1: Symptom control (pain relief) - Actual outcome: Differences in Aminosalicylate intensity from baseline to week 4 at 4 weeks; Median (range): -37 (-95-25) mesalazine; -33 (-7-–24) placebo); Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Not stated; Group 2 Number missing: 5, Reason: Not stated Protocol outcome 2: Mortality - Actual outcome: Mortality at 6 weeks; Group 1: 0/56, Group 2: 0/61 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Not stated; Group 2 Number missing: 5, Reason: Not stated	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (bowel habit) ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ;

Progression of disease: acute diverticulitis

Study	Kvasnovsky 2017[24]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=143)
Countries and setting	Conducted in United Kingdom; Setting: King's College Hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis by colonoscopy and/or CT scan
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with persistent abdominal symptoms (of at least 3 months duration) with an established diagnosis of uncomplicated diverticulosis (by colonoscopy and/or CT scar)
Exclusion criteria	Previous diagnosis of IBS, surgery for diverticulitis, right sided diverticulitis, predominant bleeding symptoms, complicated diverticulitis, co-existing inflammatory bowel disease.
Recruitment/selection of patients	Consecutive patients attending Diverticular Disease Clinic and King's College Hospital recruited.
Age, gender and ethnicity	Age - Mean (range): 61.8 (52-72). Gender (M:F): 45/98. Ethnicity: White: 62%; Black: 29%; Other: 9%
Further population details	
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Probiotics/prebiotics - Probiotics. Symprove (contains four strains of bacteria) in a water-based suspension of barley extract. To be taken at 1mL/kg each morning. Duration 3 months. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=72) Intervention 2: No intervention/placebo - Placebo. Placebo drink matched for appearance and taste. To be taken every morning. Duration 3 months. Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Academic or government funding (Authors funded by King's College Hospital)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROBIOTICS versus PLACEBO	

Protocol outcome 1: Symptom control (pain relief)
- Actual outcome: Abdominal pain at 3 months; Group 1: mean -0.7 (SD 1.6); n=56,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Back pain at 3 months; Group 1: mean -0.5 (SD 2.2); n=56,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Abdominal pain (likelihood of daily frequency of symptom) at 3 months; OR; 0.61 (95%CI 0.25 to 1.5) (p value: 0.28) ;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Back pain (likelihood of daily frequency of symptom) at 3 months; OR; 0.33 (95%CI 0.11 to 0.99) (p value: 0.047) ;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)

Protocol outcome 2: Symptom control (bowel habit)
- Actual outcome: Constipation at 3 months; Group 1: mean -0.4 (SD 1.3); n=56,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Diarrhoea at 3 months; Group 1: mean -0.4 (SD 1.4); n=56,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Per rectum bleeding at 3 months; Group 1: mean -0.02 (SD 1.2); n=56,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Mucorrhea at 3 months; Group 1: mean -0.1 (SD 1.3); n=56,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2
Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)
- Actual outcome: Dysuria at 3 months; Group 1: mean -0.2 (SD 1.2); n=56,

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Bloating at 3 months; Group 1: mean -0.8 (SD 1.8); n=56, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Constipation (likelihood of daily frequency of symptom) at 3 months; OR; 0.36 (95%CI 0.13 to 1.02) (p value: 0.05) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Diarrhoea (likelihood of daily frequency of symptom) at 3 months; OR; 0.49 (95%CI 0.21 to 1.11) (p value: 0.09) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Per rectum bleeding (likelihood of daily frequency of symptom) at 3 months; OR; 0.3 (95%CI 0.07 to 1.2) (p value 0.09) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Mucorrhea (likelihood of daily frequency of symptom) at 3 months; OR; 0.39 (95%CI 0.14 to 1.07) (p value: 0.07) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Dysuria (likelihood of daily frequency of symptom) at 3 months; OR; 0.41 (95%CI 0.14 to 1.18) (p value: 0.1) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial) - Actual outcome: Bloating (likelihood of daily frequency of symptom) at 3 months; OR; 0.65 (95%CI 0.27 to 1.6) (p value: 0.33) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial); Group 2 Number missing: 8, Reason: Lost to follow-up, adverse events, life circumstances (not related to trial)	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Lahner 2012[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Italy; Setting: Gastroenterology units
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: To quantify and localize the colonic diverticula, double contrast enema and/or colonoscopy was performed. Symptoms of patients were evaluated by assessing the presence/absence and intensity of abdominal pain lasting more or less than 24 h and the presence/absence and intensity of abdominal bloating. Patients were asked to grade the intensity of abdominal symptoms on a visual analogic scale (VAS)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Well-established diagnosis of symptomatic uncomplicated DD, and age ranging from 40 to 80 years.
Exclusion criteria	Presence of less than 5 diverticula, recent history (< 3 mo) or actual clinical evidence of acute diverticulitis, previous colonic surgery, antibiotics, mesalazine, nonsteroidal anti-inflammatory drugs or laxative use during the four weeks before enrolment, coexisting inflammatory bowel disease, diseases with possible small intestine bacterial over-growth, if dyspeptic symptoms were predominant over abdominal symptoms, and when low compliance or motivation could be expected for any reason.
Recruitment/selection of patients	Consecutive outpatients. Cluster randomization
Age, gender and ethnicity	Age - Mean (SD): High fibre + probiotics: 68.1 (8.6); high fibre diet alone: 63.8 (10.3). Gender (M:F): 17/35. Ethnicity: Not stated
Further population details	
Extra comments	Rescue medication was not allowed during the study period. All patients were given an information sheet regarding the content of dietary fibre in commonly consumed fruits, vegetables and cereals, and dietary counselling was performed.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Combination of interventions - High fibre diet + probiotics/prebiotics. High-fibre diet containing at least 30 g daily intake of dietary fibre. Flortec a natural symbiotic agent, consisting of the synergistic combination of

	Lactobacillus paracasei (L. paracasei) B21060 (probiotic component) and arabinogalactan/xylooligosaccharides (prebiotic component).7 g sachet contains 5 × 10^9 colony-forming units viable lyophilized L. paracasei B12060 to dissolve the powder preparation in 100 mL of water once daily and to ingest it immediately 2 h after lunch. Duration 6 months. Concurrent medication/care: Daily water intake of at least 1.5 L. Indirectness: No indirectness (n=22) Intervention 2: High fibre diet . High-fibre diet containing at least 30 g daily intake of dietary fibre. Duration 6 months. Concurrent medication/care: Daily water intake of at least 1.5 L. Indirectness: No indirectness
Funding	Study funded by industry (The study was in part supported by Bracco Spa (Milan, Italy))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FIBRE DIET + PROBIOTICS/PREBIOTICS versus HIGH FIBRE DIET Protocol outcome 1: Symptom control (pain relief) - Actual outcome: Abdominal pain lasting <24 h at 6 months; Group 1: mean 2.2 (SD 0.8); n=30, Group 2: mean 2 (SD 1.9); n=72; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: New onset constipation; worsening of abdominal symptoms ; Group 2 Number missing: 0, Reason: NA - Actual outcome: Abdominal pain lasting >24 h at 6 months; Group 1: mean 4.5 (SD 2.1); n=30, Group 2: mean 5.5 (SD 3.5); n=22; VAS 0-10 Top=High is poor outcome; Comments: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: New onset constipation; worsening of abdominal symptoms ; Group 2 Number missing: 0, Reason: NA	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Latella 2003[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=968)
Countries and setting	Conducted in Italy; Setting: 16 Italian cooperative centers
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 40 and 80 years, endoscopic or radiological evidence of diverticular disease of the sigmoid and/or descending colon, and the presence of troublesome symptoms attributable to the diverticular disease of the colon such as upper and/or lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, and abdominal tenderness. Only patients who had continuously had three or more of these symptoms for at least 1 month (immediately before the trial) entered in the study.
Exclusion criteria	Solitary diverticulum of the colon, signs of diverticulitis, previous colonic surgery, concomitant colonic or extracolonic cancer, use of antibiotics in the previous 4 weeks, hematological disease, immunodeficiency, pregnancy, questionable ability to cooperate, and inability to give informed consent according to the Helsinki Declaration.
Recruitment/selection of patients	Consecutive outpatients
Age, gender and ethnicity	Age - Mean (SD): Fibre+antibiotics: 62.8 (12.6); fibre: 62.9 (11.7). Gender (M:F): Define. Ethnicity: Not stated
Further population details	
Extra comments	Patients who developed complications (diverticulitis, rectal bleeding) or side effects (evaluated by an interview questionnaire and a clinic visit) were withdrawn from the study. Patients who voluntarily stopped the treatment or were lost to follow-up were considered drop-outs.
Indirectness of population	No indirectness
Interventions	(n=595) Intervention 1: Combination of interventions - Fibre supplement + antibiotic. 4 g/day glucomannan (Dicoman 5, Dicofarm, Rome, Italy) + 400 mg rifaximin (Normix, Alfa Wassermann, Bologna, Italy) twice daily for 7 days every month. Duration 12 months. Concurrent medication/care: NA. Indirectness: No indirectness (n=373) Intervention 2: High fibre diet - High fibre diet (soluble). Glucomannan (Dicoman 5, Dicofarm, Rome, Italy) 4

	g/day. Duration 12 months. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Study funded by industry (This study is supported, in part, by Alfa Wassermann, Bologna, Italy.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRE SUPPLEMENT + ANTIBIOTIC versus HIGH FIBRE DIET (SOLUBLE) Protocol outcome 1: Progression of disease: acute diverticulitis (Clinical, laboratory, and radiological examination) - Actual outcome: Diverticulitis at 12 months; Group 1: 6/595, Group 2: 11/373 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37, Reason: 10 side effect; 19 drop outs; 8 complications; Group 2 Number missing: 27, Reason: 5 side effect; 10 drop outs; 12 complications Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation) - Actual outcome: Complications (rectal bleeding) at 12 months; Group 1: 2/595, Group 2: 1/373 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37, Reason: 10 side effect; 19 drop outs; 8 complications; Group 2 Number missing: 27, Reason: 5 side effect; 10 drop outs; 12 complications Protocol outcome 3: Symptom control (pain relief) - Actual outcome: Global symptomatic score at 12 months; Group 1: mean 1 (SD 0.9); n=595, Group 2: mean 2 (SD 1.1); n=373; Comments: 6 clinical variables are considered : upper abdominal pain/discomfort, lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, and abdominal tenderness. Each variable was graded using the following score system: 0=no symptom; 1=mild, symptoms easily tolerated; 2=moderate, symptoms sufficient to cause interference with normal activities; 3=severe, incapacitating, with inability to perform normal activities, using a standard database card. A global symptomatic score was calculated by the sum of the single variable scores in each patient at every clinical visit (maximum score 18). Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37, Reason: 10 side effect; 19 drop outs; 8 complications; Group 2 Number missing: 27, Reason: 5 side effect; 10 drop outs; 12 complications Protocol outcome 4: Side effects of antibiotics: nausea and vomiting - Actual outcome: Side effects (nausea, headache, and asthenia) at 12 months; Group 1: 10/595, Group 2: 5/373 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37, Reason: 10 side effect; 19 drop outs; 8 complications; Group 2 Number missing: 27, Reason: 5 side effect; 10 drop outs; 12 complications	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: need for surgery ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: hospitalisation

Study	Mario 2005[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=170)
Countries and setting	Conducted in Italy; Setting: Gastroenterological Unit
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 18 and 85 years, endoscopic and/or radiologic evidence of DD(with the presence of more than five diverticula) of the left colon and the presence of symptoms attributable to the DD of the colon such as upper and/or lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, and dysuria. Only patients who experienced two or more symptoms for at least 1 month before enrolment entered the study.
Exclusion criteria	Solitary diverticulum of the colon, signs of diverticulitis, previous colonic surgery, concomitant colonic or extracolonic cancer, use of antibiotics in the previous 4 weeks, chronic hematological and/or hepatic and/or renal diseases, immunodeficiency, pregnancy or lactation, proven intolerability to rifaximin or mesalazine, and questionable ability to cooperate.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Rifaximin 200: 66 (7.1); Rifaximin 400: 66 (10.9); Mesalazine 400: 67 (9.5); Mesalazine 800: 67 (9.2). Gender (M:F): 88/82. Ethnicity: Not stated
Further population details	
Extra comments	Patients who developed complications or side effects, recorded by means of a structured clinical interview at every clinical evaluation or at any time required, were withdrawn from the study. Patients who voluntarily stopped the treatment or were lost to follow-up were considered dropouts.
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Antibiotics - Rifaximin. Rifaximin 200 mg twice a day for 10 days during the first part of every month. Duration 3 months. Concurrent medication/care: Recommendation for all patients to follow a high-fiber diet. Indirectness: No indirectness

	(n=43) Intervention 2: Antibiotics - Rifaximin. Rifaximin 400 mg twice a day for 10 days during the first part of every month. Duration 3 months. Concurrent medication/care: Recommendation for all patients to follow a high-fiber diet. Indirectness: No indirectness (n=40) Intervention 3: Aminosalicylates - Mesalazine. Mesalazine 400 mg twice a day for 10 days every month. Duration 3 months. Concurrent medication/care: Recommendation for all patients to follow a high-fiber diet. Indirectness: No indirectness (n=48) Intervention 4: Aminosalicylates - Mesalazine. Mesalazine 800 mg twice a day for 10 days every month. Duration 3 months. Concurrent medication/care: Recommendation for all patients to follow a high-fiber diet. Indirectness: No indirectness
Funding	Other (This work was carried out under the auspices of the Roberto Farini Foundation for Gastroenterological Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus RIFAXIMIN

Protocol outcome 1: Symptom control (pain relief)
- Actual outcome: Global Symptomatic Score of symptoms at 3 months; Group 1: mean 7.6 (SD 5.5); n=39, Group 2: mean 5.9 (SD 3.6); n=43; Global Symptomatic Score (GSS) 0-33 Top=High is poor outcome; Comments: 11 clinical variables (upper abdominal pain/discomfort, lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria) scored as follows: 0 = no symptoms; 1 = mild, symptoms easily tolerated; 2 = moderate, symptoms sufficient to cause interference with usual daily activities; and 3 = severe, incapacitating symptoms with inability to perform normal activities. The Global Symptomatic Score (GSS) is the sum of all symptom scores
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus MESALAZINE

Protocol outcome 1: Symptom control (pain relief)
- Actual outcome: Global Symptomatic Score of symptoms at 3 months; Group 1: mean 6.7 (SD 4.1); n=82, Group 2: mean 5.7 (SD 3.8); n=88; Comments: 11 clinical variables (upper abdominal pain/discomfort, lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria) scored as follows: 0 = no symptoms; 1 = mild, symptoms easily tolerated; 2 = moderate, symptoms sufficient to cause interference with usual daily activities; and 3 = severe, incapacitating symptoms with inability to perform normal activities. The Global Symptomatic Score (GSS) is the sum of all symptom scores
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE versus MESALAZINE Protocol outcome 1: Symptom control (pain relief) - Actual outcome: Global Symptomatic Score of symptoms at 3 months; Group 1: mean 6.7 (SD 4); n=40, Group 2: mean 4.9 (SD 3.4); n=48; Global Symptomatic Score (GSS) 0-33 Top=High is poor outcome; Comments: 11 clinical variables (upper abdominal pain/discomfort, lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria) scored as follows: 0 = no symptoms; 1 = mild, symptoms easily tolerated; 2 = moderate, symptoms sufficient to cause interference with usual daily activities; and 3 = severe, incapacitating symptoms with inability to perform normal activities. The Global Symptomatic Score (GSS) is the sum of all symptom scores. Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Papi 1992[36]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=217)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with uncomplicated diverticular disease.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 65 (10.7). Gender (M:F): 105/112. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=107) Intervention 1: Combination of interventions - Fibre supplement + antibiotic. 2g glucomannan/day plus rifaxamin 400mg/bid for 7 days every months. Duration 12 months. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=110) Intervention 2: High fibre diet . 2g glucomannan/day for 7 days every months. Duration 12 months. Concurrent medication/care: usual care. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRE SUPPLEMENT + ANTIBIOTIC versus FIBRE SUPPLEMENT

Protocol outcome 1: Symptom control (bowel habit)
- Actual outcome: Global symptom score at 12 months; MD; -2.1 (p: <0.001), Comments: Values read from a graph. Variance not reported.);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Lost to follow-up (7), Death (3), Complications (3); Group 2 Number missing: 13, Reason: Lost to follow-up (4), Death (1), Complications (1) - Actual outcome: Occurrence rate of symptoms at 12 months; Mean; , Comments: After 12 months the percent of symptomatic patients was significantly lower in the group treated with glucomannan plus rifaximin ($p<0.001$ for bloating and abdominal pain, $p<0.01$ for tenesmus and abdominal tenderness). No statistical difference was found for the occurrence of diarrhoea, low grade fever, or chills and fever. ; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Lost to follow-up (7), Death (3), Complications (3); Group 2 Number missing: 13, Reason: Lost to follow-up (4), Death (1), Complications (1)	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (pain relief) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Papi 1995[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=168)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by double contrast barium enema and/or colonoscopy.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients with symptomatic uncomplicated diverticular disease of the colon, diagnosed by double contrast barium enema and/or colonoscopy.
Exclusion criteria	Not reported
Recruitment/selection of patients	Outpatients. Recruitment not reported
Age, gender and ethnicity	Age - Mean (range): 61.9 (40-84). Gender (M:F): 68/100. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Combination of interventions - Fibre supplement + antibiotic. Glucomannan 2g/day plus rifaximin 400mg/bid for 7 days every month. Duration 12 months. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=84) Intervention 2: No intervention/placebo - Placebo. Glucomannan 2g/day plus placebo tablet b.d for 7 days every month. Duration 12 months. Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Study funded by industry (Alfa Wassermann)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRE SUPPLEMENT + ANTIBIOTIC versus FIBRE SUPPLEMENT + PLACEBO

Protocol outcome 1: Symptom control (bowel habit)
- Actual outcome: Global symptom score at 12 months; MD; -1.2 (p: <0.001), Comments: Values read from a graph.);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 9, Reason: Lost to follow-up (6), other disease (1), diverticulitis (2); Group 2 Number missing: 8, Reason: Lost to follow-up (3), other disease (3), diverticulitis (2) - Actual outcome: Symptom severity at 12 months; Mean; , Comments: Bloating, abdominal pain, and abdominal tenderness was significantly affected by antibiotic treatment at 12 months ($p<0.05$). No statistical difference was observed for other symptoms (upper abdominal pain, diarrhoea, and tenesmus); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9, Reason: Lost to follow-up (6), other disease (1), diverticulitis (2); Group 2 Number missing: 8, Reason: Lost to follow-up (3), other disease (3), diverticulitis (2)	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Symptom control (pain relief) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Smits 1990[43]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=43)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Proven diverticular disease.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic, proven diverticular disease, aged 18-70.
Exclusion criteria	No other abdominal pathology.
Recruitment/selection of patients	Patients referred to outpatient centre were included
Age, gender and ethnicity	Age - Mean (range): 59.5 (41-70). Gender (M:F): 15/28. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Laxatives. Lactulose: 15ml bd, to be reduced to 10ml bd if appropriate. Duration 12 weeks. Concurrent medication/care: Patients received dietetic supervision throughout the study. Indirectness: No indirectness (n=21) Intervention 2: High fibre diet . High fibre diet: provided an intake of 30-40g of fibre daily. Duration 12 weeks. Concurrent medication/care: Patients received dietetic supervision throughout the study. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LAXATIVES versus HIGH FIBRE DIET

Protocol outcome 1: Symptom control (pain relief)
- Actual outcome: Pain on bowel movement (frequency) at 12 weeks; Group 1: mean -1.5 days (SD 2.32); n=18, Group 2: mean -0.75 days (SD 1.85); n=21; Comments: Values read across from a graph
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0
- Actual outcome: Pain on bowel movement (severity) at 12 weeks; Group 1: mean -2.85 (SD 4.88); n=18,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0
- Actual outcome: Abdominal pain (frequency) at 12 weeks; Group 1: mean -2.55 days (SD 2.86); n=18, Group 2: mean -1.55 days (SD 2.86); n=21
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0
- Actual outcome: Abdominal pain (severity) at 12 weeks; Group 1: mean -3 (SD 4.32); n=18,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0

Protocol outcome 2: Symptom control (bowel habit)
- Actual outcome: Abdominal distension (frequency) at 12 weeks; Mean; , Comments: Changes from baseline to week 12 within groups and change scores between groups were not significant. ;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0
- Actual outcome: Abdominal distension (severity) at 12 weeks; Mean; , Comments: Changes from baseline to week 12 within groups and change scores between groups were not significant. ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0
- Actual outcome: Wind (frequency) at 12 weeks; Mean; , Comments: Changes from baseline to week 12 within groups and change scores between groups were not significant. ;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0
- Actual outcome: Wind (severity) at 12 weeks; Mean; , Comments: Changes from baseline to week 12 within groups and change scores between groups were not significant. ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Abdominal pain, nausea, moving from area, failure to attend clinic.; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Progression of disease: hospitalisation ; Progression of disease: need for surgery ; Progression of disease: complications (infections, abscesses, perforation) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: acute diverticulitis

Study	Tursi 2013[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Italy; Setting: Outpatients
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptomatic uncomplicated diverticular disease (SUDD) was defined as the presence of symptoms (mainly abdominal pain, but also constipation, diarrhoea and bloating) in patients with diverticulosis, in the absence of any complication (stenoses, abscesses, fistulas), in whom the presence of abdominal pain was recorded in the lower left quadrant as lasting for >24 consecutive hours. Computerised tomography was performed in case of suspected acute diverticulitis symptoms (e.g. abdominal pain associated with fever)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 years; diverticulosis showed by colonoscopy no more than 6 months prior to study entry; symptomatic episode of uncomplicated diverticular disease no more than 4 weeks prior to study entry; patients who have given their free and informed consent; negative pregnancy test at the screening visit; agreement to use a valid contraceptive method for the duration of the study; patients not requiring hospitalisation; patients willing and able to provide written informed consent
Exclusion criteria	Acute diverticulitis (both complicated and uncomplicated); diverticular colitis; active or recent peptic ulcer; chronic renal insufficiency; allergy to salicylates; lactulose-lactitol use in the 2 weeks before the enrolment and during the study; use of probiotic preparations either prescribed or over the counter within 2 weeks prior to study entry; patients with active malignancy of any type, or history of a malignancy; recent history or suspicion of alcohol abuse or drug addiction; any severe pathology that can interfere with the treatment or the clinical or instrumental tests of the trial; use of nonsteroidal anti-inflammatory drugs for 1 week before and throughout the study period (only paracetamol was permitted).
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (range): 64 (57-65). Gender (M:F): 109/101. Ethnicity: Not stated
Further population details	
Extra comments	. Concomitant medications were permitted during the course of the study, if used at a constant dosage and if they had been started at least 1 month before the baseline visit. Use of usual laxatives. only if absolutely necessary. was

	permitted, but lactulose was not allowed during the study period. The investigator was permitted to treat the patients with any supportive therapy considered necessary for the patient's health.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Aminosalicylates - Mesalazine. Active Pentacol 800, 2 tablets/day for 10 days/month plus Enterolactis Plus placebo, 1 sachet/ day for 10 days/month. Duration 12 months. Concurrent medication/care: Avoid a high fibre diet. Indirectness: No indirectness (n=55) Intervention 2: Probiotics/prebiotics - Probiotics. Active Enterolactis Plus, 1 sachet/day for 10 days/month plus Pentacol 800 placebo, 2 tablets/day for 10 days/month. Duration 12 months. Concurrent medication/care: Avoid high fibre diet. Indirectness: No indirectness (n=54) Intervention 3: Combination of interventions - Aminosalicylates + probiotics. Active Pentacol 800, 2 tablets/day plus Active Enterolactis Plus, 1 sachet/day for 10 days/month. Duration 12 months. Concurrent medication/care: Avoid high fibre diet. Indirectness: No indirectness (n=50) Intervention 4: No intervention/placebo - Placebo. Pentacol 800 placebo, 2 tablets/day and Enterolactis Plus placebo, 1 sachet/day for 10 days/month. Duration 12 months. Concurrent medication/care: Avoid high fibre diet. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Pentacol 800 and Enterolactis Plus, as well as the placebos, were supplied by the manufacturing company (Sofar S.p.A., Trezzano Rosa (MI), Italy) for the entire duration of the trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE versus PROBIOTICS

Protocol outcome 1: Progression of disease: acute diverticulitis (computerised tomography was performed in case of suspected acute diverticulitis symptoms)
- Actual outcome: Acute diverticulitis at 12 months; Group 1: 0/51, Group 2: 1/55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation)
- Actual outcome: Perforation at 12 months; Group 1: 0/51, Group 2: 0/55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE versus AMINOSALICYLATES + PROBIOTICS

Protocol outcome 1: Progression of disease: acute diverticulitis (computerised tomography was performed in case of suspected acute diverticulitis symptoms)
- Actual outcome: Acute diverticulitis at 12 months; Group 1: 0/51, Group 2: 0/54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation)
- Actual outcome: Perforation at 12 months; Group 1: 0/51, Group 2: 0/54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE versus PLACEBO

Protocol outcome 1: Progression of disease: acute diverticulitis (computerised tomography was performed in case of suspected acute diverticulitis symptoms)
- Actual outcome: Acute diverticulitis at 12 months; Group 1: 0/51, Group 2: 6/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation)
- Actual outcome: Perforation at 12 months; Group 1: 0/51, Group 2: 1/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROBIOTICS versus AMINOSALICYLATES + PROBIOTICS

Protocol outcome 1: Progression of disease: acute diverticulitis (computerised tomography was performed in case of suspected acute diverticulitis symptoms)
- Actual outcome: Acute diverticulitis at 12 months; Group 1: 1/55, Group 2: 0/54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation)
- Actual outcome: Perforation at 12 months; Group 1: 0/55, Group 2: 0/54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROBIOTICS versus PLACEBO

Protocol outcome 1: Progression of disease: acute diverticulitis (computerised tomography was performed in case of suspected acute diverticulitis symptoms) - Actual outcome: Acute diverticulitis at 12 months; Group 1: 1/55, Group 2: 6/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation) - Actual outcome: Perforation at 12 months; Group 1: 0/55, Group 2: 1/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOSALICYLATES + PROBIOTICS versus PLACEBO Protocol outcome 1: Progression of disease: acute diverticulitis (computerised tomography was performed in case of suspected acute diverticulitis symptoms) - Actual outcome: Acute diverticulitis at 12 months; Group 1: 0/54, Group 2: 6/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Progression of disease: complications (infections, abscesses, perforation) - Actual outcome: Perforation at 12 months; Group 1: 0/54, Group 2: 1/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Progression of disease: need for surgery ; Symptom control (pain relief) ; Symptom control (bowel habit) ; Mortality ; Side effects of antibiotics: nausea and vomiting ; Side effects of antibiotics: diarrhoea ; Side effects of antibiotics: infections related to antibiotics ; Progression of disease: hospitalisation

Appendix E: Forest plots

E.1 High fibre diet compared to control diet for diverticular disease

Figure 2: Symptoms: Global symptom score

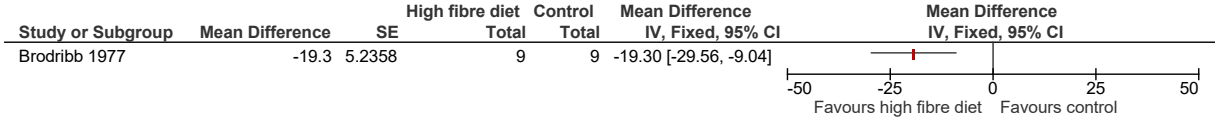
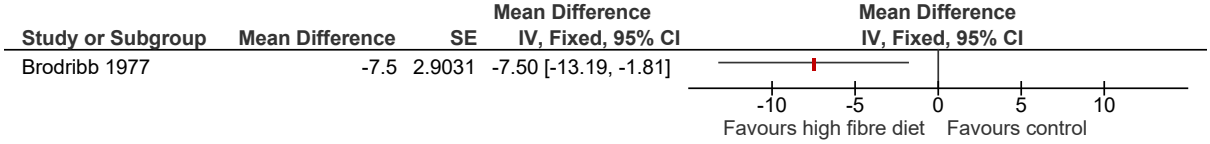


Figure 3: Symptoms: Pain score



E.2 High fibre diet + antibiotics compared to high fibre diet for diverticular disease

Figure 4: Side effects (nausea, headache, and asthenia)

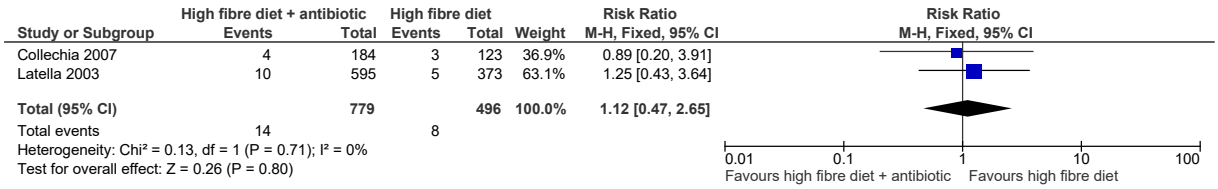


Figure 5: Progression of diseases: Diverticulitis

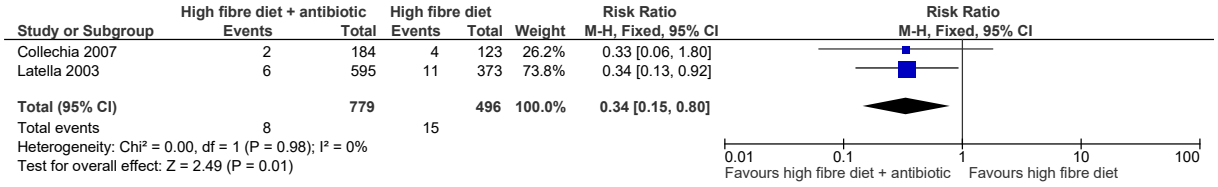


Figure 6: Complications: Rectal bleeding

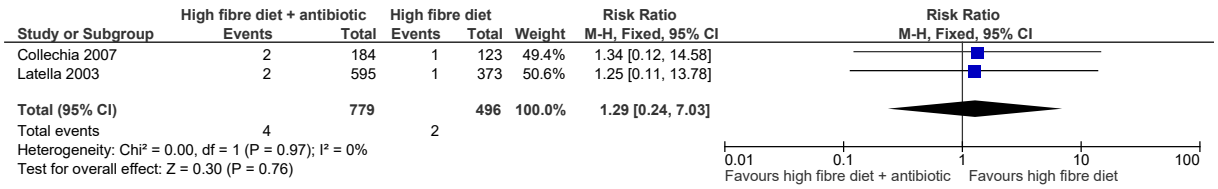
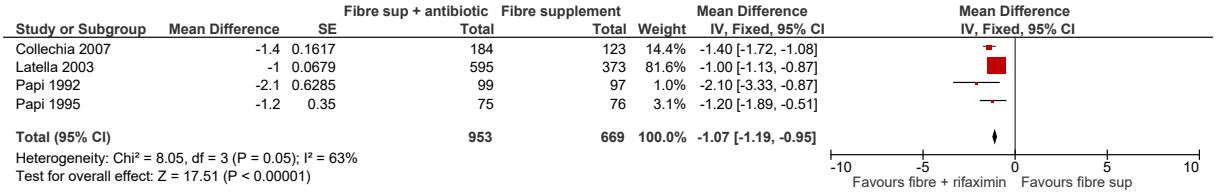


Figure 7: Symptoms: Global symptom score



E.3 High fibre diet + symbiotic compared to high fibre diet for diverticular disease

Figure 8: Symptoms: Abdominal pain lasting <24 hrs

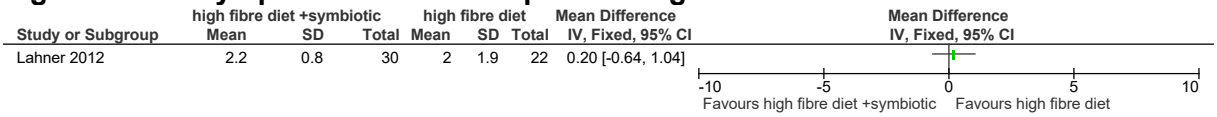
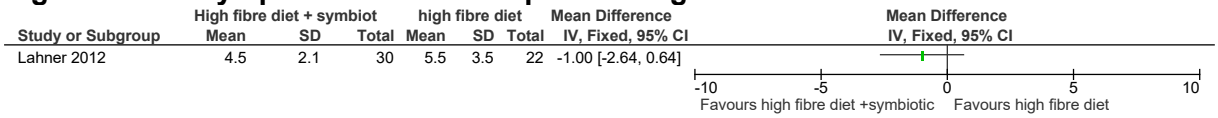


Figure 9: Symptoms: Abdominal pain lasting >24 hrs



E.4 Antibiotic (200mg) compared to antibiotic (400mg) for diverticular disease

Figure 10: Symptoms: Global symptom score (at 3 months)

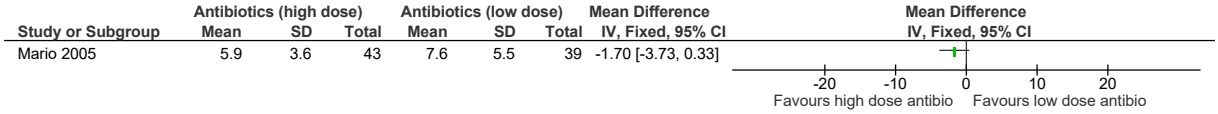
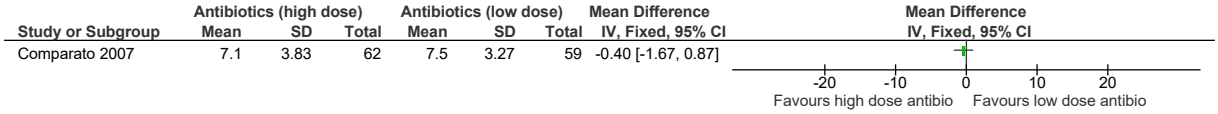


Figure 11: Symptoms: Global symptom score (at 12 months)



E.5 Aminosalicylate (400mg) compared to aminosalicylate (800mg) for diverticular disease

Figure 12: Symptoms: Global symptom score (at 3 months)

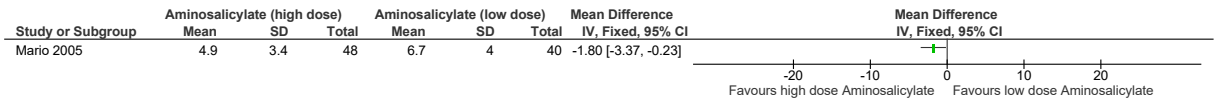
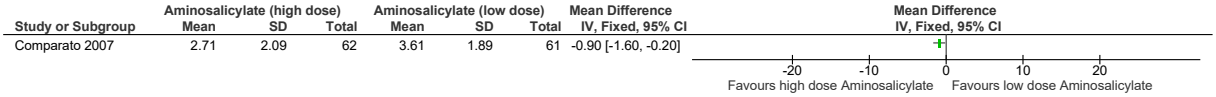


Figure 13: Symptoms: Global symptom score (at 12 months)



E.6 Antibiotic compared to aminosalicylate for diverticular disease

Figure 14: Symptoms: Global symptom score (at 3 months)

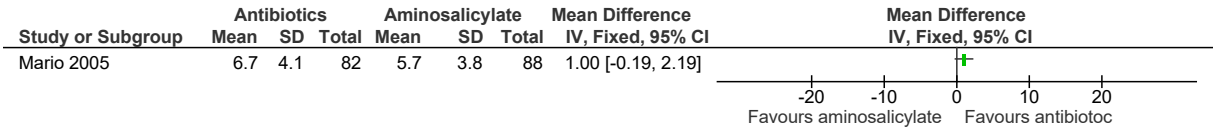
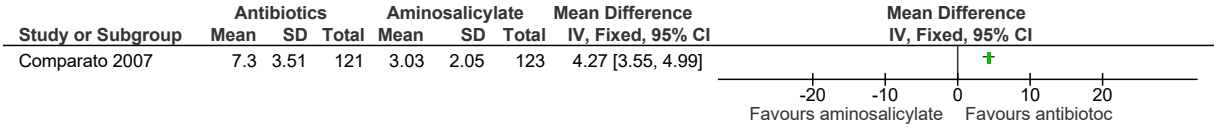


Figure 15: Symptoms: Global symptom score (at 12 months)



E.7 Aminosalicylates + probiotics compared to Aminosalicylates for diverticular disease

Figure 16: Progression of disease: Acute diverticulitis

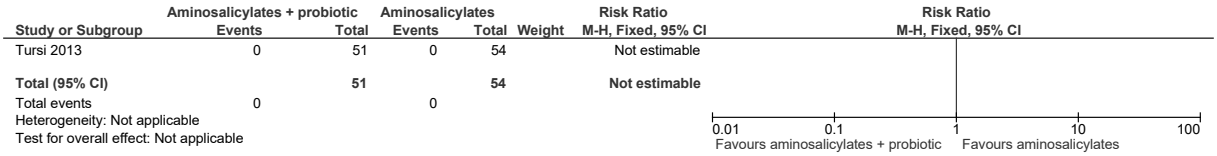
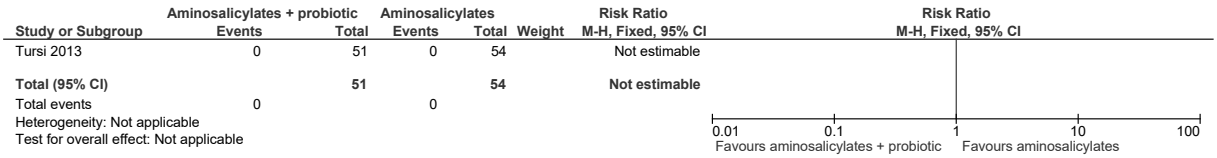


Figure 17: Complication: Perforation



E.8 Aminosalicylates + probiotic compared to Probiotic for diverticular disease

Figure 18: Progression of disease: Acute diverticulitis

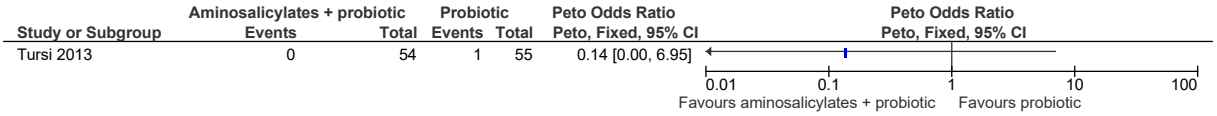
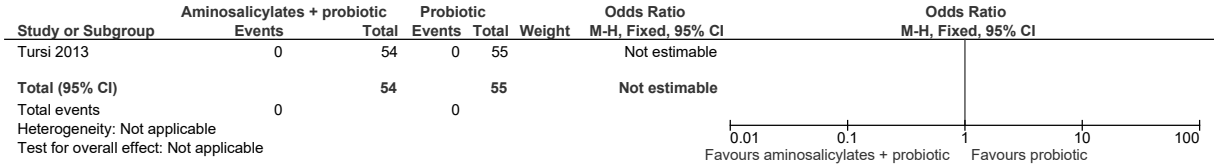


Figure 19: Complication: Perforation



E.9 Aminosalicylates + probiotic compared to placebo for diverticular disease

Figure 20: Progression of disease: Acute diverticulitis

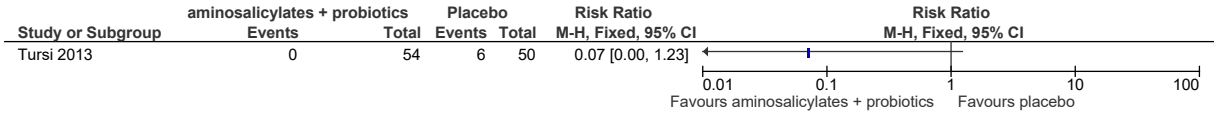
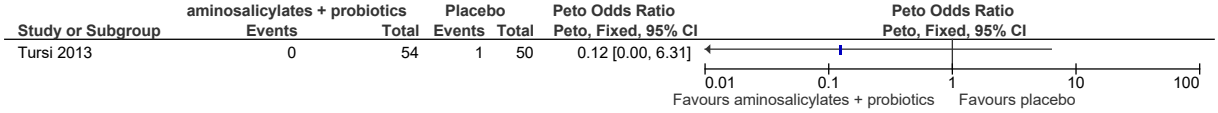


Figure 21: Complication: Perforation



E.10 Aminosalicylates compared to Probiotic for diverticular disease

Figure 22: Progression of disease: Acute diverticulitis

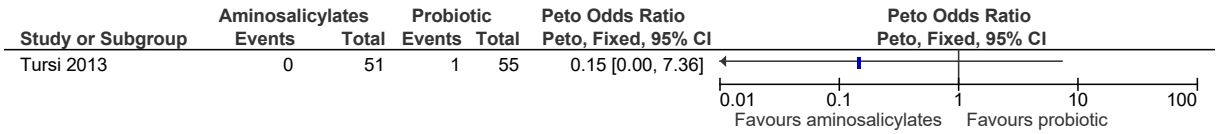
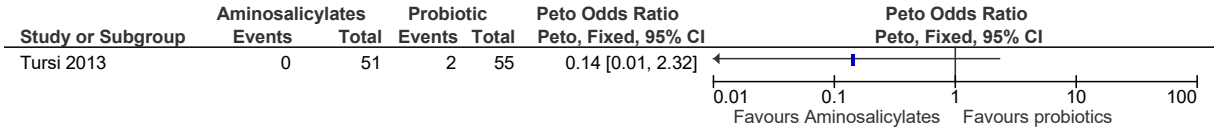


Figure 23: Complication: Perforation



E.11 Aminosalicylates compared to placebo for diverticular disease

Figure 24: Mortality

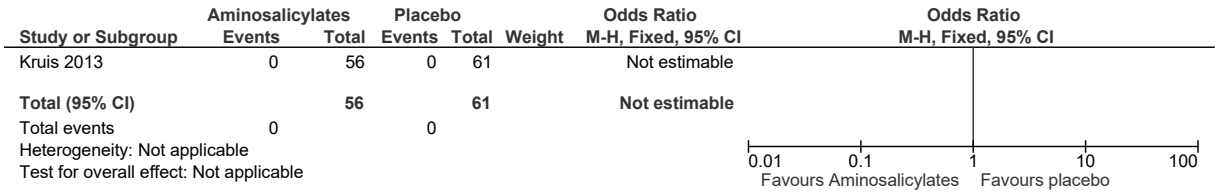


Figure 25: Progression of disease: Acute diverticulitis

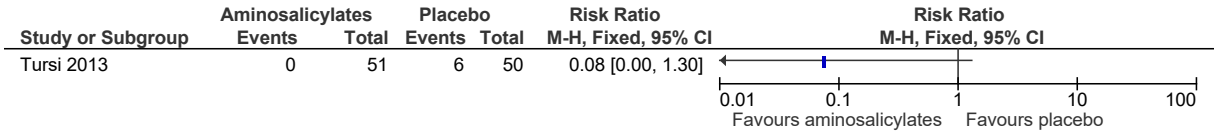
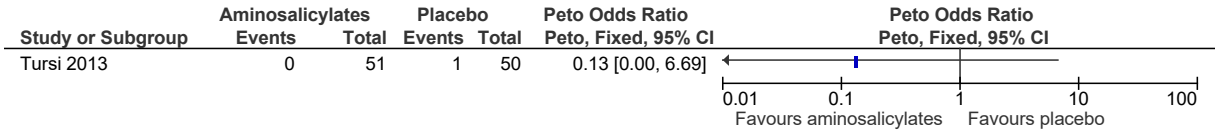


Figure 26: Complication: Perforation



E.12 Probiotic compared to placebo for diverticular disease

Figure 27: Symptoms: Abdominal pain frequency score

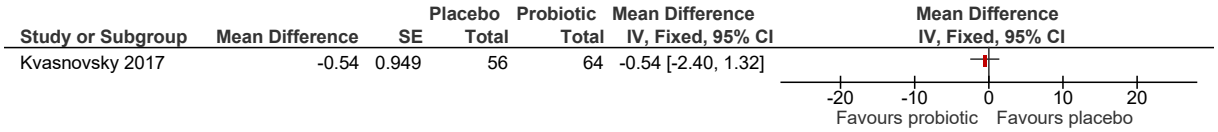


Figure 28: Symptoms: Abdominal pain frequency score

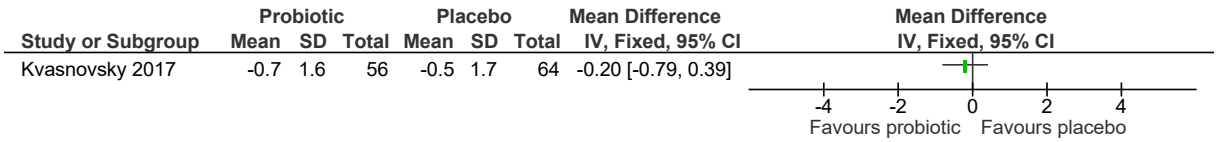


Figure 29: Symptoms: Constipation frequency score

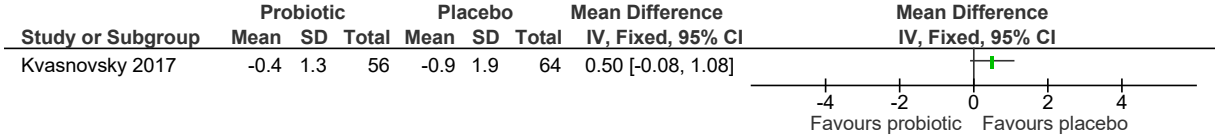


Figure 30: Symptoms: Diarrhoea frequency score

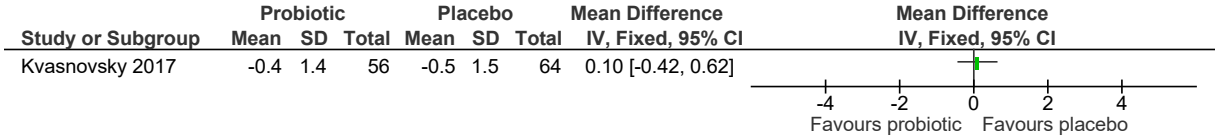


Figure 31: Complications: Rectal bleeding frequency score

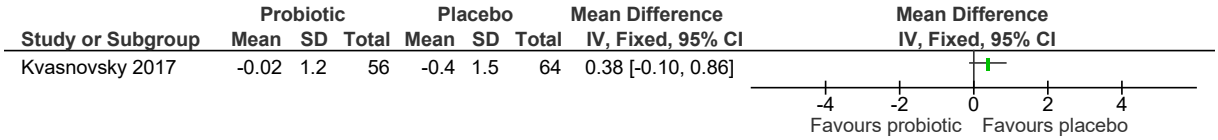


Figure 32: Symptoms: Abdominal pain (likelihood of daily frequency of symptom)

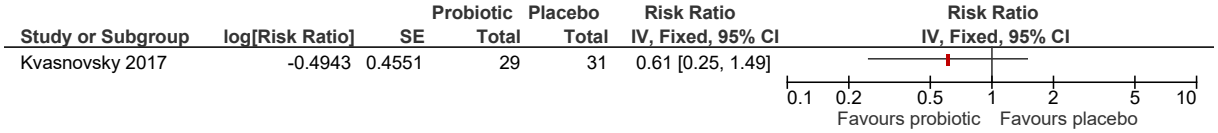


Figure 33: Symptoms: Constipation (likelihood of daily frequency of symptom)

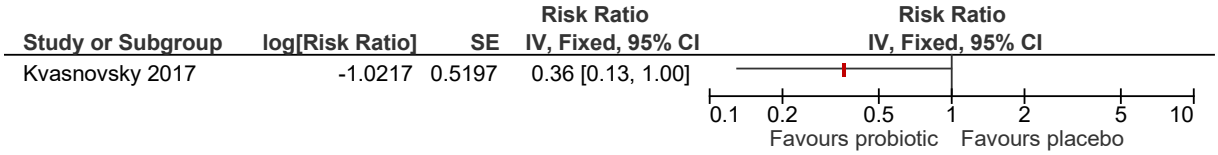


Figure 34: Symptoms: Diarrhoea (likelihood of daily frequency of symptom)

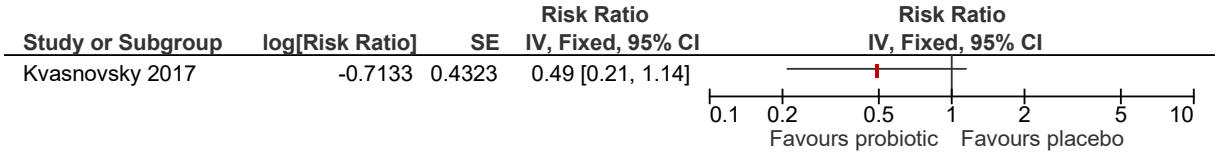


Figure 35: Complications: Rectal bleeding (likelihood of daily frequency of symptom)

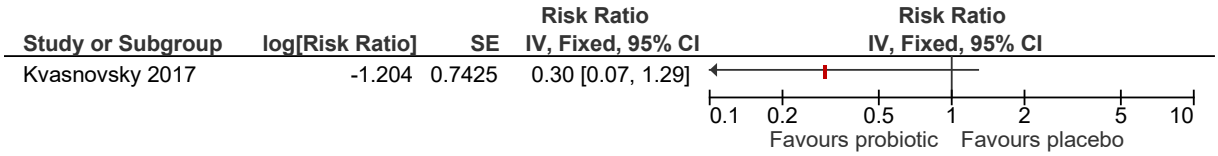


Figure 36: Progression of disease: Acute diverticulitis

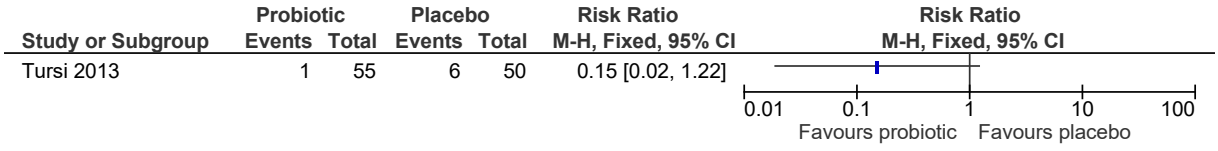
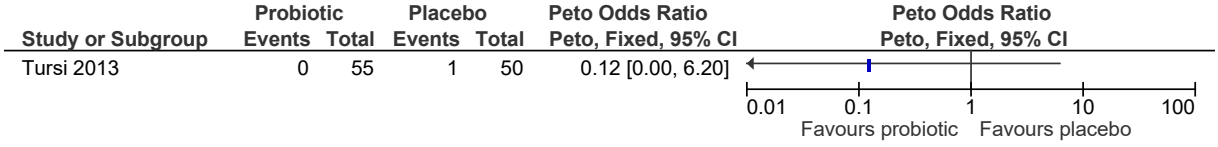


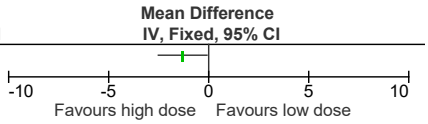
Figure 37: Complication: Perforation



E.13 Symbiotic (2 sachets) compared to Symbiotic (1 sachet) for diverticular disease

Figure 38: Symptoms: Pain

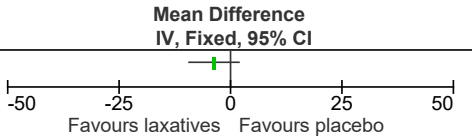
Study or Subgroup	Symbiotic (high dose) Mean	SD	Total	Symbiotic (low dose) Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Annibale 2011	0.6	0.9	13	1.9	2.2	15	-1.30 [-2.52, -0.08]



E.14 Laxatives compared to placebo for diverticular disease

Figure 39: Symptoms: Symptom score

Study or Subgroup	Laxatives Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hodgson 1977	13	4.2	16	16.7	8.8	11	-3.70 [-9.29, 1.89]



E.15 Laxatives compared to high fibre diet for diverticular disease

Figure 40: Symptoms: Abdominal pain (frequency)

Study or Subgroup	Laxative Mean	SD	Total	High fibre diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Smits 1990	-2.55	2.8634	18	-1.55	2.8602	21	-1.00 [-2.80, 0.80]

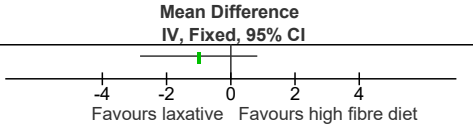
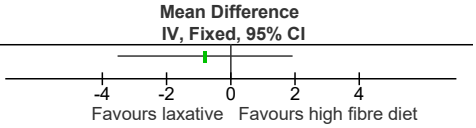


Figure 41: Symptoms: Abdominal pain (severity)

Study or Subgroup	Laxative Mean	SD	Total	High fibre diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Smits 1990	-3	4.3177	18	-2.2	4.2552	21	-0.80 [-3.50, 1.90]



Appendix F: GRADE tables

Table 32: Clinical evidence profile: High fibre diet compared to control diet for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High fibre diet	Control diet	Relative (95% CI)	Absolute		
Global symptom score (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 19.3 lower (29.56 to 9.04 lower)	⊕⊕OO LOW	CRITICAL
Pain score (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9	9	-	MD 7.5 lower (13.19 to 1.81 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 33: Clinical evidence profile: High fibre diet + antibiotics compared to high fibre diet for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High fibre diet + antibiotics	High fibre diet	Relative (95% CI)	Absolute		
Side effects (nausea, headache, and asthenia) (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/779 (1.8%)	1.9%	RR 1.12 (0.47 to	2 more per 1000 (from 10 fewer to 31	⊕OOO VERY LOW	IMPORTANT

									2.65)	more)		
Progression of diseases (diverticulitis) (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/779 (1%)	3.1%	RR 0.34 (0.15 to 0.8)	20 fewer per 1000 (from 6 fewer to 26 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Complications (rectal bleeding) (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/779 (0.51%)	0.5%	RR 1.29 (0.24 to 7.03)	1 more per 1000 (from 4 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Global symptomatic score (follow-up 12-24 months; range of scores: 0-15; Better indicated by lower values)												
4	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	953	669	-	MD 1.07 lower (1.19 to 0.95 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 34: Clinical evidence profile: High fibre diet + symbiotic compared to high fibre diet for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High fibre diet + symbiotic**	**High fibre diet**	**Relative (95% CI)**	**Absolute**		
Abdominal pain lasting <24h (follow-up mean 6 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	22	-	MD 0.2 higher (0.64 lower to 1.04 higher)	⊕⊕OO LOW	CRITICAL
Abdominal pain lasting >24h (follow-up mean 6 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	22	-	MD 1 lower (2.64 lower to 0.64 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 35: Clinical evidence profile: Antibiotic (200mg) compared to antibiotic (400mg) for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic (low dose)	Antibiotic (high dose)	Relative (95% CI)	Absolute		
Global Symptomatic Score at 3 months (follow-up mean 3 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43	39	-	MD 1.7 lower (3.73 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL
Global Symptomatic Score at 12 months (follow-up mean 12 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	59	62	-	MD 0.4 lower (1.67 lower to 0.87 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence profile: Aminosalicylate (400mg) compared to aminosalicylate (800mg) for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate (low dose)	Aminosalicylate (high dose)	Relative (95% CI)	Absolute		
Global Symptomatic Score at 3 months (follow-up mean 3 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	48	-	MD 1.8 lower (3.37 to 0.23 lower)	⊕OOO VERY LOW	CRITICAL

Global Symptomatic Score at 12 months (follow-up mean 12 months; range of scores: 0-33; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	62	-	MD 0.9 lower (1.6 to 0.2 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 37: Clinical evidence profile: Antibiotic compared to aminosalicylate for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic**	**Aminosalicylate**	**Relative (95% CI)**	**Absolute**		
Global Symptomatic Score at 3 months (follow-up mean 3 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	82	88	-	MD 1 higher (0.19 lower to 2.19 higher)	⊕OOO VERY LOW	CRITICAL
Global Symptomatic Score at 12 months (follow-up mean 12 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	121	123	-	MD 4.27 higher (3.55 to 4.99 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 38: Clinical evidence profile: Aminosalicylates + probiotics compared to Aminosalicylates for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylates + probiotics**	**Aminosalicylates**	**Relative (95% CI)**	**Absolute**		

Acute diverticulitis (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/51 (0%)	0%	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
Perforation (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/51 (0%)	0%	-	-	⊕⊕⊕⊕ HIGH	CRITICAL

Table 39: Clinical evidence profile: Aminosalicylates + probiotic compared to Probiotic for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylates + probiotic**	**Probiotic**	**Relative (95% CI)**	**Absolute**		
Acute diverticulitis (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/54 (0%)	2.6%	Peto OR 0.14 (0.0 to 6.95)	22 fewer per 1000 (from 26 fewer to 155 more)	⊕⊕OO LOW	CRITICAL
Perforation (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/54 (0%)	0%	not pooled	not pooled	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 40: Clinical evidence profile: Aminosalicylate + probiotic compared to placebo for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylate + probiotic**	**Placebo**	**Relative (95% CI)**	**Absolute**		

Acute diverticulitis (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/54 (0%)	12%	Peto OR 0.11 (0.02 to 0.58)	107 fewer per 1000 (from 50 fewer to 96 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Perforation (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/54 (0%)	2%	Peto OR 0.12 (0 to 6.31)	18 fewer per 1000 (from 20 fewer to 106 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 41: Clinical evidence profile: Aminosalicylates compared to Probiotic for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylates**	**Probiotic**	**Relative (95% CI)**	**Absolute**		
Acute diverticulitis (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/51 (0%)	2.6%	Peto OR 0.15 (0.04 to 3.37)	22 fewer per 1000 (from 26 fewer to 165 more)	⊕⊕OO LOW	CRITICAL
Perforation (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/51 (0%)	3.6%	Peto OR 0.14 (0.01 to 2.32)	31 fewer per 1000 (from 36 fewer to 48 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 42: Clinical evidence profile: Aminosalicylate compared to placebo for diverticular disease

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate	Placebo	Relative (95% CI)	Absolute		
Mortality (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/56 (0%)	0%	-	-	⊕⊕⊕O MODERATE	CRITICAL
Acute diverticulitis (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/51 (0%)	12%	RR 0.08 (0 to 1.3)	110 fewer per 1000 (from 120 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Perforation (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/51 (0%)	2%	Peto OR 0.33 (0 to 6.69)	13 fewer per 1000 (from 20 fewer to 114 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: Clinical evidence profile: Aminosalicylate (continuous) compared to aminosalicylate (cyclic) for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate (continuous)	Aminosalicylate (cyclic)	Relative (95% CI)	Absolute		
Progression of disease: acute diverticulitis (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/18 (0%)	6.3%	Peto OR 0.12 (0 to 6.06)	55 fewer per 1000 (from 63 fewer to 319 more)	⊕OOO VERY LOW	CRITICAL
Symptom free (overall symptomatic score=0) (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/18 (77.8%)	56.3%	RR 1.38 (0.84 to 2.27)	214 more per 1000 (from 90 fewer to 715 more)	⊕⊕OO LOW	CRITICAL

Irregularly slight or mild symptoms (overall symptomatic score=12) (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/18 (11.1%)	18.8%	RR 0.59 (0.11 to 3.11)	77 fewer per 1000 (from 167 fewer to 397 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 44: Clinical evidence profile: Probiotic compared to placebo for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Probiotic**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Abdominal pain severity (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	64	-	MD 0.54 lower (2.4 lower to 1.3 higher)	⊕⊕⊕O MODERATE	CRITICAL
Abdominal pain (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	64	-	MD 0.2 lower (0.79 lower to 0.39 higher)	⊕⊕⊕O MODERATE	CRITICAL
Constipation (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56	64	-	MD 0.5 higher (0.08 lower to 1.08 higher)	⊕⊕OO LOW	CRITICAL
Diarrhoea (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	64	-	MD 0.1 higher (0.42 lower to 0.62 higher)	⊕⊕⊕O MODERATE	CRITICAL
Per rectum bleeding (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56	64	-	MD 0.38 higher (0.1 lower to 0.86 higher)	⊕⊕OO LOW	CRITICAL

Abdominal pain (likelihood of daily frequency of symptom) (follow-up mean 3 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/29 (0%)	0%	RR 0.61 (0.25 to 1.49)	-	⊕OOO VERY LOW	CRITICAL
Constipation (likelihood of daily frequency of symptom) (follow-up mean 3 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/29 (0%)	0%	RR 0.36 (0.13 to 1)	-	⊕⊕OO LOW	CRITICAL
Diarrhoea (likelihood of daily frequency of symptom) (follow-up mean 3 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/29 (0%)	0%	RR 0.49 (0.21 to 1.14)	-	⊕⊕OO LOW	CRITICAL
Per rectum bleeding (likelihood of daily frequency of symptom) (follow-up mean 3 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/29 (0%)	0%	RR 0.3 (0.07 to 1.29)	-	⊕OOO VERY LOW	CRITICAL
Acute diverticulitis (follow-up mean 12 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/55 (1.8%)	12%	RR 0.15 (0.02 to 1.22)	102 fewer per 1000 (from 118 fewer to 26 more)	⊕⊕⊕O MODERATE	CRITICAL
Perforation (follow-up mean 12 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/55 (0%)	2%	Peto OR 0.12 (0 to 6.2)	18 fewer per 1000 (from 20 fewer to 104 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 45: Clinical evidence profile: Symbiotic (2 sachets) compared to Symbiotic (1 sachet) for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Symbiotic	Symbiotic	Relative	Absolute		

studies		bias				considerations	(high dose)	(low dose)	(95% CI)			
Pain (follow-up mean 6 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	15	-	MD 1.3 lower (2.52 to 0.08 lower)	⊕⊕OO LOW	CRITICAL
Bloating (follow-up mean 6 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13	15	-	MD 0.5 lower (2.03 lower to 1.03 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 46: Clinical evidence profile: Laxatives compared to placebo for diverticular disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laxatives	Placebo	Relative (95% CI)	Absolute		
Symptoms score (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	11	-	MD 3.7 lower (9.29 lower to 1.89 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 47: Clinical evidence profile: Laxatives compared to high fibre diet for diverticular disease

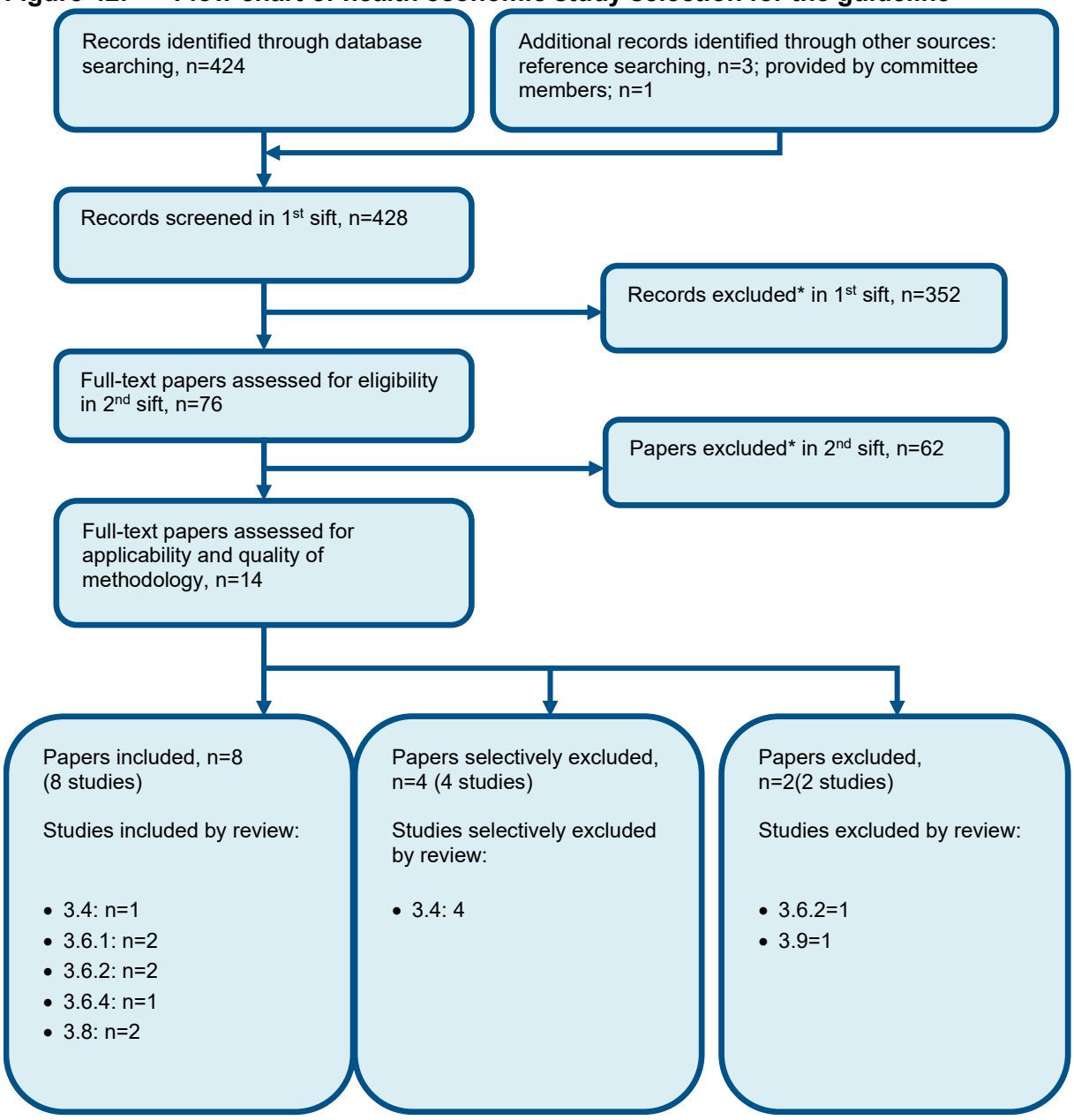
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laxative	High fibre diet	Relative (95%	Absolute		

									CI)			
Pain on bowel movement (frequency) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	21	-	MD 0.75 lower (2.08 lower to 0.58 higher)	⊕OOO VERY LOW	CRITICAL
Pain on bowel movement (severity) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	21	-	MD 1.3 lower (3.93 lower to 1.33 higher)	⊕OOO VERY LOW	CRITICAL
Abdominal pain (frequency) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	21	-	MD 1 lower (2.8 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Abdominal pain (severity) (follow-up mean 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	21	-	MD 0.8 lower (3.5 lower to 1.9 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 42: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3.4 Non-surgical treatment of acute diverticulitis (Evidence review H)

3.6.1 Timing of surgery (Evidence review J)

3.6.2 Laparoscopic versus open resection (Evidence review K)

3.6.4 Primary versus secondary anastomosis (Evidence review M)

3.8 Laparoscopic lavage versus resection for perforated diverticulitis (Evidence review O)

3.9 Management of recurrent diverticulitis (Evidence review P)

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 48: Studies excluded from the clinical review

Study	Exclusion reason
Barbara 2016[2]	Systematic review: studies already included in review
Brandimarte 2004[3]	No comparison group
Brodribb 1976[5]	Observational study. Evidence already attained through RCTs.
Campbell 1991[6]	Inappropriate comparison
Carabotti 2017[7]	Systematic review: studies already included in review
Carter 2012[8]	Protocol only
Cianci 2014[9]	No relevant outcome
Cuomo 2017[12]	Systematic review: studies already included in review
D'incà 2007[13]	Crossover study
Eastwood 1978[14]	Incorrect study design – case-control study
Freckelton 2017[15]	Incorrect interventions
Fric 2003[16]	Incorrect interventions
Gatta 2010[18]	Systematic review: studies already included in review
Gatta 2012[17]	Observational study. Evidence already attained through RCTs.
Heaton 1981[19]	Incorrect study design – literature review
Hyland 1980[21]	No comparison group
Kruis 2014[22]	Incorrect study design – literature review/guideline
Lahner 2016[25]	Systematic review: studies already included in review
Lamiki 2010[27]	No relevant outcome
Leahy 1985[29]	Not review population
Maconi 2017[30]	No relevant outcomes
Makola 2007[31]	Incorrect study design – literature review
Moniuszko 2017[33]	No comparison group

Ornstein 1981[35]	Crossover study
Picchio 2016[38]	Systematic review: methods are not adequate/unclear
Pistoia 2004[39]	No comparison group
Rocco 2009[40]	Systematic review: studies already included in review
Schug-pass 2010[41]	Not review population
Smith 1981[42]	Incorrect interventions
Sopena 2011[44]	Incorrect study design – literature review
Stallinger 2014[45]	No comparison group
Strate 2009[46]	Not review population
Suchowiecky 1987[47]	Crossover study
Talbot 1981[48]	Incorrect study design – review/editorial (summary of technical report)
Tarleton 2011[49]	Literature review
Tarpila 1978[50]	No relevant outcome
Taylor 1976[51]	Crossover study
Trespi 1997[53]	Not in English
Trespi 1999[52]	Not in English
Tursi 2007[57]	Not review population
Tursi 2008[58]	Incorrect study design – case-control study
Tursi 2008[55]	No relevant outcomes
Tursi 2013[54]	Commentary - insufficient information reported
Tursi 2013[59]	Observational study. Evidence already attained through RCTs.
Tursi 2016[60]	Systematic review: studies already included in review
Unlu 2012[61]	Systematic review: studies already included in review
Zullo 2010[62]	Incorrect study design – literature review

H.2 Excluded health economic studies

None.

Appendix I: Research recommendations

I.1 Management of diverticular disease

Research question: What is the most clinically and cost effective treatment for diverticular disease?

Why this is important:

Diverticular disease causes significant patient discomfort and morbidity. It accounts for a significant number of GP consultations each year in England and Wales. If symptoms are poorly controlled, diverticular disease can lead to specialist hospital referral, investigations and related health related expense.

The committee did not consider that the available evidence was of sufficient quality or quantity to be able to make a definitive recommendation for any intervention in the management of diverticular disease

Table 49: Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults (>18 years) with symptoms suggestive of Diverticular disease (intermittent abdominal pain and tenderness in left lower quadrant, often triggered by eating and relieved by defecation associated with changes in bowel habit), with confirmed findings of Diverticulae on either luminal endoscopy or imaging e.g. CT scan. **Intervention / Comparison:** **1.** Use of bulk-forming laxatives e.g. Ispaghula Husk (Fybogel), Methylcollulose (Celevac) or Sterculia (Normacol) in addition to guidance on an healthy, balanced diet vs. Guidance on an healthy balanced diet including whole grains, fruit and vegetables only **2.** Regular Use of Antispasmodics e.g. Mebeverine or Hyoscine Butylbromide, in addition to simple analgesia i.e. Paracetamol Vs. Simple Analgesia i.e. Paracetamol only **3.** Use of Probiotics/Prebiotics vs Placebo **Outcomes:** • Quality of Life (QoL) scores • Pain scores • Frequency of GP appointments and hospitalisation • Rate of future development of Acute Diverticulitis
Importance to	If a particular strategy can be identified that is most clinically and cost

patients or the population	effective, it could increase the number of people treated with confidence in primary care and reduce the rate of specialist referral.
Relevance to NICE guidance	There is current uncertainty and lack of evidence about optimal medical management of symptomatic Diverticular disease.
Relevance to the NHS	Research in this area will inform NICE recommendations around conservative management
Current evidence base	The committee did not consider that the available evidence was of sufficient quality or quantity to be able to make a clear recommendation for any intervention in the management of diverticular disease
Equality	Patients of Asian origin may develop right sided Diverticular disease and so present differently e.g. right sided abdominal pain
Study design	Large well conducted placebo controlled RCT's If RCT not possible, then a non-randomised cohort study with adequate adjustment for key confounders including a pre-existing diagnosis of Irritable Bowel Syndrome, age, ethnicity, co-morbidities and some measure of baseline health e.g. Quality of Life.
Feasibility	There is a potentially large population of patients with this condition who could be recruited to a trial in primary care. Some patients may require further investigation at the time of recruitment/ onset of the trial to exclude Acute Diverticulitis such as FBC and CRP blood tests.
Other comments	Symptoms of Diverticular disease can overlap with other medical conditions e.g. co-existent Irritable Bowel Syndrome, which presents a risk of confounding.
Importance	Medium