Appendectomy versus antibiotic treatment for acute appendicitis (Review)

Wilms IMHA, de Hoog DENM, de Visser DC, Janzing HMJ

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[Intervention Review]

Appendectomy versus antibiotic treatment for acute appendicitis

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Editorial group: Cochrane Colorectal Cancer Group.
Publication status and date: New, published in Issue 11, 2011.
Review content assessed as up-to-date: 3 October 2011.

Citation: Wilms IMHA, de Hoog DENM, de Visser DC, Janzing HMJ. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD008359. DOI: 10.1002/14651858.CD008359.pub2.

ABSTRACT

Background

Acute appendicitis is one of the most common causes of acute abdominal pain. Present day treatment of choice for acute appendicitis is appendectomy, however complications are inherent to operative treatment. Though surgical appendectomy remains the standard treatment, several investigators have investigated conservative antibiotic treatment of acute appendicitis and reported good results.

Objectives

Is antibiotic treatment as effective as surgical appendectomy (laparoscopic or open) in patients with acute appendicitis on recovery within two weeks, without major complications (including recurrence) within one year?

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 6, 2011); MEDLINE (until June 2011); EMBASE (until June 2011); Prospective Trial Registers (June 2011) and reference lists of articles.

Selection criteria

Randomised and quasi-randomised clinical trials (RCT and qRCT) comparing antibiotic treatment with appendectomy in patients with suspected appendicitis were included. Excluded were studies which primarily focused on the complications of acute appendicitis.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. The review authors contacted the trial authors for additional information if required. Statistical analysis was carried out using Review Manager and MetaAnalyst. A non-inferiority analysis was performed, comparing antibiotic treatment (ABT) to the gold standard (appendectomy). By consensus, a 20% margin of non-inferiority was considered clinically relevant.

Main results

Five RCT's (901 patients) were assessed. In total 73.4% (95% CI 62.7 to 81.9) of patients who were treated with antibiotics and 97.4 (95% CI 94.4 to 98.8) patients who directly got an appendectomy were cured within two weeks without major complications (including recurrence) within one year. The lower 95% CI was 15.2% below the 20% margin for the primary outcome.

Authors' conclusions

The upper bound of the 95% CI of ABT for cure within two weeks without major complications crosses the 20% margin of appendectomy, so the outcome is inconclusive. Also the quality of the studies was low to moderate, for that reason the results should be interpret with caution and definite conclusions cannot be made. Therefore we conclude that appendectomy remains the standard treatment for acute appendicitis. Antibiotic treatment might be used as an alternative treatment in a good quality RCT or in specific patients or conditions were surgery is contraindicated.

PLAIN LANGUAGE SUMMARY

Antibiotic therapy compared to appendectomy in the treatment of acute appendicitis.

Acute appendicitis is one of the most common surgical causes of acute abdominal pain. Appendectomy is the treatment of choice, however surgical complications are inherent to operative treatment. Recent research on primary antibiotic therapy (without surgery) reported good results.

This review investigates whether antibiotic therapy is as effective as appendectomy in patients with uncomplicated appendicitis. Included endpoints were cure within two weeks without major complications (including recurrent appendicitis) within one year, major and minor complications and duration of hospital stay. We could not conclude whether antibiotic treatment is or is not inferior to appendectomy. Because of the low to moderate quality of the trials, appendectomy remains the standard treatment for acute appendicitis.

BACKGROUND

Acute appendicitis is one of the most common causes of acute abdominal pain. The life time risk of appendicitis is approximately 7-8%, with the highest incidence in the second decade (Addis 1990).

Although the etiology of acute appendicitis is poorly understood, it is probably in the majority of cases caused by an obstruction of the lumen (Addis 1990). The luminal obstruction can be caused by fecaliths, lymphoid hyperplasia, foreign bodies, parasites and both primary (carcinoid, adenocarcinoma, Kaposi sarcoma and lymphoma) and metastatic (breast and colon) tumors. Once appendiceal obstruction occurs, the continued secretion of mucus results in elevated intraluminal pressure and luminal distention. This eventually exceeds capillary perfusion pressure, which leads to venous engorgement, arterial compression and tissue ischemia. As the epithelial mucosal barrier becomes compromised, luminal bacteria multiply and invade the appendiceal wall, which causes transluminal inflammation (Birnbaum 2000). The most common bacteria that can cause acute appendicitis are intestinal bacteria including the Escherichia Coli and bacteria belonging to the Bacteroides Fragilis group (Bennion 1990; Rautio 2000). Continued ischemia results in appendiceal infarction and perforation. However some studies report that non-complicated and complicated (perforated) appendicitis are different entities, and that many cases of acute appendicitis will resolve spontaneously (Mason 2008).

Fitz described in 1886 the signs and symptoms of acute and perforated appendicitis, outlined the progression from acute lower quadrant inflammation through peritonitis and iliac fossa abscess formation, and recommended early appendectomy if there were signs of spreading peritonitis or clinical deterioration. Since McBurney in 1894 defined the surgical appendectomy, the surgical removal of the diseased appendix had been the treatment of choice for acute appendicitis, because it lowered the mortality rate drastically (Birnbaum 2000; Fischer 2007). Surgical appendectomy is a successful treatment modality with good results, but complications are inherent to operative treatment. The most common operative complications are wound infection, intraabdominal abscess and ileus caused by intraabdominal adhesions, which vary in frequency between open and laparoscopic appendectomy (Nakhamiyayev 2009; Sauerland 2004). The overall complication rates for open and laparoscopic appendectomy are respectively 11.1% and 8.7%, with a mortality rate less than 0.5% (Guller 2004). The clinical diagnosis of acute appendicitis remains difficult. Though present day diagnostic tools including ultrasonography (US) and computed tomography (CT) reduce the number of negative findings at surgery (Randen v 2008).

Despite the fact that surgical appendectomy is the standard treatment of acute appendicitis, several investigators have studied the conservative antibiotic treatment of acute appendicitis with good results. They described a low morbidity and mortality rate, and a

recurrence rate between 7-15% (Coldrey 1959; Hansson 2009a).

Even though the non-operative antibiotic management of other intraabdominal inflammations (uncomplicated diverticulitis, salpingitis, and neonatal enterocolitis) is an established fact, the antibiotic treatment of appendicitis remains largely unexplored (Mason 2008). Because of the high prevalence of acute appendicitis, change of treatment modality will have major implications, therefore review of all available data is necessary.

OBJECTIVES

Is antibiotic treatment as effective as surgical appendectomy (laparoscopic or open) in patients with acute appendicitis on recovery within two weeks, without major complications (including recurrence) within one year?

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised and quasi-randomised clinical trials (RCT and qRCT) in which antibiotic treatment is compared with appendectomy in patients with suspected appendicitis. Superiority and non-inferiority RCT's are included. Quasi-randomised trials are those with a non-random non-concealed allocation (e.g. simple alternation, date of birth, hospital admission number). Excluded were studies which primarily focus on complications of acute appendicitis like abscesses and/or perforations.

Types of participants

All patients with suspected acute appendicitis were included. There were no restrictions for age or gender.

Types of interventions

Antibiotic treatment (intravenous or oral) compared with surgical appendectomy (open or laparoscopic).

Types of outcome measures

Primary outcomes

1. Cure within two weeks (free of symptoms such as abdominal pain, fever, inflammatory parameters), without major complications (including recurrence) within one year.

Secondary outcomes

1. Major complications defining the need of further invasive treatment or prolonged admission (e.g. abscesses, ileus, deep wound infection, recurrence, (re)operation, secondary perforation)
2. Minor complications (e.g. negative appendectomy, diarrhoea, superficial wound infection)
3. Duration of hospital stay (in days)
4. Period of sick leave (in days)
5. Cost effectiveness

Search methods for identification of studies

The following electronic databases were searched:

- Central Register of Controlled Trials (*The Cochrane Library*, Issue 6, 2011)
- MEDLINE, from 1966 to June 2011
- EMBASE, from 1980 to June 2011
- Prospective Trial Registers (ClincalTrials.gov, Controlled-trials.com and trialregister.nl; June 2011)

The search terms that were used are: appendicitis [MeSH]) or appendic* or appendicitis acuta, antibiotic* therap* or antibiotic* treatment*, appendectom* [Mesh] or appendicectom*.
The exact search protocol, designed by the CCCG Trials Search Coordinator Susse Wegeberg and repeated by Marija Barbatedkovic, is described in appendices 1 to 3. For the MEDLINE and EMBASE search, filters are added to find RCTs and CCTs.
The reference lists of potentially relevant articles were screened for further potentially relevant citations.
We did not apply language or publication status restrictions.

Data collection and analysis

Selection of studies

Two authors (IW and DdH or HJ) examined all citations and abstracts derived from the electronic search strategy and independently selected trials that were included in the review. Disagreement was resolved by discussion. Full copies of all (potentially) relevant studies were obtained. A standardized form was used to assess eligibility of trials for inclusion.

Data extraction and management

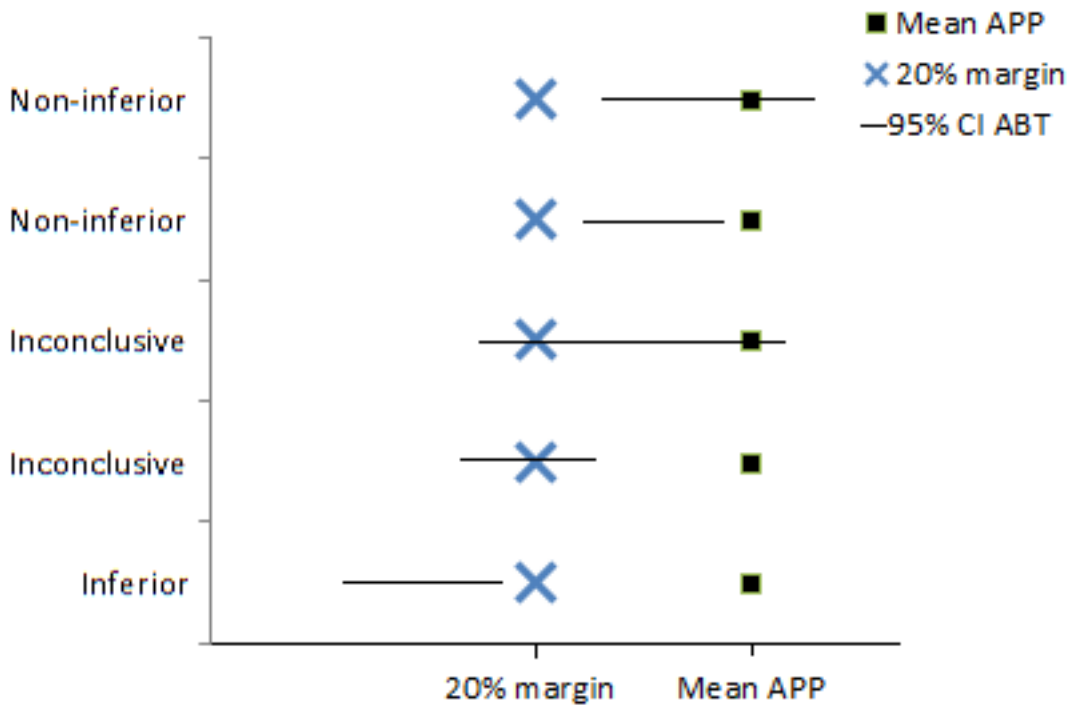
Two authors (IW and DdH or HJ) independently extracted the data from the studies using standardised data forms, according to the criteria as described in the Cochrane Handbook (Higgins 2008). Disagreement was resolved by discussion.

Measures of treatment effect

As mentioned above, appendectomy (APP) is a successful treatment with good results, and a relatively low complication rate. For obvious reasons it has a higher risk of surgery related complications than antibiotic treatment (ABT). APP is also more expensive than ABT. A non-inferiority analysis was performed because ABT is compared with the gold standard and ABT could have the advantage above APP to be more patient friendly. A non-inferiority analysis investigates if ABT is as effective as APP or only slightly less effective as treatment modality. By consensus a 20% margin of non-inferiority was considered clinically relevant.

So ABT was considered to be not inferior to APP when it was not more than 20% less effective than APP. For the primary outcome, the major and minor complications, the mean (in percentages) with 95% confidence interval (CI) was calculated. This was computed for the ABT group, the APP group and of the pooled data in both groups. To calculate whether antibiotic treatment was not inferior to appendectomy within a 20% margin, 20% of the mean APP was calculated and then subtracted from the mean in the appendectomy group and compared with the lower 95% CI tail of the ABT. Whenever the 95% CI of ABT was within the 20% margin, we assumed no clinical relevant differences between both groups. In this case the results are non-inferior. When only a part of the 95% CI of APP was in the 20% margin, the results were considered inconclusive. Inferior are the results when the whole 95% CI of ABT was below the 20% margin (see also the explanation Figure 1). In statistics it is more common to calculate with positive outcomes instead of negative outcomes. For this reason the mean with 95% CI was calculated for patients who had no major or minor complications.The minimal number to treat was calculated with a 95% CI (two-sided) and a power of 80% using the online binary outcome non-inferiority trial power (sample size) calculator as programmed on SealedEnvelope.com (SealedEnvelope).

Figure 1. Explanation of the non inferiority principle



As described in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008), we calculated the mean difference and the standardized mean difference (SMD) for continuous data.

Dealing with missing data

In case of missing data, we tried to obtain the missing information

by contacting the trial author. When this was not possible we attempted to make assumptions of the missing data and performed a sensitivity analysis to assess how sensitive the results were to reasonable changes in the assumptions that were made, additionally we addressed the potential impact of missing data on the findings of the review in the discussion (Higgins 2008).

Assessment of heterogeneity

Heterogeneity was assessed using chi-square test with P value of <0.05 considered as statistically significant. I^2 was assessed to quantify the degree of heterogeneity present. A fixed-effects model was used when there was no or little heterogeneity (I^2 < 30%), and random-effects model was used when there was statistically significant moderate heterogeneity (I^2 up to 50%), and no pooling when substantial heterogeneity was present (I^2 >75%). Sources of heterogeneity were identified by subgroup analysis. And we tried to describe the probable cause for heterogeneity.

Assessment of reporting biases

We reported which studies identified bias and their type. When there was suspicion or direct evidence for selective outcome reporting, the trial author was contacted for additional information (Higgins 2008).

Data synthesis

Any data which had been reported in the included studies and was relevant to the primary and secondary outcomes of this review was analysed by two authors (IW and DdH or HJ). RevMan 5 and MetaAnalyst (RevMan 2008, MetaAnalyst 2009) were used to analyse the results. Data was reported according to Cochrane Collaboration criteria.

Subgroup analysis and investigation of heterogeneity

If possible a subgroup analysis was applied for age and gender.
The diagnostic methods used in the studies could be a source for heterogeneity.

Sensitivity analysis

A sensitivity analysis was performed using RevMan 5, to determine whether poor quality studies or studies with doubtful eligibility should be included or excluded.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See: Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies

Results of the search

In the electronic search initially 305 studies were retrieved. After screening the abstracts we (IW and DdH) considered 18 articles as possibly eligible and obtained the full text articles. From the reference list of these articles a further six new articles were retrieved, however these were eventually excluded after full text assessment. Eventually five articles were included in the meta-analysis.
In the Prospective Trial registers three relevant randomised trials were found. Two trials had been completed and published yet (Hansson 2009a; Vons 2011). One trial had begun enrolling participants in 2009 (NCT01022567).

Included studies

In first instance we included 6 studies, five RCT's (Eriksson 1995; Malik 2009; Styrud 2006; Turhan 2009; Vons 2011) and one qRCT (Hansson 2009a). But eventually we had to exclude the qRCT from analysis because of its poor quality.
Five studies were finally included and analysed (Eriksson 1995; Malik 2009; Styrud 2006; Turhan 2009; Vons 2011). The characteristics of the five included studies are summarized in the Characteristics of included studies tables. In total 901 patients were included in the studies, the study sample size ranged between 40 and 290 patients. The mean age was 28.2 years (range 13 to 75 years) and 73.8% of the patients was male. One study (Styrud 2006) included only male patients by decision of the local ethics committee. All included participants had (suspected) acute appendicitis and the initial diagnosis was based on disease history, clinical status and laboratory findings (CRP and/or WBC levels). Additional diagnostic examination like ultrasound (US) was standard in Eriksson 1995 and Malik 2009. All patients in Vons 2011 had a CT scan to diagnose uncomplicated appendicitis. Nevertheless Turhan 2009 performed US and CT only in the antibiotic treatment group after randomisation. The most commonly measured outcomes were: clinical improvement, histopathological findings of the appendix, recurrent appendicitis, wound infection and other complications. The duration of follow up ranged between 30 days and 1 year. All studies readmitted patients with recurrent appendicitis within one year.
In four trials the limit for no clinical improvement with antibiotic treatment was two weeks. In one study (Vons 2011), this interval was, in theory, four weeks. But all patients that did not heal with antibiotic treatment and needed surgery were operated on within 15 days.
There was little or no cross over in the studies.
In four trials (Eriksson 1995; Malik 2009; Styrud 2006; Turhan 2009) the patients in the antibiotic treatment (ABT) group re-

ceived intravenous (iv) antibiotics for 24 hours to 3 days. In Vons 2011 patients received oral antibiotics. Iv antibiotics were restricted to patients with nausea or vomiting. Patients who had iv antibiotics had no oral intake during this period; with the exception of the patients in the Styrud 2006 trial, who were allowed to eat at the second day after inclusion. If the clinical condition was satisfactory, the patient was discharged and received oral antibiotics for 7 to10 days. Different antibiotics were used in the studies, although all treatment regimes covered the same spectrum. Four studies performed an appendectomy in case of no (clinical) improvement or recurrence. One study used therapeutic antibiotics for a second time in some cases of recurrence.

All patients in the appendectomy group had appendectomy, laparoscopic or open. Almost all the appendices were sent for histopathological examination (except one (macroscopic) gangrenous appendix). Two studies gave prophylactic antibiotics (Malik 2009, Vons 2011), one study did not and the other studies did not mention this in their articles. Four studies reported that they gave post-operative antibiotics in case of perforated or gangrenous appendix or when there was abdominal spillage.

Excluded studies

In total 13 articles were eventually excluded. See also: Characteristics of excluded studies. As mentioned before one study (Hansson 2009a) was excluded from analysis because of the poor quality. It was a quasi randomised trial, the allocation was based on date of birth.Uneven date of birth was allocated to antibiotic treatment (ABT), even date of birth was allocated to appendectomy (APP). There was a major cross-over between both groups by preference of patient or surgeon. Only 52.5% completed the intended antibiotic therapy and 92.2% patients in the surgery group had appendectomy. The remaining patients crossed over to the other intervention group.Hansson et al outlines the reasons to switch, but the numbers identified in tables and in the text were inconsistent.This study also tried to analyse the results after one year. But 32.8% of the patients in the antibiotic treatment group and 28.0% of the patients in the appendectomy group the results were not included in this one year analysis.

Six studies were not randomised controlled trials or quasi randomised controlled trials, five articles were comments on included studies. One RCT was a diagnostic trial which matched the outcome of the Alvarado score with the intervention (antibiotic treatment or appendectomy) in patients with acute appendicitis.

Risk of bias in included studies

Two authors (IW and DdH or HJ) assessed the quality of all included studies and recorded the randomisation methods, blinding, number of withdrawals, dropouts and lost-to-follow-up in the studies. Missing information from reports of trials was sought by contacting the authors. The overall quality of the studies was low to moderate. The randomisation methods (sequence generation and allocation of concealment) were not well reported. Only two studies had an adequate method for sequence generation and allocation of concealment (Styrud 2006,Vons 2011). The remaining other articles did not fully describe their methods of randomisation.

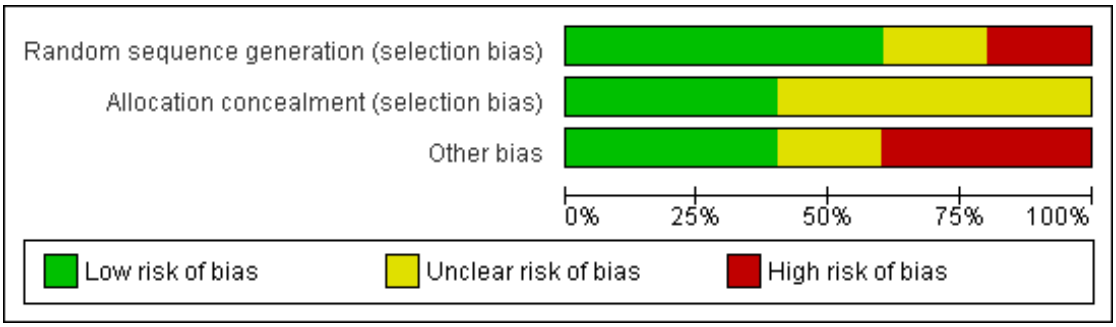
The basic workup for diagnosing appendicitis was similar, although some studies performed more additional investigations to confirm the diagnosis appendicitis. Turhan 2009 performed more extensive investigations in the antibiotic group than in the appendectomy group. Because of obvious reasons blinding was not possible.

One study gave oral antibiotics when the patient was not nauseous of vomiting (Vons 2011). Although the same dose was given oral en iv, it is expected that patients with abdominal illness do not absorb the antibiotics as well as patients without abdominal illness. The study did not mentioned this in the analysis.

Antibiotic prophylaxis is effective in the prevention of post-operative complications after appendectomy (Andersen 2009), nevertheless only two studies mentioned the use of prophylactic antibiotics, one study did not apply prophylactic antibiotics and for the two other studies it is not known. Two studies reported the number of withdrawals (Eriksson 1995; Styrud 2006) before inclusion. Dropouts were described. None of the trials mentioned or investigated whether patients who were treated conservatively with antibiotics had an appendectomy or were followed up in another hospital than the research hospital. This could all bias the results.

See also Figure 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

In total 901 patients were included in the studies of which 415 initially received antibiotic treatment and 486 patients had appendectomy.

Cured within two weeks, without major complications (including recurrence) within one year

Eriksson et al included 40 patients, with a fifty-fifty percentage randomisation antibiotic treatment group (ABT) versus appendectomy group (APP) according to the protocol. Eventually 60.0% (95% CI 38.0 to 78.6) of the patients in de ABT group were cured within two weeks and had no major complications, versus 95.0% (95% CI 71.8 to 99.3) in the APP group (Eriksson 1995). In the trial of Malik et al 80 patients were included, 40 patients in each group. In the ABT group 85.0% (95% CI 70.4 to 93.1) and in the APP group 92.5% (95% CI 79.2 to 97.6) patients were successfully cured within two weeks without major complications (Malik 2009). 252 patients were included by Styrud et al, 128 in de ABT group and 124 in the APP group. 75.0% (95% CI 66.8 to 81.7) of patients and 98.4% (95% CI 93.8 to 99.6) of patients were cured in the ABT and APP group respectively (Styrud 2006). Turhan et al conducted their trial with 290 patients, 107 in the ABT and 193 in the APP group. 81.3% (95% CI 72.8 to 87.6) in the ABT group and 98.9% (95% CI 95.7 to 99.7) in the APP group cured. (Turhan 2009). Vons et al included 243 patients, but direct after randomisation four patients refused to participate. Eventually 239 were included, of which 120 in de ABT group and 119 in the APP group. In the ABT group 60.8% (95% CI 51.8 and 69.1) was cured within two weeks without major complications in one year, in de APP group 98.3% (95% CI 93.5 to 99.6)(Vons 2011). See Figure 3 and Figure 4.

Figure 3. Primary outcome for antibiotic treatment. Outcomes are measured in percentages.

Cured within two weeks, without major complications (including recurrence) within one year

Study	Antibiotic treatment				95% CI, random	
	Events	Subjects	Weight	Mean	Lower	Upper
Eriksson 1995	12	20	0,305	60,00	38,00	78,60
Malik 2009	34	40	0,325	85,00	70,40	93,10
Styrud 2006	96	128	1,527	75,00	66,80	81,70
Turhan 2009	87	107	1,035	81,30	72,80	87,60
Vons 2011	73	120	1,819	60,80	51,80	69,10
Total		**415**		**73,40**	**62,70**	**81,90**

Heterogeneity: $Tau^2 = 0,184$; $I^2 = 43,3\%$

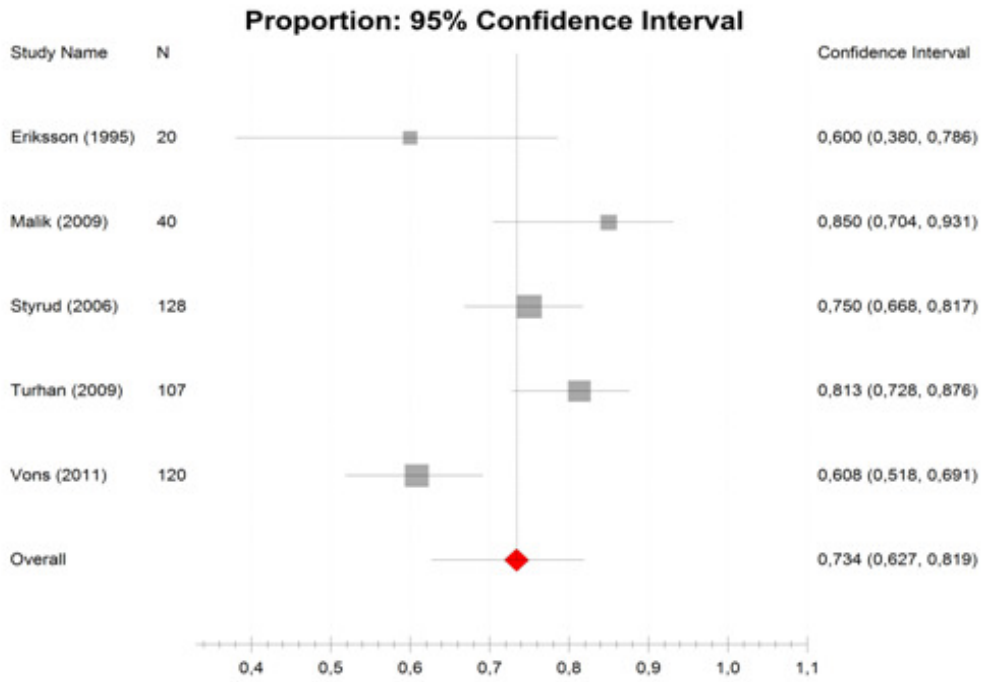
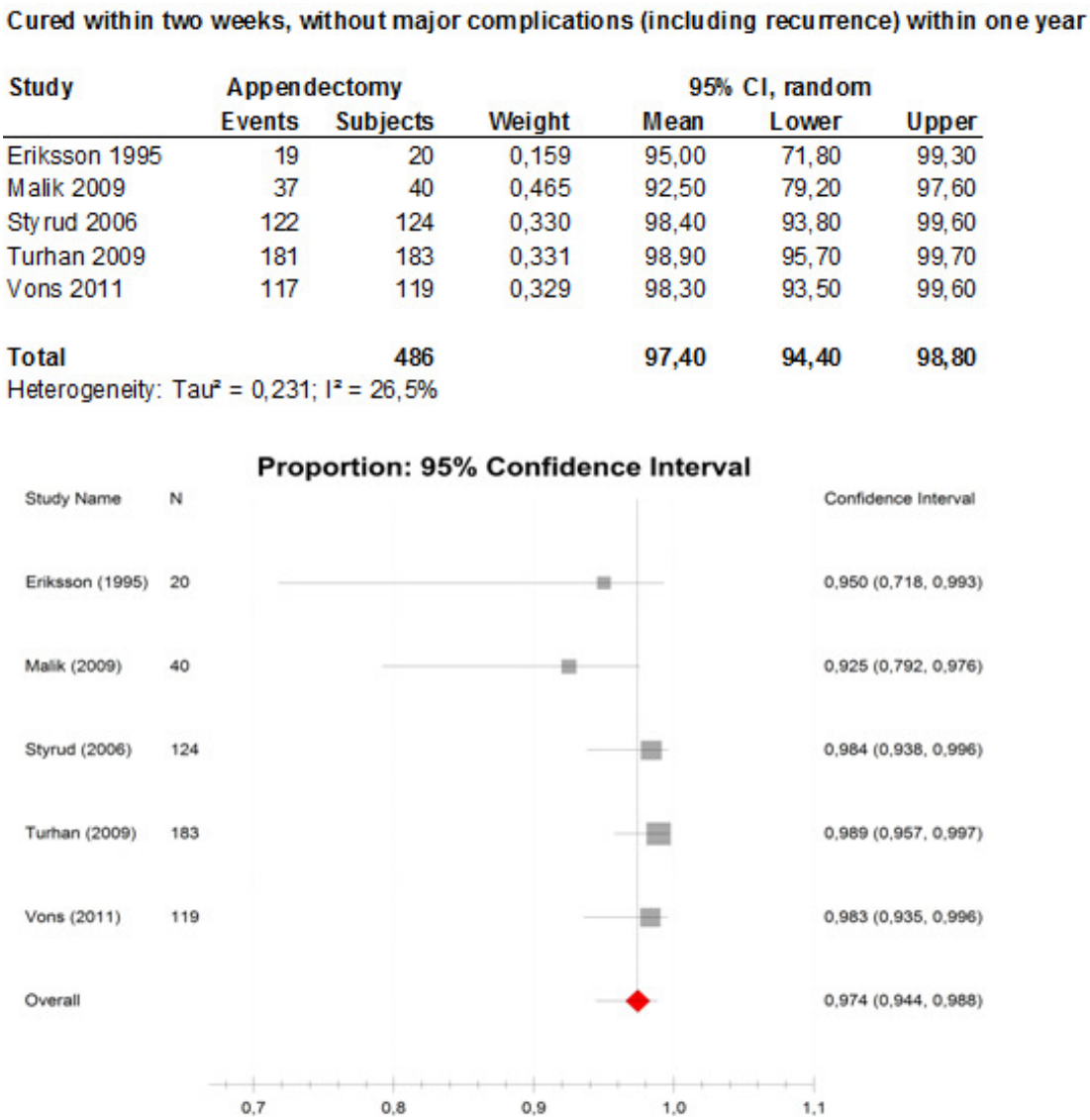
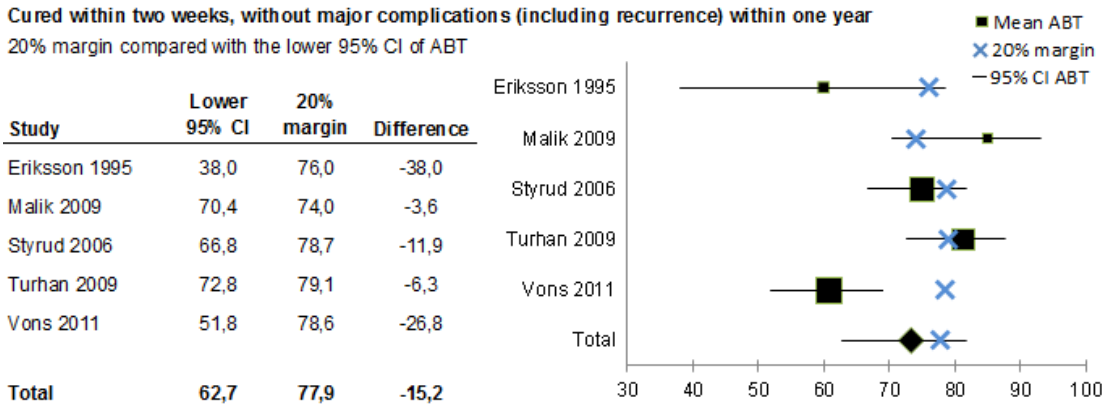


Figure 4. Primary outcome for appendectomy. Outcomes are measured in percentages.



In total 73.4% (95% CI 62.7 and 81.9) patients who received antibiotics and 97.4% (95% CI 94.4 and 98.8) patients who directly received an appendectomy were successfully cured within two weeks and had no major complications (including recurrence) within one year. The random effect model was used because of the moderate amount of heterogeneity (ABT: I^2= 43.3 versus APP: I^2 = 26.5). In all trails the lower 95% CI of ABT was below the 20% margin (range -38.0 and -3.6). In total the lower 95% CI was 15.2% below the 20% margin (Figure 5).

Figure 5. Primary outcome, the lower 95% CI of ABT was compared to the 20% margin of APP.



Study	Lower 95% CI	20% margin	Difference
Eriksson 1995	38,0	76,0	-38,0
Malik 2009	70,4	74,0	-3,6
Styrud 2006	66,8	78,7	-11,9
Turhan 2009	72,8	79,1	-6,3
Vons 2011	51,8	78,6	-26,8
Total	**62,7**	**77,9**	**-15,2**

Because de major difference between the mean ABT and APP an indefinite sample size was required to prove a non inferior difference of more than 20% (alpha= 5%, beta= 80%)..

Major complications

Major complications were defined as complications requiring need of further (invasive) treatment or prolonged admission (e.g. abscesses, ileus, deep wound infection, recurrence, (re)operation, secondary perforation). Not all complications were reported in every trial, however wound infection and recurrence were always mentioned. Though it was difficult to discover infection severity (deep or superficial wound infection). All wound infections that required readmission or were classified as deep wound infection were identified as a major complication. In Turhan 2009 further information was lacking on infection severity. The mentioned wound infections were assumed to be superficial wound infections (in the ABT and APP group respectively 5 and 6 patients). Besides the earlier mentioned complications, another major complication described was enterocutaneous fistula. In the included trials recurrence was described as clinical symptoms of acute appendicitis within one year, after a symptom free period. It was not possible to discover if the patients had a secondary perforation. It was also not possible to retrieve the information whether patients with more severe appendicitis had more complications.The amount of complications was calculated, not the number of patients with complications. It was assumed that the number of patients with more than one complication was small.

As mentioned earlier, the patients who had no major complications were calculated. In 83.2% (95% CI 72.0 and 90.5) of the patients who received primarily antibiotics no major complications occurred. No major complications were described in 97.1% (95% CI 92.6 to 98.9) patients who had initially appendectomy. In three out of five trails the 95% CI of ABT was within the 20% margin (range -33.4 to 2.2). In total the 95% CI of ABT was also within the 20% margin. Because of the heterogeneity in both groups a random-effects model was used (Figure 6; Figure 7; Figure 8). The sample size that was needed to prove a difference of more than 20% between the APP and ABT group was 586 patients (alpha= 5%, beta= 80%). There were enough patients included.

Figure 6. Secondary outcome for antibiotic treatment; major complications. Outcomes are measured in percentages.

No major complications

Study	Antibiotic treatment				95% CI, random	
	Events	Subjects	Weight	Mean	Lower	Upper
Eriksson 1995	13	20	0,508	65,00	42,60	82,30
Malik 2009	36	40	0,402	90,00	76,20	96,20
Styrud 2006	111	128	1,646	86,70	79,70	91,60
Turhan 2009	98	107	0,920	91,60	84,60	95,60
Vons 2011	87	120	2,672	72,50	63,80	79,70
Total		**415**		**83,20**	**72,00**	**90,50**

Heterogeneity: $Tau^2 = 0,299$; $I^2 = 44,6\%$

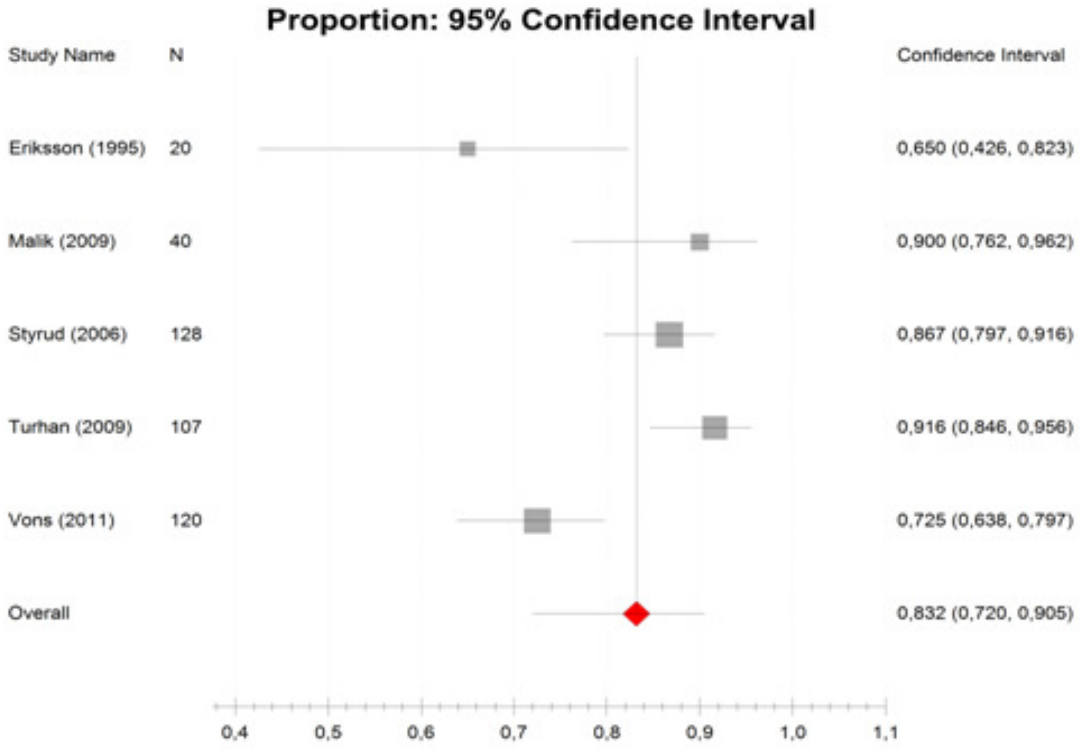


Figure 7. Secondary outcome for appendectomy; major complications. Outcomes are measured in percentages.

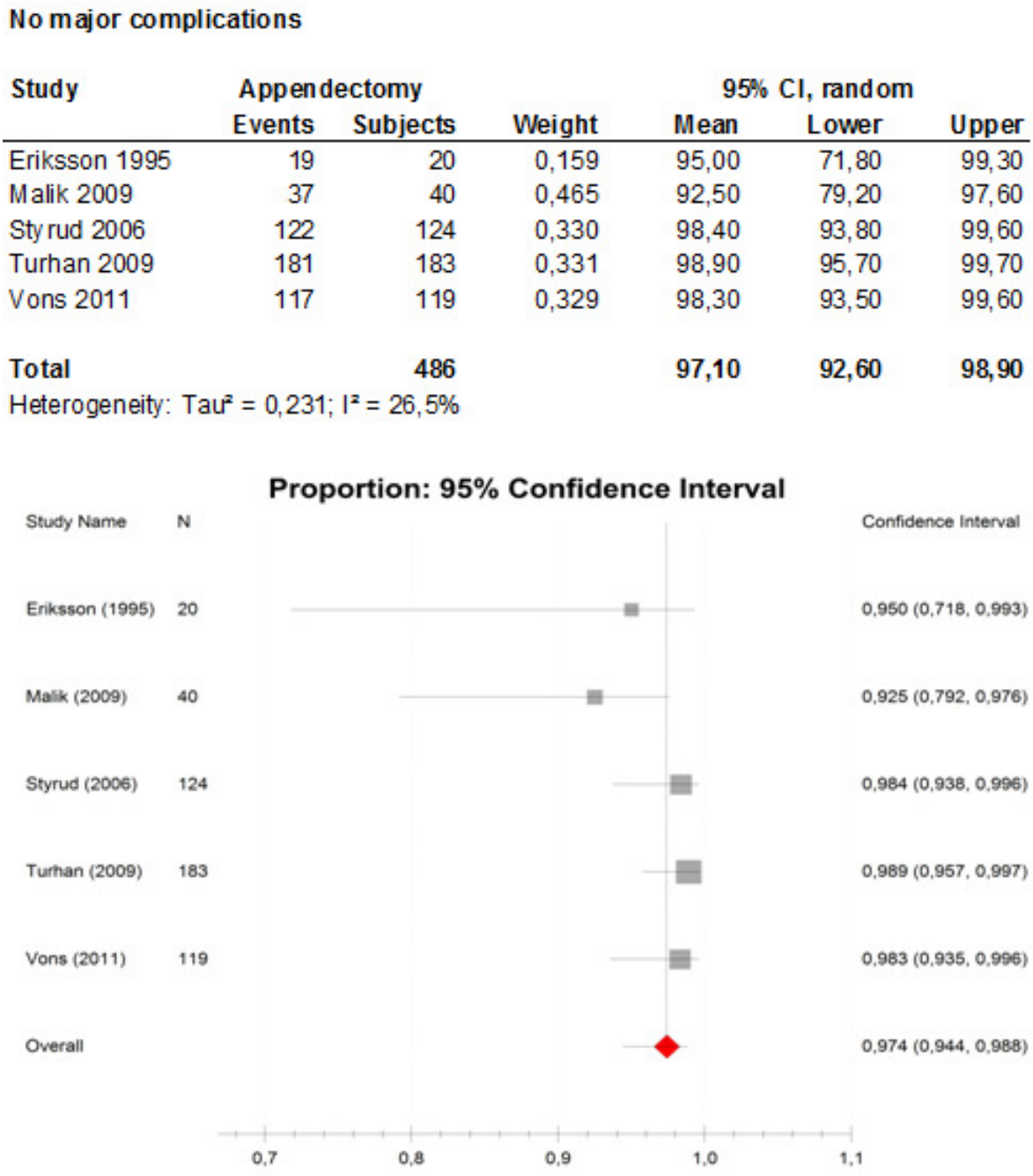
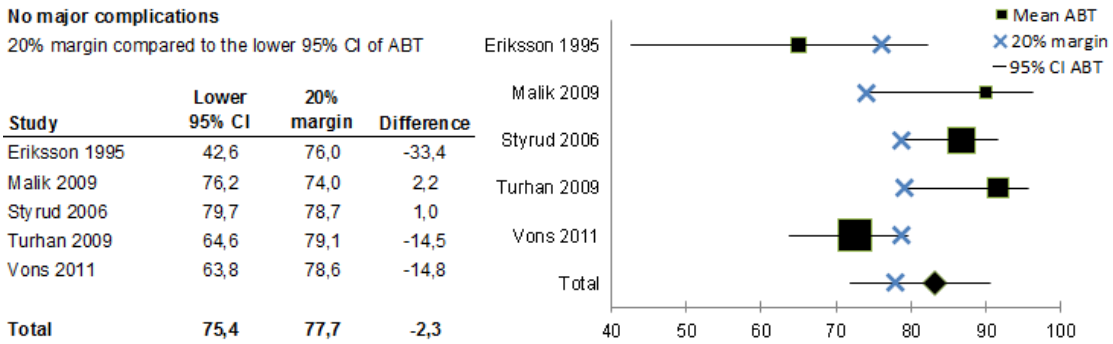


Figure 8. Secondary outcome (no major complications): the lower 95% CI of ABT was compared to the 20% margin of APP.



Minor complications

A few minor complications were described in the trials. Complications that were frequently registered were: (superficial) wound infections, negative appendices at histopathological examination (no appendicitis) and diarrhoea. Other minor complications that were mentioned include: clostridium or fungal infection and urinary tract infection

Instead of calculating occurrence of minor complications, the patients without minor complication occurrence were calculated. Overall, 95.6% (95% CI 93.1 to 97.3) of the patients in the ABT group and 91.4% (95% CI 82.9 to 95.9) of the patients in the APP group had no minor complications. In total the 95% CI of ABT lied within the 20% margin: 20.0(range 7.3 to 24.2). For this calculation the random-effects model was used, because of the moderate heterogeneity (Figure 9; Figure 10; Figure 11). In total 28 patients are needed in total to demonstrate a difference of 20% between the ABT and APP group (alpha= 5%, beta= 80%).

Figure 9. Secondary outcome for antibiotic treatment; minor complications. Outcomes are measured in percentages.

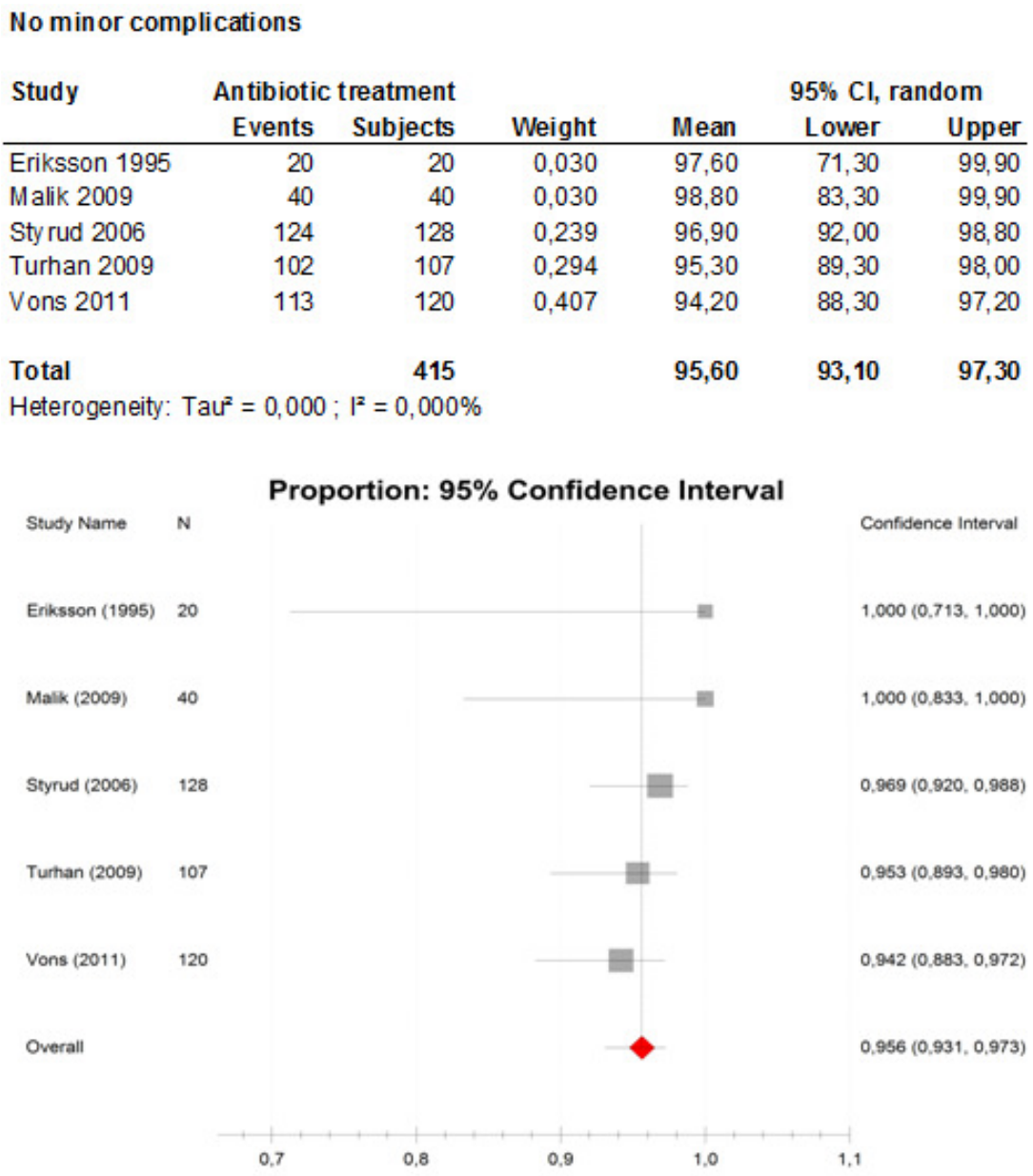


Figure 10. Secondary outcome for appendectomy; minor complications. Outcomes are measured in percentages.

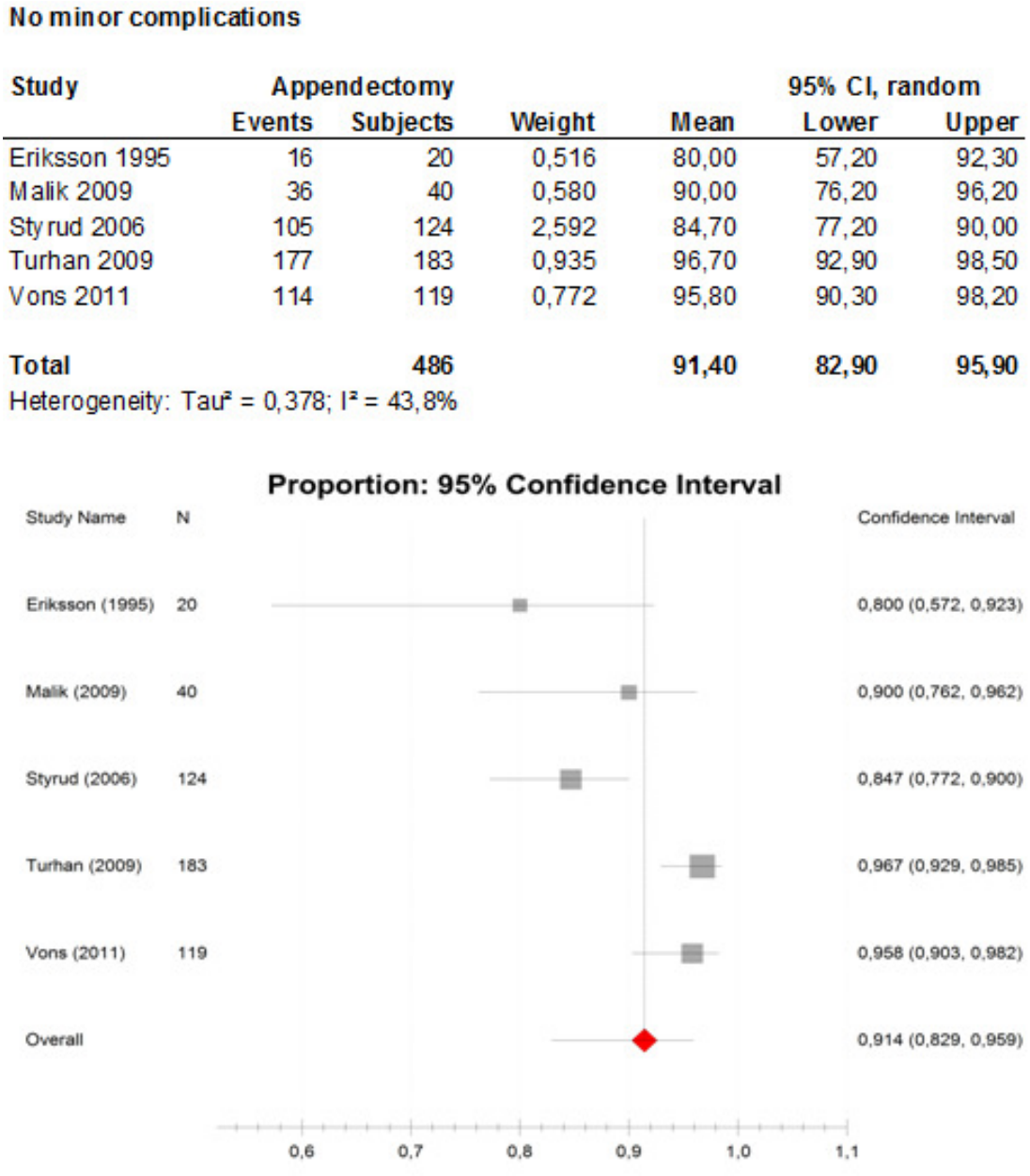
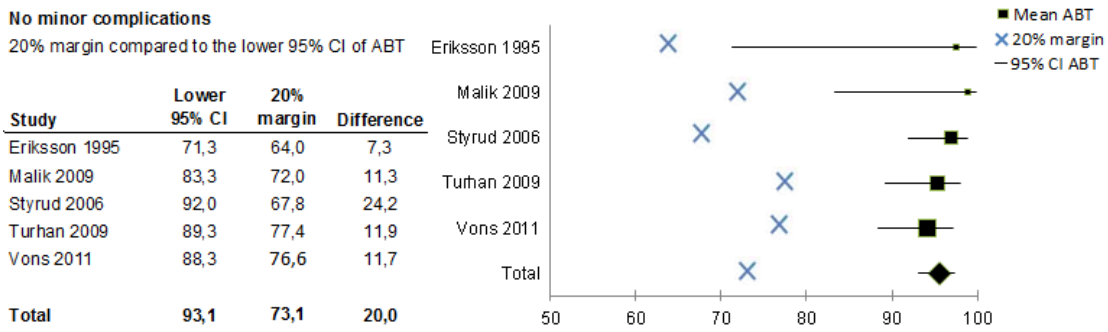


Figure 11. Secondary outcome (no minor complications): the lower 95% CI of ABT was compared to the 20% margin of APP



Other secondary outcomes

Beside major and minor complications we also attempted to calculate the total duration of hospital stay, the duration of sick leave and the cost effectiveness.

All studies described the duration of hospital stay in both groups. The overall odds ratio (OR) for duration of hospital stay was 0.66 (95% CI 0.44 to 0.87) in favour of APP. By eyeballing it was obvious that Malik was causing heterogeneity, for that reason we excluded the trial from this analysis. Without Malik the I^2 was 33% and therefore a random effects model was used. See Figure 12. Only two studies described the duration of sick leave. The OR was -0,69 (95% CI -1.65 to 0.27) in favour of antibiotic treatment. See Figure 13

Figure 12. Forest plot of comparison: 1 Antibiotic treatment versus appendectomy, outcome: 1.1 Duration of hospital stay (days).

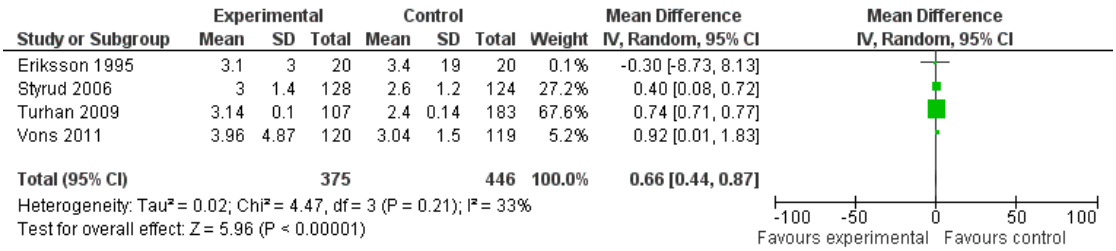
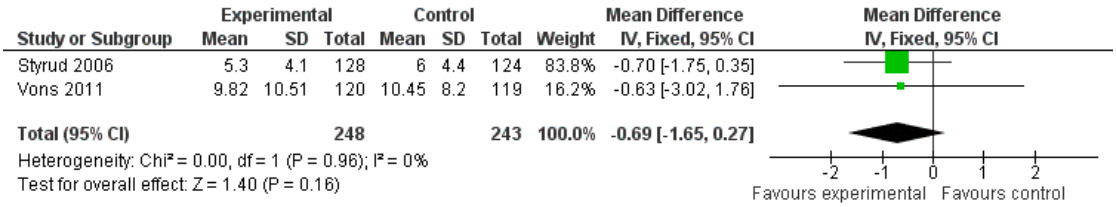


Figure 13. Forest plot of comparison: 1 Antibiotic treatment versus appendectomy, outcome: 1.2 Period of sick leave.



It was not possible to calculate cost effectiveness because only one trial described this outcome.

DISCUSSION

For many years, appendectomy had been the treatment of choice for patients with acute appendicitis. Since Coldrey reported appendicitis could be treated with antibiotics alone in 1959, very few doctors followed his lead (Coldrey 1959). Even today conservative treatment of uncomplicated acute appendicitis remains a controversial topic.

In this meta-analysis we attempted to investigate whether antibiotic treatment is as effective as surgical appendectomy (laparoscopic or open) in patients with acute appendicitis on recovery within two weeks, without major complications (including recurrence) within one year. The effectiveness of antibiotic treatment and appendectomy was analysed in all the included patients with acute appendicitis.

Because of the small numbers of patients who were enrolled in the studies and the lack of specified patient characteristics, it was not possible to make a subgroup analysis. Age, gender and the way of diagnostic technique could probably influence the outcomes. Appendicitis is mostly seen in the second decade. The age in the included studies ranged between 13 and 75 years. Four out of the five studies only included patients older than 17 years. These patients probably do not represent the majority of the patients in the clinic. It was not possible to discover whether age influenced the outcomes. More men than women were included in the studies. The differential diagnosis of right lower quadrant pain in women is more diverse than in men because of additional gynaecological disease. This could cause more negative appendectomies in women and probably more antibiotic treatable diseases. Also the diagnostic methods could lead to differences between the ABT en APP group. Whereas one study performed only minimal investigations, others performed additional examinations which led to more accurate diagnosis.

ABT was compared to the gold standard APP, on the assumption that ABT had some advantages above APP. For that reason a non-inferiority analyses was used. If the difference between the antibiotic group and the appendectomy group would be within the 20% margin, it would be clinically relevant. In that case antibiotic treatment should be classified as not inferior to appendectomy. The lower 95% CI of ABT was 15.2% under the 20% margin of non-inferiority, the upper bound of the 95% CI of ABT crosses the 20% margin of appendectomy. Therefore the results are inconclusive. But is a margin of 20% a realistic assumption? In that situation we would accept that 1 in 5 patients will not be cured or suffer from complications? Because the results are inconclusive, calculated was the margin that was needed for a non-inferior and inferior conclusion. This was respectively 35.7% margin and 15.9% margin. What can we accept? That approximately 1 in 3 patients treated with antibiotics for acute appendicitis will not be cured within two weeks, without major complications (including recurrence) within one year? These patients will have a longer (re)admission or require operative treatment. Is this acceptable?

Most of the studies did not accurately describe the method of randomisation. This can lead to a difference between the study groups. It also diminished the quality of the studies.

The meta-analysis of Andersen 2009 showed the effectiveness of antibiotic prophylaxis in the prevention of post-operative complications in patients who had appendectomy. It should be considered for routine use in emergency appendicectomy. Not all studies reported or used prophylactic antibiotics. Only two studies reported the use of prophylactic antibiotics. Not using prophylactic antibiotics in the appendicectomy group would cause a higher complication rate (mainly wound infections) in the APP group. None of the trials differentiated the complications between open and laparoscopic appendectomy, A meta-analysis showed a difference in complications between laparoscopic and open surgery for acute appendicitis (Sauerland 2004). More wound infections were reported in open surgery and more intraabdominal abscesses in laparoscopic appendectomy. Also the experience of the operating surgeon played a crucial role.

In our study it was difficult to compare complications in both

groups, because not all complications can occur in both groups. For example recurrence can only occur in the group that was treated with antibiotics alone, whereas wound infections can only occur in patients who underwent surgery. It was also impossible to trace whether all patients in the antibiotic group really had appendicitis.

Major complications were frequently measured. Not all trials reported whether there was a deep or superficial infection nor the use of antibiotics for this complication. The lower 95% CI of the ABT was below the 20% margin . The upper bound of the 95% CI of ABT crosses the 20% margin of appendectomy. Which implies that the results for the major complications are inconclusive.

A lot of minor complications can occur in the treatment of acute appendicitis, although it is doubtful whether all studies reported all minor complications. Only one study mentioned a higher number of minor complications, while the others only reported diarrhoea or minor wound infections. The 95% CI of the ABT was within the 20% margin in patients who had none of the mentioned minor complications. Which implies that ABT is not inferior to APP for the minor complication occurrence.

Patients who underwent appendectomy had a significant shorter hospital stay than the patients who were treated with antibiotics. For sick leave the difference between the ABT and APP group was not significant.

The follow up in the studies ranged between 30 days and 1 year, however all studies investigated if conservative treated patients had recurrent appendicitis within one year after initial presentation. Recurrences after one year were not mentioned. We found no literature about recurrence after one year for non complicated appendicitis. However there is some evidence for the risk of recurrence in complicated appendicitis. The accepted treatment for appendiceal abscess is non-operative with or without an interval appendectomy. The meta-analysis of Andersson 2007 showed that the risk of recurrence is 8.9% (95% CI 4.4 to 13.3). The majority of recurrences occurred within 6 months after the initial hospital stay. The risk of recurrence was often associated with an appendicolith and had a milder course than the primary attack. It is therefore important to inform patients who received antibiotic treatment about the risk of recurrence.

An advantage of appendectomy in comparison with antibiotic therapy is the opportunity to perform histopathological examination of the removed appendix. In some cases no acute appendicitis will be found. This can be divided in a negative appendectomy with or without extra-appendiceal pathology and other pathologies of the appendix. The last mentioned can be subdivided in inflammatory (e.g. appendiceal diverticulitis, Crohn´ s disease) and neoplastic changes. It is important to detect neoplastic changes in the appendix, because it can influence the further treatment. The most common neoplastic deformity is the carcinoid tumour (about 1% of the appendectomies for acute appendicitis). This tumour often presents as appendicitis. In most cases, it is found during appendectomies and its diagnosis is rarely suspected before histological examination *(*Ma 2010; Connor 1997; Tchana-Sato 2006*)*. Of the 594 histopathological examined appendices in our analysis, no malignant tumours were found so we cannot confirm the earlier mentioned occurrence of 1%.

During the protocol phase of this review another meta-analysis has been published about this subject (Varadhan 2009). They included only two out of the five trials we have included and the Hansson trial. The three trials were not included probably because they had not been published at the time of their search. Difference between their meta-analysis and ours, is that they performed a superiority analyses and calculated risk ratios. The primary outcomes in Varadhan et al were the complications, as described in the individual RCT's. As secondary outcome they took the length of hospital stay and readmission rates. They concluded that there is evidence to support the safe use of antibiotic therapy in selected patients with acute appendicitis without signs of perforation or peritonitis. Antibiotic therapy was associated with a trend toward decreased risk of complications without a prolonged hospital stay. But they also mentioned that the conclusions presented were limited, for several (mainly methodological) reasons. Eventually they concluded that appendectomy was still the gold standard for the treatment of acute appendicitis.

Authors' conclusions

AUTHORS' CONCLUSIONS

Implications for practice

The upper bound of the 95% CI of ABT crosses the 20% margin of appendectomy for cure within two weeks without major complications, so the results are inconclusive for the primary outcome. The results of the major complications are also inconclusive. Only for the minor complications antibiotic treatment proved to be not inferior to appendectomy. Patients who underwent appendectomy have a shorter duration of hospital stay. The quality of the studies was low to moderate, and subgroup analysis could not be made, for that reason the results should be interpret with caution and definite conclusions can not be made. Therefore we conclude that appendectomy remains the standard treatment for acute appendicitis. Antibiotic treatment might be used as an alternative treatment in a good quality RCT or in specific patients or conditions were surgery is contraindicated.

Implications for research

Better quality RCT's on the effectiveness of antibiotic therapy compared with appendectomy are needed, with randomisation performed properly. However, performing a good RCT with a high methodological quality for this subject remains difficult.

It is important that both study groups are diagnosed in the same way. High diagnostic accuracy is required in diagnosing patients with acute appendicitis. Besides history taking, physical examination and laboratory test, additional radiological imaging is required for a more accurate diagnosis. CT should be used in all patients with suspected appendicitis.

Also all patients who undergo appendectomy should have antibiotic prophylaxis, as recommended in de Cochrane review of Andersen 2009.

More research is needed whether antibiotic treatment is more effective in specific patient populations. It can be argued that those patients with extremes of age and excessive comorbidity will have higher risk of complications during or after surgery. Also, patients in whom appendicitis is diagnosed early in the disease process could have an advantage of antibiotic therapy. A RCT must report the results of these outcomes clearly, and whenever possible make a subgroup analysis. Future research might give more directives on specific treatment for these subgroups.

It is unknown whether patients who were treated conservatively for uncomplicated appendicitis, may have recurrent appendicitis after one year because follow up in the included studies was only one year. Also trials with a longer follow up are required.

ACKNOWLEDGEMENTS

We are greatly indebted to Mr. G. Koffeman for carefully reviewing the text of the first draft if this review on its grammatical content.

We would like to thank all authors who provided us with additional data and details of the trial: Styrud (Stockholm, Sweden), Bari (Srunagar, India), Vons (Paris, France).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Eriksson 1995

Methods	RCT, unclear how randomisation was performed Study duration: 2 months Center: one
Participants	Participants: Patients with a typical history and clinical signs of acute appendicitis, with positive findings at ultrasonography (US) and either increased WBC and CRP values, or high CRP or WBC levels on two occasions within a 4-hour interval. The duration of the abdominal pain was less than 72 hours. Diagnosis: typical history, clinical signs, US and laboratory tests (WBC and CRP). Number included patients: 20 patients in both antibiotic treatment (ABT) and appendectomy (APP) group. Mean age (range): ABT 27.8 (18-53) years and APP 35.0 (19-75) years. Sex (male): ABT 70% and APP 65%. Country: Sweden
Interventions	ABT • Antibiotics: Cefotaxime 2 g 12 hourly and tinidazole 800 mg daily were given for 2 days. During this time patients received intravenous fluids, nothing else. Pain (VAS) was registered every 6h and oral temperature was measured twice a day. • Discharge: after 2 days and received oral treatment with ofloxacin 200 twice daily and tinidazole 500 mg twice daily for 8 days. APP • Operation: not mentioned whether open or laparoscopic appendectomy • Antibiotic prophylaxis: not mentioned • Postoperative antibiotics: only in the event of perforation or for 24 hours in case of abdominal spillage. • Histologic examination appendix: yes • Discharge:When conditions were satisfactory and they wished to return home.
Outcomes	Duration of pain, morphine dosis, hospital stay, wound infection, recurrent appendicitis, course of CRP, WBC, VAS score and temperature within the follow up and clostridium difficile toxin in faeces
Notes	Follow up: 6, 10 and 30 days after admission. WBC and CRP were checked and the VAS score and oral temperature were measured. Abdominal and rectal examination at day 6 and 10. At day 30 the stool was examined for Clostridium difficile toxin. US at day 10 and 30. Recurrent appendicitis until one year after initial presentation All conservative treated patients with suspected recurrent appendicitis underwent surgery Exclusion criteria: non mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement

Eriksson 1995 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Other bias	Low risk	No additional bias

Malik 2009

Methods	RCT, patients were randomly allocated into two groups by systematic random sampling with an equal size of 40 to maintain balance. Study duration: 25 months Center: one
Participants	Participants: patients with typical history and clinical signs of appendicitis as described in Alvarado's score, positive findings at ultrasonography (US) and either increased WBC and CRP values, or high CRP or WBC levels on two occasions within a 4 hour interval. All patients were examined by the same surgeon before inclusion. Diagnosis: Modified Alvarado score, US, laboratory tests like estimation of total WBC count and CRP levels were used as diagnostic tools to identify patients with a high probability of acute appendicitis. Computed tomography (CT) scanning of the abdomen was not done in any patient because high cost for CT in this part of world Number included patients: Both antibiotic treatment (ABT) en appendectomy (APP) group 40 patients Mean age (range): ABT 28.7(17-56) and APP 32.6 (18-64) years Sex (male): ABT 65% and APP 70%. Country: India
Interventions	ABT • Antibiotics: ciprofloxacin 500 mg 12 hourly and metronidazole 500 mg 8 hourly were given for 2 days. Patients received intervenous (IV) fluids only during this period. • Pain was registered every 6 hour using VAS and oral temperature was measured twice daily. • Discharge: within 3 days and received oral treatment with ciprofloxacin 500 mg twice daily an tinidazole 600 mg twice for 7 days. APP • Operation: not mentioned whether open or laparoscopic appendectomy • Antibiotic prophylaxis: yes, cephalosporins and imidazole • Postoperative antibiotics: only in the event of perforation or in cases of abdominal spillage for 48 hours. • Pain was registered every 6 hours using VAS and oral temperature was measured twice daily. • Histologic examination appendix: yes • Discharge: once conditions were satisfactory
Outcomes	Analgesic consumption, pain, hospital stay, wound infection, recurrence, US follow up findings. Course of WBC, CRP and temperature

Malik 2009 (*Continued*)

Notes	Follow-up: 7, 12 and 30 days after admission. During follow-up, blood sample (WBC and CRP levels), pain (VAS) and oral temperature was registered. Patient with recurrent appendicitis within one year were readmitted All conservative treated patients with suspected recurrent appendicitis underwent surgery Exclusion criteria: non mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "allocated into two groups by systematic random sampling"
Allocation concealment (selection bias)	Unclear risk	Unclear
Other bias	Low risk	No additional bias

Styrud 2006

Methods	RCT: randomisation of each participant was performed by a telephone call to Danderyd Hospital where a sealed envelope was opened and revealed the assignment of surgery or antibiotic therapy. Study duration: 40 months. Centers: six
Participants	Participants: All male patients admitted for suspected acute appendicitis with a CRP level > 10 mg/l in whom perforation was not suspected. Diagnosis: disease history, clinical status and CRP > 10 mg/l Number included patients: ABT 128 and APP 124 patients Age: Total 18-50 years (range), mean age "about 23 years" (according to author after correspondence) Sex (male): 100% in both groups Country: Sweden
Interventions	ABT • Antibiotics: 2 days of iv cefotaxime 2 g 12 hourly, and tinidazole 0.8 g daily. Patients received intravenous fluids during the first 24 hours and were allowed to eat during the second hospital day. • Discharge: after 2 days and received oral treatment with ofloxacin 200 mg twice daily, and tinidazole 500 mg twice daily for 10 days. APP • Operation: open or laparoscopic, at surgeon's discretion. Laparoscopic appendectomy: 6.5%, open appendectomy: 93.5%. • Antibiotic prophylaxis: no • Postoperative antibiotics: only in case of abdominal spillage • Histologic examination: yes • Discharge: when condition was satisfactory

Styrud 2006 (*Continued*)

Outcomes	Hospital stay, sick leave, time off work, complication, histopathological diagnosis (in case of appendectomy), recurrence rate within 1 year, lack of improvement symptoms within 24 hours, CRP, WBC and temperature
Notes	Follow-up: after 1 week, 6 weeks and 1 year. Exclusion criteria: suspicion of perforation, CRP < 10 mg/l, allergy to antibiotics No women were enrolled by decision of the local ethics committee Appendectomy in case of no improvement within the first 24 hours, or recurrent appendicitis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Yes, "telephone call to Danderyd Hospital where a sealed envelope was opened"
Allocation concealment (selection bias)	Low risk	Yes, sealed envelopes
Other bias	Unclear risk	Only men included

Turhan 2009

Methods	RCT. Randomisation method not stated Study duration: 13 months Center: one
Participants	Participants: patients presenting to the Emergency Department with acute appendicitis Diagnosis: - ABT group: physical examination, complete blood cell count, US, CT and a modified Alvarado score - APP group: physical examination, complete blood cell count, modified Alvarado score. Number included patients: 107 patients ABT and 183 patients in the APP group Mean age (range): ABT 30.98 (16-65) years and APP 26.25 (13-59) years Sex (male): ABT 61% and APP 68%. Country: Turkey
Interventions	BT • Antibiotics: Intravenous fluids + antibiotic therapy with ampicillin (1g 4x 1 daily) + gentamicin (160 mg/day) + metronidazole (500 mg 3x1 daily) and analgesic with diclofenac sodium (50-75 mg 3x1 i.m. daily). • Daily follow up with complete blood cell count, fever, physical examination and US. • Discharge: Patients with clinical improvement on the third day with oral antibiotic therapy completed to 10 days. APP • Operation: 82.0% of the patients open appendectomy and 18.0% of the patients laparoscopic appendectomy

Turhan 2009 (*Continued*)

	• Antibiotic prophylaxis:not mentioned • Postoperative antibiotics: not mentioned • Histologic examination appendix: yes, but did not report the outcome in the article • Discharge:not mentioned
Outcomes	Resistence to therapy, recurrence, costs, complications, hospital stay, histopathologic outcome appendix, mortality and morbidity, Alvarado score
Notes	Follow-up: at day 10, after 2 and 6 months and 1 year. In the ABT group with US and hemograms Exclusion criteria: not mentioned Appendectomy in all patients with no improvement and appendectomy in case of recurrence except in two patients (of which one is eventually operated)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Unclear, but a significant difference in patients included in the ABT and APP group
Allocation concealment (selection bias)	Unclear risk	Unclear
Other bias	High risk	Only CT scan in ABT group and reporting bias (not reporting the histopathological outcomes of the removed appendices)

Vons 2011

Methods	RCT: randomisation of each participant was performed by computer generated randomisation. Opaque, sealed, and sequentially numbered envelopes were provided to each trail site Non-inferiority trail Study duration: between 11 March 2004 and 15 January 2007 (34 months) Centers: six
Participants	Participants: Patients with suspected acute appendicitis and had a CT scan with the diagnosis uncomplicated acute appendicitis Diagnosis: by CT imaging Number included patients:243, 4 patients refused to participate in the trail shortly after randomisation. 239 patients were analysed. Mean age (range): ABT 31 years and APP 34 years. Total age range: 18-69 year Sex (male): 59.8% Country: France

Interventions	ABT • Antibiotics: amoxicillin plus clavulanic acid (3 gram per day for patients weighing <90 kg, and 4 gram per day for patients ≥90kg), given intravenously to those with nausea or vomiting, and orally to all others. • Patients continued the same antibiotic treatment at home, with the same dose for 8 days, and were seen on day 8. • Discharge: if pain and fever resolved rapidly APP • Operation:laparoscopic (65.5%) and open (McBurney)(34.5%) • Antibiotic prophylaxis:yes,2 gram amoxicillin plus clavulanic acid • Postoperative antibiotics:only in case of complicated appendicitis • Histologic examination appendix: yes, however pathophysiological outcomes were not mentioned • Discharge:after resolution of pain, fever, and any digestive symptoms
Outcomes	Occurrence of peritonitis within 30 days of initial treatment Number of days with a post intervention VAS pain score ≥4, length of hospital stay and absence of work, incidence of complications other than peritonitis within one year (post-operative wound abscess, incisional hernia, adhesive occlusion) and recurrence of appendicitis after antibiotic treatment
Notes	• Follow-up: day 15, 30, 90, 180 and 360 • Exclusion criteria: age less than 18 years, antibiotic treatment 5 days before, allergy to beta lactam antibiotics, known intolerance to amoxicillin plus clavulanic acid (nausea, vomiting), receiving steroid or anticoagulant treatments, past history of inflammatory bowel disease, pregnancy or a positive pregnancy test, life expectancy less than one year, allergy to iodine of blood creatinine 200µmol/L of more, or inability to understand information about the protocol or to sign the consent form. After performing a CT scan all patients with complicated or no appendicitis were excluded. Also patients with an appendix diameter greater than 15 mm were excluded form the study (because the high risk of malignancy). • If the symptoms and abdominal tenderness did not resolve after 48 hours, immediate appendectomy was undertaken. In case of persistence of pain or fever prompted a CT scan and possible appendectomy. In case of a normal CT scan but a sustained high WBC or high CRP, the antibiotic treatment was prolonged with 8 days. Persistence of similar biological disorders on day 15 prompted appendectomy without additional CT scan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation.
Allocation concealment (selection bias)	Low risk	Opaque, sealed, and sequentially numbered envelopes.

Other bias	High risk	Use of oral and iv antibiotics, depending on nausea and vomiting

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

Study	Reason for exclusion
Andrén-Sandberg 1985	No RCT or qRCT. Prophylactic antibiotics in appendectomy.
Farahnak 2007	RCT, matched the outcome of the Alvarado score with the intervention (antibiotic treatment or appendectomy) in patients with acute appendicitis
Greig 1995a	Comment on Eriksson 1995
Greig 1995b	Comment on Eriksson 1995
Hansson 2009a	A lot of bias in this trial, which would affect the results. Quasi-RCT: allocation by date of birth. Uneven date of birth was allocated to antibiotic treatment (ABT), even date of birth was allocated to appendicectomy (APP). There was a lot cross-over between both groups by preference patient or surgeon 52.5% completed the intended antibiotic therapy and 92.2% patients in the surgery group had appendectomy. The remaining patients crossed over to the other intervention group. Hansson et al outlines the reasons to switch, but the numbers identified in tables and in the text were inconsistent This study also tried to analyse the results after one year. But 32.8% of the patients in the antibiotic treatment group and 28.0% of the patients in the appendectomy group the results were not analysed after one year
Hansson 2009b	Comment on Hansson 2009a
Kaneko 2004	No RCT or qRCT, matched the outcome of a diagnostic test (ultrasound) with the intervention (antibiotic treatment or appendectomy) in patients with acute appendicitis
Mason 2008	No RCT or qRCT. Narative review combined with a meta-analyses about antibiotic treatment versus appendectomy in acute appendicitis
McLeod 2006	No RCT or qRCT. Descibes the value of RCT in surgery.
Nozoe 2002	No RCT or qRCT, combined the outcome of the SIRS score with the intervention (antibiotic treatment or appendectomy) in patients with acute appendicitis
Ozguc 2007	Comment on Styrud 2006
Ozgüc 1995	Comment on Eriksson 1995

(*Continued*)

Winn 2004	No RCT or qRCT, matched the outcome of the Alvarado score with the intervention (antibiotic treatment or appendectomy) in patients with acute appendicitis

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

NCT01022567

Trial name or title	NCT01022567
Methods	RCT, method of randomisation not stated
Participants	Inclusion criteria: age range from 18 to 60 years; CT scan diagnosed uncomplicated acute appendicitis Exclusion criteria: below 18 years of age or older than 60 years; pregnancy or breast-feeding; allergy to contrast media or iodine; renal insufficiency; metformin medication (DM); peritonitis (a perforated appendix); lack of co-operation (unable to give consent); a severe other medical condition; CT-scan: other diagnosis, fecal lithiasis in appendix, perforation, abscess, suspicion of a tumour
Interventions	Antibiotic treatment: ertapenem 1 g x 1 iv for three days + after discharge levofloxacin 500 mg 1x1 + metronidazole 500 mg 1x3 for 7 days p.o Operative treatment: regular open appendicectomy
Outcomes	The success of antibiotic treatment in patients with acute uncomplicated appendicitis [Time Frame: one to three days, one week, two months, one year and three, five and ten years
Starting date	November 2009
Contact information	Salminen P, Turku University Hospital, Department of Surgery
Notes	

DATA AND ANALYSES

Comparison 1. Antibiotic treatment versus appendectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital stay (days)	4	821	Mean Difference (IV, Random, 95% CI)	0.66 [0.44, 0.87]
2 Period of sick leave	2	491	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.65, 0.27]

Analysis 1.1. Comparison 1 Antibiotic treatment versus appendectomy, Outcome 1 Duration of hospital stay (days).

Review: Appendectomy versus antibiotic treatment for acute appendicitis

Comparison: 1 Antibiotic treatment versus appendectomy

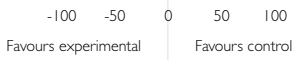
Outcome: 1 Duration of hospital stay (days)

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Eriksson 1995	20	3.1 (3)	20	3.4 (19)		0.1 %	-0.30 [-8.73, 8.13]
Styrud 2006	128	3 (1.4)	124	2.6 (1.2)		27.2 %	0.40 [0.08, 0.72]
Turhan 2009	107	3.14 (0.1)	183	2.4 (0.14)		67.6 %	0.74 [0.71, 0.77]
Vons 2011	120	3.96 (4.87)	119	3.04 (1.5)		5.2 %	0.92 [0.01, 1.83]
Total (95% CI)	**375**		**446**			**100.0 %**	**0.66 [0.44, 0.87]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.47$, df = 3 (P = 0.21); $I^2 = 33\%$

Test for overall effect: Z = 5.96 (P < 0.00001)

Test for subgroup differences: Not applicable

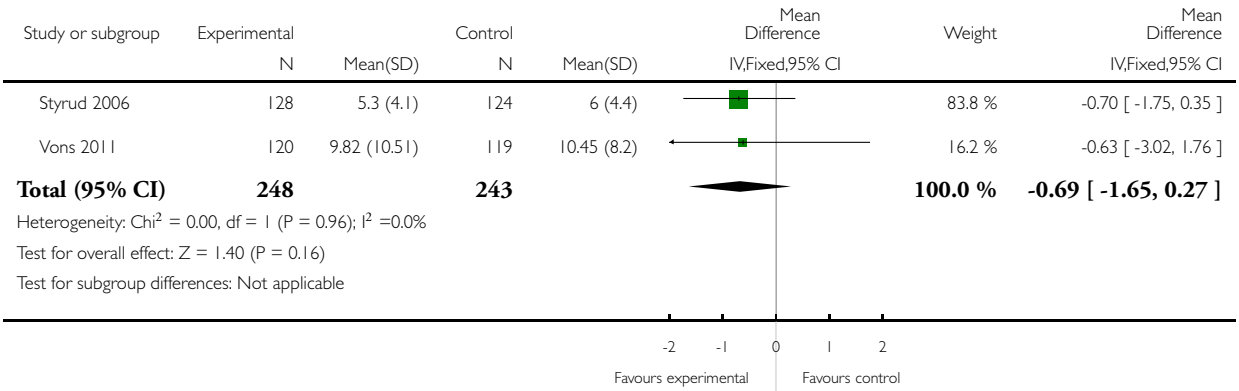


Analysis 1.2. Comparison 1 Antibiotic treatment versus appendectomy, Outcome 2 Period of sick leave.

Review: Appendectomy versus antibiotic treatment for acute appendicitis

Comparison: 1 Antibiotic treatment versus appendectomy

Outcome: 2 Period of sick leave



APPENDICES

Appendix 1. Cochrane Libary search strategy

#1 MeSH descriptor **Appendectomy** explode all trees
#2 (appendicectom* OR appendectom*)
#3 (#1 OR #2)
#4 MeSH descriptor **Appendicitis** explode all trees
#5 (appendic* OR appendicitis acuta)
#6 (#4 OR #5)
#7 (antibiotic*)
#8 (antibiotic* ADJ treatment*) or (antibiotic* therap*)
#9 (#7 OR #8)
#10 (#3 AND #6 AND #9)

Appendix 2. MEDLINE search strategy

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trial.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9
11. exp Appendectomy/
12. (appendectom* or appendicectom*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. 11 or 12
14. exp Appendicitis/
15. (appendic* or appendicitis acuta).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. 14 or 15
17. antibiotic*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. (antibiotic* adj treatment*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. (antibiotic* adj therap*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. 18 or 19 or 17
21. 10 and 13 and 16 and 20

Appendix 3. EMBASE search strategy

1. randomised controlled trial/
2. randomization/
3. controlled study/
4. multicenter study/
5. phase 3 clinical trial/
6. phase 4 clinical trial/
7. double blind procedure/
8. single blind procedure/
9. ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.
10. (random* or cross* over* or factorial* or placebo* or volunteer*).ti,ab.
11. 6 or 3 or 7 or 9 or 2 or 8 or 4 or 1 or 10 or 5
12. "human*".ti,ab.
13. (animal* or nonhuman*).ti,ab.
14. 13 and 12
15. 13 not 14
16. 11 not 15
17. exp Appendectomy/
18. (appendectom* or appendicectom*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
19. 17 or 18
20. exp Appendicitis/
21. (appendic* or appendicitis acuta).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
22. 20 or 21

23. antibiotic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
24. (antibiotic* adj treatment*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
25. (antibiotic* adj therap*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
26. 24 or 25 or 23
27. 22 and 16 and 19 and 26

HISTORY

Protocol first published: Issue 2, 2010

Review first published: Issue 11, 2011

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of the final draft of the review.

IW: searched for trials, selected trials, designed the data extraction sheets, extracted the data from all trials, contacted many of the trialists, conducted most of the analysis, interpret the analysis and wrote the first draft of the review

DdH: selected trials, extracted the data from most trials, cross-checked the analysis and helped in writing the first draft of the review.

DdV: provided statistical support, made comments on early drafts of the review.

HJ: developed the idea for the review, selected trials, extracted the data from a few trials, made comments on early and final drafts of the review.

The trial search coordinators of the CCCG (Susse Wegeberg and repeated by Marija Barbatedkovic) developed a search strategy.

DECLARATIONS OF INTEREST

None known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol a minimal detectable difference (MDD) of 20% was considered clinically relevant. Whenever the MDD of 20% was within the 95% CI of ABT, we assumed no clinical relevant difference. To calculate whenever antibiotic treatment was not inferior to appendectomy with a MDD of 20%, 20% of the mean APP was calculated and subtracted from the mean in appendectomy group and compared with the upper 95% CI tail of ABT.

However to confirm that ABT is not-inferior to APP, a 20% margin of non-inferiority is needed instead of a 20% MDD. Because we assumed that appendectomy would be more effective than antibiotic treatment, we compared the lower 95% CI of ABT with the 20% margin of APP. Whenever the 20% margin was below the lower 95% CI of ABT, we assumed that antibiotic treatment was not-inferior to appendectomy.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Appendectomy [*methods]; Appendicitis [*drug therapy; *surgery]; Randomized Controlled Trials as Topic

MeSH check words

Humans