

## Systematic review

# Meta-analysis of antibiotics *versus* appendicectomy for non-perforated acute appendicitis

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**Background:** For more than a century, appendicectomy has been the treatment of choice for appendicitis. Recent trials have challenged this view. This study assessed the benefits and harms of antibiotic therapy compared with appendicectomy in patients with non-perforated appendicitis.

**Methods:** A comprehensive search was conducted for randomized trials comparing antibiotic therapy with appendicectomy in patients with non-perforated appendicitis. Key outcomes were analysed using random-effects meta-analysis, and the quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

**Results:** Five studies including 1116 patients reported major complications in 25 (4.9 per cent) of 510 patients in the antibiotic and 41 (8.4 per cent) of 489 in the appendicectomy group: risk difference  $-2.6$  (95 per cent c.i.  $-6.3$  to  $1.1$ ) per cent (low-quality evidence). Minor complications occurred in 11 (2.2 per cent) of 510 and 61 (12.5 per cent) of 489 patients respectively: risk difference  $-7.2$  ( $-18.1$  to  $3.8$ ) per cent (very low-quality evidence). Of 550 patients in the antibiotic group, 47 underwent appendicectomy within 1 month: pooled estimate  $8.2$  (95 per cent c.i.  $5.2$  to  $11.8$ ) per cent (high-quality evidence). Within 1 year, appendicitis recurred in 114 of 510 patients in the antibiotic group: pooled estimate  $22.6$  ( $15.6$  to  $30.4$ ) per cent (high-quality evidence). For every 100 patients with non-perforated appendicitis, initial antibiotic therapy compared with prompt appendicectomy may result in 92 fewer patients receiving surgery within the first month, and 23 more experiencing recurrent appendicitis within the first year.

**Conclusion:** The choice of medical *versus* surgical management in patients with clearly uncomplicated appendicitis is value- and preference-dependent, suggesting a change in practice towards shared decision-making is necessary.

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## Introduction

Acute appendicitis is the most common indication for emergency abdominal surgery worldwide: approximately one in every ten individuals will have acute appendicitis during their lifetime<sup>1</sup>. In the UK alone, approximately 40 000 appendicectomies are performed every year. Although appendicectomy is a routine surgical procedure with low mortality, 5–28 per cent of patients develop a complication<sup>2</sup>.

Since surgeons identified appendicitis as a source of pelvic sepsis and subsequent high mortality,

appendicectomy has been considered mandatory<sup>3,4</sup>. In 1956, Coldrey<sup>5</sup> challenged this view in a report of 137 patients with acute appendicitis for more than 24 h treated with antibiotics rather than surgery. In 1977, researchers from China<sup>6</sup> reported successful treatment of 92.9 per cent of 425 patients with acute appendicitis by traditional Chinese medicine alone. Nevertheless, appendicectomy remained the standard treatment for appendicitis<sup>7</sup>.

Another challenge to convention appeared in 1995 when a small randomized clinical trial (RCT)<sup>8</sup> comparing antibiotics with appendicectomy suggested no difference

in efficacy. In the past 10 years, improved CT, allowing more accurate diagnosis of acute appendicitis and preoperative differentiation of perforated *versus* non-perforated appendicitis, has encouraged the conduct of additional RCTs<sup>9–14</sup>.

A number of systematic reviews<sup>15–25</sup> have attempted to synthesize the published evidence. However, earlier systematic reviews were limited by varying outcome definitions for antibiotic treatment *versus* surgery<sup>18,22,23</sup>, inclusion of retracted studies<sup>22,23,25</sup>, and inclusion of a study<sup>11</sup> at very high risk of bias<sup>16,22,25</sup>. Furthermore, since the publication of the most recent meta-analysis<sup>15</sup>, the results of two additional eligible RCTs have become available<sup>13,14</sup>.

The present systematic review and meta-analysis evaluated the relative merits of antibiotic therapy *versus* appendicectomy in patients with acute non-perforated appendicitis. The approach was to consider the studies in a practical or pragmatic way, rather than using a mechanistic or explanatory perspective<sup>26</sup>. The interest was not in comparing appendicectomy with an antibiotic for all management, but rather in comparing a management strategy of immediate appendicectomy *versus* the clinically sensible alternative of antibiotics initially, with appendicectomy as necessary, depending on the response to antibiotics. This perspective guided presentation of the results.

## Methods

### Eligibility of studies

RCTs that compared antibiotic treatment with appendicectomy in patients with suspected acute non-perforated appendicitis were included. Quasi-RCTs were also included, but only in the sensitivity analysis. Studies with a very high risk of bias, in which both the description of methods and the baseline characteristics indicated that many patients randomized were not included, were excluded.

### Data sources and searches

The comprehensive search conducted in the 2011 Cochrane systematic review of Wilms and colleagues<sup>22</sup>, which extended until June 2011, was updated. This consisted of three blocks of search terms for the concepts appendicitis, appendicectomy and antibiotic treatment, limited by the Cochrane filters for RCTs and the McMaster University Health Information Research Unit Clinical Queries hedges for therapeutic studies. The searches were adapted and run without language restrictions in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1 January 2011

to 4 December 2015. PubMed was also searched for in-process citations, and the major clinical trial registries (ClinicalTrials.gov: <http://clinicaltrials.gov/>; International Clinical Trials Registry Platform Search Portal (ICTRP): <http://apps.who.int/trialsearch/>) were searched for ongoing trials. *Appendix S1* (supporting information) shows details of the search strategy. In addition, reference lists of other previous systematic reviews<sup>15–21,23,24</sup> comparing antibiotic treatment with appendicectomy in patients with non-perforated appendicitis were searched.

### Study selection

Using standard, pilot-tested forms and working in teams of two, reviewers screened all titles and abstracts identified by the literature search independently, and obtained full-text articles of any article identified as potentially eligible by either reviewer. The reviewers used standard, pilot-tested forms to evaluate the full texts for eligibility and resolved disagreement by discussion or, if necessary, by consulting with a third reviewer.

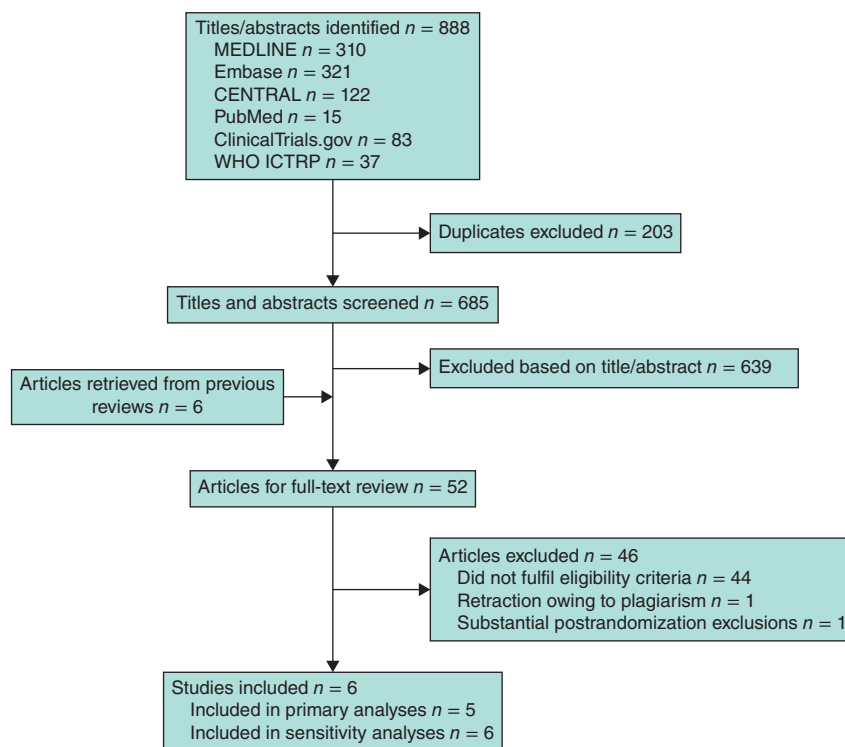
### Data extraction

Using standard pilot-tested forms along with detailed instructions and working in teams of two, reviewers extracted data independently. A clinician–methodologist adjudicator resolved disagreements. Finally, authors were contacted to check the data for accuracy, and to provide additional information regarding the original studies, when needed.

The following data were extracted: sample size, participants' characteristics, antibiotic regimens and details of surgical management (laparoscopic or open, any antibiotic use), and the following outcomes (for both treatment groups): major complications at 1 year, including Clavien–Dindo complication classification grade III or above (conditions requiring endoscopic, radiological or surgical intervention, or causing organ dysfunction or death), such as appendiceal perforation, as well as deep infections, incisional hernias and adhesive bowel obstruction not requiring intervention; minor complications at 1 year, such as superficial wound infections, diarrhoea and abdominal discomfort; confirmed or suspected recurrence of appendicitis between 1 month and 1 year; rate of appendicectomy within 1 month of intervention; duration of hospital stay; and duration of sick leave.

### Risk of bias

In the risk-of-bias assessment, each study was evaluated using a modified version of the Cochrane Collaboration's



**Fig. 1** Flow chart showing selection of articles for review. WHO, World Health Organization; ICTRP, International Clinical Trials Registry Platform Search Portal

instrument<sup>27</sup> according to four criteria: random sequence generation, allocation concealment, blinding and completeness of data. For each criterion, studies were judged to be at either high or low risk of bias.

### Statistical analysis

Complete-case analyses were carried out (including only patients who were followed and whose outcomes were available). Pooled estimates of risk differences were calculated by a random-effects meta-analysis using the DerSimonian and Laird approach (Freeman–Tukey double arcsine transformation). Heterogeneity was assessed for each outcome across studies using the  $I^2$  statistic and Cochran's Q. For outcomes in which five or more studies were available, subgroup analyses were planned to examine the study level variables as potential sources of heterogeneity. These variables and the pre-specified hypotheses that results would favour antibiotics were: those with CT confirmation of the diagnosis of non-perforated appendicitis; and those with low risk of bias (separately for each risk-of-bias domain with at least 2 studies with high and at least 2 studies with low risk of bias).

For outcomes in which there was a significant difference between groups, sensitivity analyses were planned in which results were imputed for missing data in a manner that challenged the robustness of these differences<sup>28–30</sup>. If missing data were minimal (5 per cent or less), the plan was not to conduct these analyses.

### Quality of evidence assessment

Guidance from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group<sup>31,32</sup> provided the methodology for assessing quality of evidence.

### Results

The search yielded 685 potentially relevant reports. After screening titles and abstracts and trial registries, and including six studies<sup>8–12,33</sup> in previous reviews<sup>15–25</sup> (Fig. 1), 52 reports were retrieved for full-text screening, of which a total of six RCTs were included: five in the final primary analysis<sup>8,9,12–14</sup> and, in addition, one quasi-RCT<sup>10</sup> in a sensitivity analysis. Two RCTs were excluded: one because of subsequent retraction owing to plagiarism<sup>33</sup> and

Table 1 Characteristics of the included studies

Reference	Study design	Participants	Intervention (antibiotic therapy)	Control (appendicectomy)	Outcomes assessed	Funding and conflict of interest statement
Eriksson and Granström <sup>8</sup>	Single-centre randomized trial	Patients ( <i>n</i> = 41) aged 18–75 years with history and clinical signs of acute appendicitis, positive findings at ultrasonography, and raised levels of inflammatory markers (CRP or WBC)	Intravenous cefotaxime 2 g twice daily and tinidazole 800 mg once daily for 2 days, followed by oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 8 days  Proceeded to appendicectomy based on clinician's judgement – no prespecified criteria	Open appendicectomy (100%)  Antibiotics given only to patients with perforation or abdominal spillage	Appendicectomy rate within index admission Success of treatment Complications (at 1 year) Recurrence (at 1 year) Length of stay Pain (VAS) Pain (use of medication)	Funding: Karolinska Institute, Swedish Hoechst, Pfizer, Mutual Group Life Insurance Company Förenade Liv No conflict of interest reported
Salminen <i>et al.</i> <sup>13</sup>	Multicentre randomized trial	Patients ( <i>n</i> = 530) aged 18–60 years admitted to the emergency department with clinical suspicion of uncomplicated acute appendicitis diagnosed by CT. Excluded if any of the following: appendicolith, perforation, abscess or suspicion of tumour	Intravenous ertapenem sodium 1 g once daily for 3 days, followed by oral levofloxacin 500 mg once daily and metronidazole 500 mg three times per day for 7 days  Appendicectomy performed if progressive infection, perforated appendicitis or peritonitis suspected on examination within 12–24 h after admission	Open (94%) or laparoscopic (6%) appendicectomy with prophylactic antibiotics  Postoperative antibiotics given only in patients with suspected wound infection	Primary outcome Antibiotic group: resolution of appendicitis resulting in discharge from hospital without need for surgical intervention and no recurrent appendicitis during a minimum follow-up of 1 year Appendicectomy group: successful appendicectomy  Secondary outcomes Overall postinterventional complications Late recurrence after 1 year (unreported*) Length of stay Length of sick leave Postoperative pain (VAS) Use of pain medication (unreported*)	Funding: Government research grant (EVO Foundation) awarded to Turku University Hospital Dr Salminen reported receiving personal fees for lectures from Merck and Roche; no other disclosures
Styrud <i>et al.</i> <sup>9</sup>	Multicentre randomized trial	Men ( <i>n</i> = 252) aged 18–50 years with clinically suspected acute non-perforated appendicitis and CRP > 10 mg/l	Intravenous cefotaxime 2 g twice daily and tinidazole 800 mg once daily for 2 days, followed by oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 10 days  Proceeded to appendicectomy based on clinician's judgement – no prespecified criteria	Open (94%) or laparoscopic (6%) appendicectomy  Unclear whether prophylactic or postoperative antibiotics given	Appendicectomy rate within index admission Success of treatment Complications (at 1 year) Recurrence (at 1 year) Length of stay Length of sick leave Pain (unreported*)	Funding: Swedish Society of Medicine, Karolinska Institute, Wallenius Corporation, Aventis Pharma No conflict of interest reported
Svensson <i>et al.</i> <sup>14</sup>	Single-centre randomized (pilot) trial	Children ( <i>n</i> = 50) aged 5–15 years with clinical diagnosis of acute appendicitis  Exclusion criteria: Suspicion of perforated appendicitis on the basis of generalized peritonitis  An appendiceal mass diagnosed by clinical examination and/or imaging  Previous non-operative treatment of acute appendicitis  All patients had at least one ultrasound examination, 4 had CT	Intravenous meropenem 10 mg/kg three times daily and metronidazole 20 mg/kg once daily for at least 48 h. Once the child was well clinically and tolerating oral intake, antibiotics continued with oral ciprofloxacin 20 mg/kg twice daily and metronidazole 20 mg/kg once daily for 8 days  Proceeded to appendicectomy based on clinician's judgement – no prespecified criteria	Laparoscopic appendicectomy (100 per cent) Prophylactic antibiotics given to all. Intravenous antibiotic continued for 24 h to patients with gangrenous appendicitis and for 3 days in those with perforated appendicitis	Primary outcome: resolution of symptoms without significant complications (defined as length of stay over 7 days, abscess, need for surgery within 48 h (antibiotic group only), recurrence of appendicitis within 3 months, or negative appendicectomy).  Secondary outcomes Length of stay Other complications (wound infection, wound dehiscence, diarrhoea, etc.) Recurrent appendicitis at 1 year Total costs	Funding: Crown Princess Lovisa's Foundation, the Hirsch Foundation No conflict of interest reported

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Table 1 continued

Reference	Study design	Participants	Intervention (antibiotic therapy)	Control (appendicectomy)	Outcomes assessed	Funding and conflict of interest statement
Vons <i>et al.</i> <sup>12</sup>	Multicentre randomized trial	Patients (n = 243) aged 18–68 years with uncomplicated acute appendicitis, diagnosed by CT	Amoxicillin plus clavulanic acid 3–4 g per day for 8–15 days, intravenously to those with nausea or vomiting, and orally to all others Appendicectomy undertaken if: Symptoms and abdominal tenderness failed to resolve after 48 h Persistence of pain or fever at 8 days prompted CT and possible appendicectomy or Sustained high WBC or high CRP concentration on day 15 prompted appendicectomy without additional CT	Open (34%) or laparoscopic (66%) appendicectomy with single-dose prophylactic antibiotics Postoperative antibiotics given if complicated appendicitis found	Primary outcome: occurrence of peritonitis within 30 days of initial treatment (defined as perforated appendicitis in antibiotic group, postoperative peritonitis in appendicectomy group) Secondary outcomes Complications (other than peritonitis) at 1 year Recurrence (defined as appendicectomy performed between 30 days and 1 year, with confirmed diagnosis of appendicitis) Pain (number of days with VAS 4 or more) Length of stay Length of sick leave	Funding: French Ministry of Health, Programme Hospitalier de Recherche Clinique 2002 No conflict of interest reported

CRP, C-reactive protein; WBC, white blood cell count; VAS, visual analogue scale. \*Outcome prespecified as a secondary outcome but no data presented in publication.

Table 2 Risk of bias

Reference	Random sequence generation	Allocation concealment	Blinding	Completeness of data
Eriksson and Granström <sup>8</sup>	+	–	–	+
Salminen <i>et al.</i> <sup>13</sup>	+	+	–	+
Styrud <i>et al.</i> <sup>9</sup>	+	+	–	–
Svensson <i>et al.</i> <sup>14</sup>	+	+	–	+
Vons <i>et al.</i> <sup>12</sup>	+	+	–	–

+, Low risk of bias; –, high risk of bias.

the other because of postrandomization exclusions that led to serious prognostic imbalance<sup>11</sup>. Four of the six authors (including the author of the quasi-RCT) confirmed the accuracy of the consensus data extraction, corrected some errors or provided additional information<sup>10,12–14</sup>; two<sup>8,9</sup> were unable to assist with the requests or could not be contacted.

Table 1 summarizes the characteristics of studies included in primary analyses. The five included RCTs had a total 1116 adult patients; four studies<sup>8,9,12,13</sup> recruited adults and one<sup>14</sup> children. The quasi-RCT<sup>10</sup> included 369 adults (Tables S1 and S2, supporting information). Definitions of complications varied across the included studies, and were also different between the treatment groups in some studies (Table S3, supporting information). Postoperative

complications were reported consistently in all studies, but none used one of the common classification systems. For this review, complications were counted as minor or major based on their description in the original studies.

Histopathological diagnosis of acute appendicitis was made using standard criteria (mucosal inflammation) in one study<sup>12</sup>, using stringent criteria in another (intramural inflammation required)<sup>13</sup>, but remained unclear in most<sup>8–10,14</sup>. In the included trials, rates of negative appendicectomy varied from 0 to 15 per cent, with median of 3 per cent in the appendicectomy arms.

### Risk-of-bias assessment

All studies probably generated random sequence adequately; one study likely failed to conceal randomization. None of the studies blinded patients, healthcare providers, outcome assessors or data analysts (Table 2; Table S2, supporting information). Loss to follow-up at 1 year was substantial, varying from 7 to 22 per cent, and was similar in the two groups within each study<sup>8,12–14</sup>, although unclear in one study report<sup>9</sup>.

### Outcome assessment

#### Rate of appendicectomy within 1 month

Some 561 of the 562 patients allocated to surgery underwent appendicectomy (range across studies 99.6–100 per

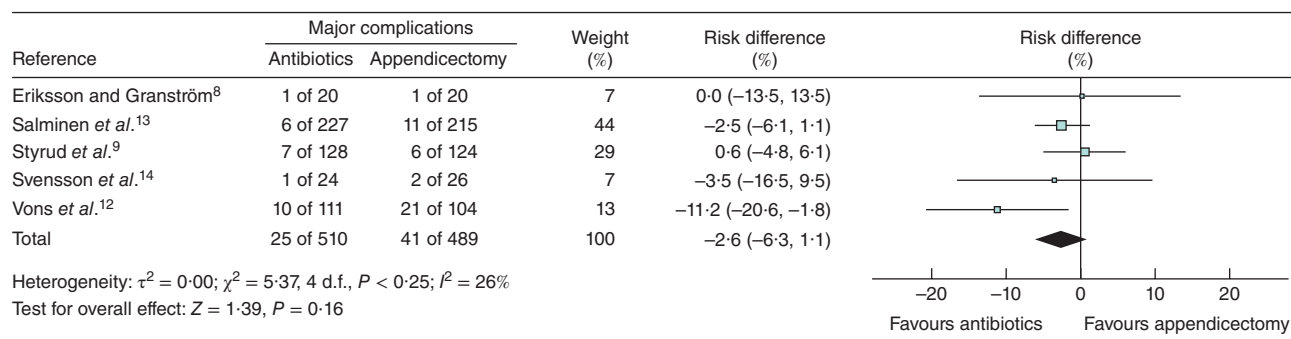
**Table 3** GRADE evidence profile: antibiotic therapy *versus* appendicectomy for acute non-perforated appendicitis

No. of patients with data*	Quality assessment				Summary of findings					
	Time frame	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Antibiotic therapy	Appendicectomy	Absolute risk difference†	Certainty in estimates
<b>Major complications</b>										
999 (5) 1 year	Serious limitations: major and minor complications likely under-reported in antibiotics group	No serious limitations	No serious limitations	Serious limitations: 95% confidence interval crosses 0, indicating no difference	Undetected	25 of 510 (4.9)	41 of 489 (8.4)	-2.6 (-6.3, 1.1)% Favours antibiotic therapy	Low	
<b>Minor complications</b>										
999 (5) 1 year	Serious limitations: major and minor complications likely under-reported in antibiotics group	Serious limitations: inconsistent forest plot estimates	No serious limitations	Serious limitations: 95% confidence interval crosses 0, indicating no difference	Undetected	11 of 510 (2.2)	61 of 489 (12.5)	-7.2 (-18.1, 3.8)% Favours antibiotic therapy	Very low	
<b>Recurrence of appendicitis</b>										
999 (5) 1 year	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	114 of 510 (22.4)	0 of 489 (0)	22.6 (15.6 to 30.4)% Favours appendicectomy	High	
<b>Rate of appendicectomy within 1 month</b>										
1112 (5) 1 month	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	47 of 550 (8.5)	561 of 562 (99.8)	91.8 (88.2, 94.8)% Favours antibiotic therapy	High	
<b>Length of hospital stay</b>										
1100 (5) In hospital	No serious limitations	No serious limitations	Serious limitations: most patients operated on using open approach; laparoscopic approach would shorten length of hospital stay	No serious limitations	Undetected			0.41 (0.26 to 0.57) days Favours appendicectomy	Moderate	
<b>Length of sick leave</b>										
1017 (3) 1 month	No serious limitations	Serious limitations: inconsistent forest plot estimates	Serious limitations: most patients operated on using open approach; laparoscopic approach would shorten length of sick leave	Serious limitations: 95% confidence interval crosses 0, indicating no difference	Undetected			-3.58 (-8.27, 1.11) days Favours antibiotic therapy	Very low	

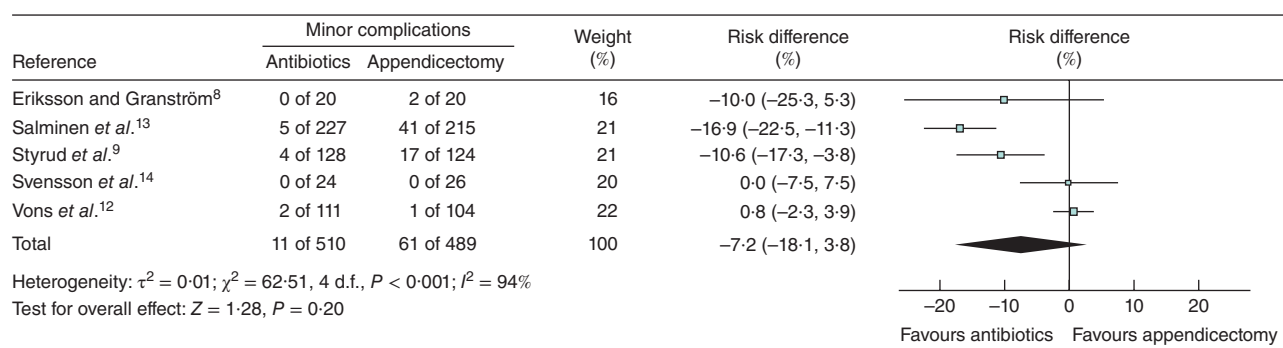
Values in parentheses are percentages unless indicated otherwise; values are \*number of studies and †95 per cent confidence interval.

cent). The pooled estimate was 99.6 (95 per cent c.i. 98.9 to 100) per cent (high-quality evidence). Of the appendicectomies, 434 (77.4 per cent) were open and 127 (22.6 per cent) laparoscopic. Of the 550 patients

allocated to antibiotic therapy, 47 underwent an appendicectomy within 1 month (range across studies 4.8–11.7 per cent). The pooled estimate was 8.2 (5.2 to 11.8) per cent (high-quality evidence) (Table 3).



**Fig. 2** Forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy group. Risk differences are shown with 95 per cent c.i.



**Fig. 3** Forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy group. Risk differences are shown with 95 per cent c.i.

### Major complications

Of the 510 patients allocated to antibiotic therapy, 25 had major complications *versus* 41 of 489 patients in the appendicectomy group: risk difference  $-2.6$  (95 per cent c.i.  $-6.3$  to  $1.1$ ) per cent (low-quality evidence) (Fig. 2, Table 3). Major complications in the appendicectomy group included 32 appendiceal perforations, five deep infections, two incisional hernias, one laparoscopic adhesiolysis and one death. Major complications in the antibiotic therapy group included 23 appendiceal perforations, one adhesive bowel obstruction and one death. The quality of evidence was rated as low because of imprecision and high risk of bias (Table 3).

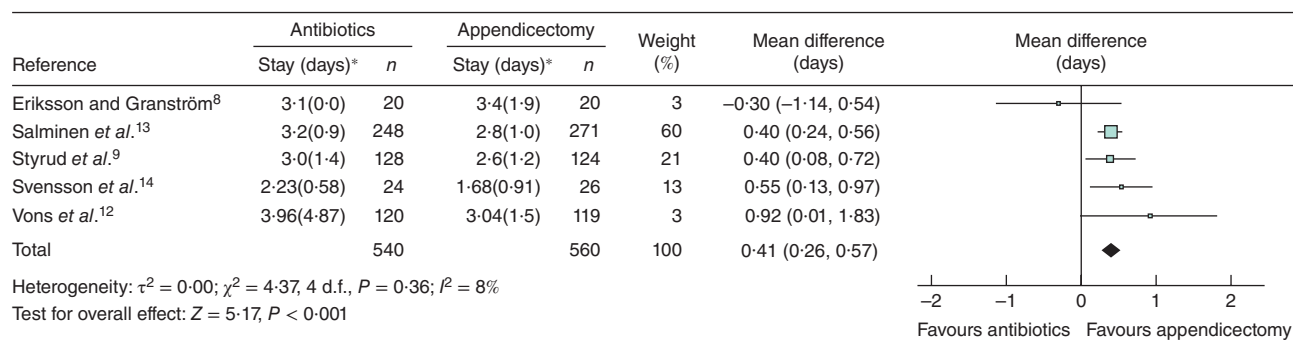
### Minor complications

Of the 510 patients allocated to antibiotic therapy, 11 had minor complications *versus* 61 of 489 patients in the appendicectomy group: risk difference  $-7.2$  (95 per cent c.i.  $-18.1$  to  $3.8$ ) per cent (very low-quality evidence) (Fig. 3). Minor complications included 38 superficial wound infections, 22 instances of abdominal or incisional discomfort at 1 year (reported only by Salminen and colleagues<sup>13</sup>), and

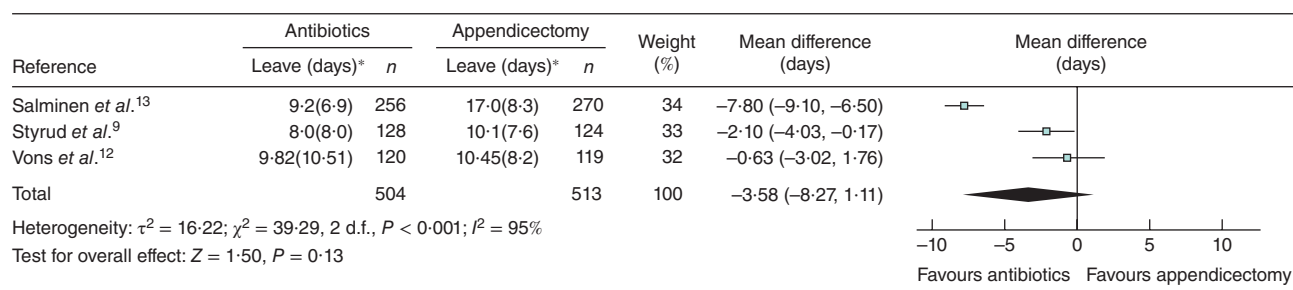
one case of diarrhoea in the appendicectomy group. Minor complications in the antibiotic group included three superficial wound infections, 4 instances of abdominal or incisional discomfort at 1 year (reported only by Salminen and colleagues<sup>13</sup>), and four complications that were not stated in more detail. None of the included trials reported any adverse effects of antibiotic treatment (such as diarrhoea or allergic reaction). The quality of evidence was rated as very low because of imprecision, inconsistency and high risk of bias in reporting complications (Table 3).

### Recurrence of appendicitis within 1 year

None of the patients who underwent appendicectomy were reported to have recurrent appendicitis. The pooled estimate of recurrence in the antibiotic group, of whom 114 of 510 patients had a suspected or proven recurrence of appendicitis within 1 year, was  $22.6$  (15.6 to 30.4 per cent) (high-quality evidence) (Table 3). Of these 114 appendices, 14 (12.3 per cent) were not inflamed on subsequent histopathology. Average (mean or median) time from initial conservative treatment with antibiotics to recurrence varied between 3.4 and 7.0 months in the included trials.



**Fig. 4** Forest plot showing mean difference in length of hospital stay in antibiotic therapy *versus* appendicectomy group. Mean differences are shown with 95 per cent c.i. \*Values are mean(s.d.)



**Fig. 5** Forest plot showing mean difference in length of sick leave in antibiotic therapy *versus* appendicectomy group. Mean differences are shown with 95 per cent c.i. \*Values are mean(s.d.)

#### Duration of hospital stay

Three studies<sup>8,9,12</sup> reported, and two authors<sup>13,14</sup> later provided data on hospital stay. Patients in the appendicectomy arms had a modestly shorter duration of hospital stay: mean difference 0.41 (95 per cent c.i. 0.26 to 0.57) days (moderate-quality evidence) (Fig. 4, Table 3).

#### Duration of sick leave

Two studies<sup>9,12</sup> reported, and one author<sup>13</sup> later provided data on sick leave. One study<sup>14</sup> enrolled only children, and so sick leave was not applicable. The duration of sick leave did not differ materially between the groups; the mean difference was -3.58 (95 per cent c.i. -8.27 to 1.11) days, favouring antibiotic therapy (very low-quality evidence) (Fig. 5, Table 3).

#### Subgroup and sensitivity analyses

Neither the prespecified subgroup analyses nor the sensitivity analyses explained differences in minor or major complication rates (Figs S1–S6, supporting information).

## Discussion

Five RCTs that followed more than 1100 patients with non-perforated appendicitis for 1 year demonstrated

both advantages and disadvantages to an initial management strategy of antibiotics with appendicectomy only as necessary *versus* immediate appendicectomy. Advantages of the antibiotic regimen include a potentially lower rate of major complications (primarily appendiceal perforations) (2.6 per cent less, low-quality evidence), a potentially lower rate of minor complications (7.2 per cent less, very low-quality evidence), potentially shorter sick leave (4 days shorter, very low-quality evidence), and a lower rate of appendicectomies in the first month after presentation (91.8 per cent less, high-quality evidence). These advantages need to be traded off against a 22.6 per cent incidence of recurrence of appendicitis at 1 year (high-quality evidence) and potentially longer hospital stay (by 0.4 days, moderate-quality evidence) (Table 3).

Relative to previous systematic reviews, this analysis has many strengths. Use of explicit eligibility criteria led to the exclusion of two trials<sup>11,33</sup> inappropriately included in other reviews<sup>16,22,23,25</sup>: one that has been retracted owing to plagiarism<sup>33</sup> and another trial that suffered from serious prognostic imbalance<sup>11</sup>. A comprehensive search led to the inclusion of two recently published trials<sup>13,14</sup>. Two reviewers determined eligibility, assessed risk of bias, and abstracted data independently and in duplicate, with



adjudication by a third reviewer as necessary. Rigorous meta-analyses were conducted and prespecified subgroup effects were explored. Sensitivity analysis including a quasi-randomized study did not change the results appreciably. The GRADE approach<sup>31,32</sup> was applied to assess quality of evidence for each outcome (Table 3).

Limitations of this review are largely those of the primary studies. As the diagnosis of appendicitis was made without CT in three of the RCTs<sup>8,9,14</sup>, they included patients with complicated appendicitis, and those without appendicitis at all. For studies that used CT, the rate of perforated appendix was variable: 18 per cent in the appendectomy group in the French study<sup>12</sup>, but only 1 per cent in the Finnish trial<sup>13</sup>. This could be due to inaccuracy of the CT scans or progression of initially non-perforated appendicitis. CT is far from perfect in differentiating complicated from uncomplicated appendicitis<sup>34</sup>, whereas scoring systems might be more helpful in selecting patients in future trials<sup>35</sup>.

The rate of operation in patients who did not have appendicitis on histopathology was very low in the included trials (0–3 per cent in most, and 15 per cent in 1 using clinical diagnosis only<sup>8</sup>). Although CT is limited in differentiating uncomplicated from complicated appendicitis, it has a high level of accuracy in differentiating patients with, and without appendicitis, leading to low rates of negative appendectomy where CT was used routinely<sup>36</sup>. Another factor is that the threshold for the diagnosis of appendicitis based on histopathological findings (undefined in most of the studies) may have been low or very low. Only the Finnish study<sup>13</sup> reported use of stringent criteria, which require inflammation in the muscularis of the appendix. Such strict criteria have been reported to yield higher negative appendectomy rates<sup>37</sup>.

Risk of bias is a problem in all studies, with major limitations in some regarding allocation concealment, in all for blinding, and in many with respect to loss to follow-up. There were also reporting problems that required some inferences in data abstraction (for example no study classified complications according to their severity, thus requiring reviewers' inferences regarding whether complications were major or minor). All authors failed to report complications of antibiotic therapy (such as diarrhoea or allergic reactions) and most failed to report appendectomy complications in detail in patients who initially received antibiotics, but who went on to have appendectomy for recurrent appendicitis<sup>8,9,12,13</sup>.

Enrolment was slow in two of the biggest trials<sup>12,13</sup>, which recruited approximately one to three patients per month per hospital. The largest trial<sup>13</sup> was able to recruit less than 20 per cent of the patients treated for

uncomplicated appendicitis in the trial hospitals during the enrolment period, and the study was actually terminated prematurely owing to slow enrolment. Thus, it is possible that only the least sick patients were enrolled in these trials. If that is so, the results of antibiotic treatment may not be as good if administered to sicker patients.

It is possible that some patients would prefer to avoid an appendectomy because of rare but serious potential complications of general or spinal anaesthesia, but also because of possible short- and long-term pain associated with surgery, with decreased quality of life. Unfortunately, investigators did not measure pain consistently or rigorously, and did not report quality of life at all.

Generalizability to current clinical practice is also a concern. Only 22.6 per cent of procedures in the appendectomy group were performed laparoscopically. Systematic reviews<sup>38,39</sup> of RCTs comparing open with laparoscopic appendectomy have shown that the laparoscopic approach is associated with reduced wound infections, as well as a lower rate of bowel obstruction. As the majority of minor complications were wound infections and incisional discomfort, it is likely that a laparoscopic approach will reduce the rate of minor complications. Furthermore, more frequent use of a laparoscopic approach should shorten hospital stay and sick leave<sup>38,39</sup>. On the other hand, all RCTs reported in-hospital intravenous antibiotic treatment for 2–3 days, and it might be possible to reduce length of stay by using a different antibiotic regimen.

Other limitations included insufficient follow-up in all of the included studies. The rate of recurrent appendicitis was approximately 23 per cent during the first year; it is unknown how much this rate might rise with longer follow-up. Similarly, introducing broad-spectrum antibiotics to a large patient population carries the risk of worsening antibiotic resistance. It could be argued that antibiotics should be reserved for patients with a definitive diagnosis of uncomplicated appendicitis.

Despite the limitations of the available studies, they provide valuable evidence regarding the outcomes of antibiotic first *versus* immediate surgery for acute non-perforated appendicitis. The trade-off between the antibiotic-first approach – potentially 3 per cent fewer major complications, 7 per cent fewer minor complications, 4 days' shorter sick leave and 92 per cent fewer appendectomies in the first month – must be balanced against the disadvantages: a 23 per cent recurrence rate within 1 year and slightly longer hospital stay (half a day). Patients averse to surgery are likely to choose an initial trial of antibiotics; those averse to the possibility of recurrence may prefer immediate appendectomy. Ensuring that the decision is

consistent with patients' values and preferences requires shared decision-making<sup>40</sup>.

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### Supporting information

Additional supporting information may be found in the online version of this article:

**Appendix S1** Search strategies (Word document)

**Table S1** Characteristics of the study by Hansson and colleagues<sup>10</sup> (Word document)

**Table S2** Risk of bias in the study by Hansson and colleagues<sup>10</sup> (Word document)

**Table S3** Complications considered (Word document)

**Fig. S1** Sensitivity analysis examining effect of inclusion of data from Hansson *et al.*<sup>10</sup>: forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy groups (Word document)

**Fig. S2** Sensitivity analysis examining effect of inclusion of data from Hansson *et al.*<sup>10</sup>: forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy groups (Word document)

**Fig. S3** Subgroup analysis of studies with or without CT confirmation of diagnosis: forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy groups (Word document)

**Fig. S4** Subgroup analysis of studies with or without CT confirmation of diagnosis: forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy groups (Word document)

**Fig. S5** Subgroup analysis according to completeness of data (high or low risk of bias): forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy groups (Word document)

**Fig. S6** Subgroup analysis according to completeness of data (high or low risk of bias): forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy groups (Word document)