Supplemental Online Content

de Almeida Leite RM, Seo DJ, Gomez B, et al. Nonoperative vs operative management of uncomplicated acute appendicitis: a systematic review and meta-analysis. *JAMA Surg*. Published online July 27, 2022. doi:10.1001/jamasurg.2022.2937

eAppendix. Protocol and Statistical Analysis Plan

eFigure 1. RR for Treatment Success (30 days of Follow-up)

eFigure 2. RR for Treatment Success (12 months)

eFigure 3. Recurrent Appendicitis Rate in Antibiotics Group

eTable. Bias Table

This supplemental material has been provided by the authors to give readers additional information about their work.

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eAppendix. Protocol and Statistical Analysis Plan

PICO Table

Systematic Review Terms

Do-file Commands

Publication Bias Analysis

Heterogeneity - Meta Regression

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PICO Table

PICO TAble

Part II. PICO table.

Citation (AMA format)	P Who is the patient/what problem is being addressed?	I What is the intervention or exposure?	C What is the comparison group?	O What is the outcome or endpoint?
Salminen P, Paajanen H, Rautio T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. *JAMA*. 2015;313(23):2340–2348. doi:10.1001/jama.2015.6154	• ED patients aged 18 to 60 years. • Clinical suspicion of uncomplicated acute appendicitis confirmed by a CT scan.	• Antibiotic Therapy. Ertapenem was chosen as the antibiotic for this study because of its efficacy as a monotherapy for serious intra- abdominal infections	• Open OR laparoscopic appendectomy. • AND Prophylactic antibiotics (1.5 g of cefuroxime and 500 mg of metronidazole) 30 minutes before the incision. No further antibiotics were given to patients in the surgical group unless a wound infection was suspected postoperatively.	• Resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgical intervention. • AND no recurrent appendicitis during a minimum follow-up of 1 year.
			Open appendectomy	
Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, Rex L, Badume I, Granström L. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg. 2006 Jun;30(6):1033-7. doi: 10.1007/s00268-005-0304-6. PMID: 16736333.	• All adult patients admitted for suspected acute appendicitis with a CRP level >10 mg/l in whom perforation was not suspected.	• Antibiotic therapy at the time the decision was taken that surgery was needed. 2 days of i.v. cefotaxime (Claforan; Aventis Pharma, Stockholm, Sweden), 2 g 12 hourly, and tinidazole (Fasigyn; Pfizer, Ta¨by, Sweden), 0.8 g daily for 10 days.		Complications in a one year follow up
CODA Collaborative, Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, Sanchez SE, Drake FT, Fischkoff K, Johnson J, Patton JH, Evans H, Cuschieri J, Sabbatini AK, Faine BA, Skeete DA, Liang MK, Sohn V, McGrane K, Kutcher ME, Chung B, Carter DW, Ayoung-Chee P, Chiang W, Rushing A, Steinberg S, Foster CS, Schaetzel SM, Price TP, Mandell KA, Ferrigno L, Salzberg M, DeUgarte DA, Kaji AH, Moran GJ, Saltzman D, Alam HB, Park PK, Kao LS, Thompson CM, Self WH, Yu JT, Wiebusch A, Winchell RJ, Clark S, Krishnadasan A, Fannon E, Lavallee DC, Comstock BA, Bizzell B, Heagerty PJ, Kessler LG, Talan DA. A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis. N Engl J Med. 2020 Nov 12;383(20):1907-1919. doi: 10.1056/NEJMoa2014320. Epub 2020 Oct 5. PMID: 33017106.	• Consecutive English- or Spanish-speaking adults (≥18 years of age) in ED who had appendicitis. • Confirmed on imaging.	• An intravenous formulation for at least 24 hours, followed by pills, for a 10-day total course. Clinical teams selected antibiotics from the Surgical Infection Society.	• Laparoscopic OR conventional (open). The technique was not standardized. Usual preoperative and postoperative care and discharge criteria were used.	• 30-day health status, as assessed with the use of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire18.
O'Leary DP, Walsh SM, Bolger J, Baban C, Humphreys H, O'Grady S, Hegarty A, Lee AM, Sheehan M, Alderson J, Dunne R, Morrin MM, Lee MJ, Power C, McNamara D, McCawley N, Robb W, Burke J, Sorensen J, Hill AD. A Randomized Clinical Trial Evaluating the Efficacy and Quality of Life of Antibiotic-only Treatment of Acute Uncomplicated	• Patients aged 16 and over. (**because patients between 16 and 18 years old are less than 10 % of the trial participants, we decided to include the trial in the analysis.** • Clinical suspicion of acute appendicitis: right iliac fossa pain and a raised white cell count and/or C-reactive protein,	• Intravenous antibiotic (co-amoxiclav, 1.2 g, 3 times daily) until there was a clinical improvement followed by 5 days of oral co-amoxiclav (625 mg 3 times a day for 5 days). Clinical improvement was defined as a significant interval improvement in patient's signs	• Laparoscopic appendectomy. • Antibiotics (co-amoxiclav, 1.2 g, iv upon confirmation of diagnosis soon after imaging was performed). • A further dose was administered at induction of anesthesia if necessary. • Three further doses were administered post-surgery.	• Success rate of antibiotic treatment only for acute uncomplicated appendicitis at 1-year follow-up. • In the operative treatment arm, the primary endpoint was defined as successful appendectomy, which was expected to be 100%. • Secondary end-points included a comparison

Appendicitis: Results of the COMMA Trial. Ann Surg. 2021 Aug 1;274(2):240-247. doi: 10.1097/SLA.0000000000004785. PMID: 33534226.	negative B-HCG (female patients only). • English proficiency.	and symptoms as assessed by the attending surgeon. A patient with penicillin allergy was prescribed cefuroxime and metronidazole.		of quality of life, cost, and length of stay between the 2 study groups.
Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, Karoui M, Alves A, Dousset B, Valleur P, Falissard B, Franco D. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet. 2011 May 7;377(9777):1573-9. doi: 10.1016/S0140-6736(11)60410-8. PMID: 21550483.	• Adults examined in the ED and suspected to have acute appendicitis. • Diagnosis of uncomplicated appendicitis was assessed by CT imaging. • Clear visualization of the appendix (appendix diameter >6 mm and no opacifi cation of the appendix in patients with an enema). • Absence of any of the three following criteria of complicated appendicitis with peritonitis: extraluminal gas, periappendiceal fluid, or disseminated intraperitoneal fluid. (1)An appendix diameter greater than 15 mm was a criterion for exclusion from the study, because of risk of malignancy.	• IV Amoxicillin plus clavulanic acid (3 g per day for patients weighing <90 kg, and 4 g per day for patients ≥90 kg) to those with nausea or vomiting. Orally to all others. • If symptoms and abdominal tenderness did not resolve after 48 h, immediate appendicectomy was undertaken. • Patients continued the same antibiotic treatment at home, with the same dose, for 8 days, and were seen on day 8. Persistence of pain or fever prompted a CT scan and possible appendicectomy. • A sustained high white-blood-cell count or a high C-reactive-protein concentration resulted in the extension of antibiotic treatment for a further 8 days. The persistence of similar biological	• Appendicectomy was done according to surgeons' standard practice (a McBurney incision or laparoscopy). • Patients were given one injection of amoxicillin plus clavulanic acid (2 g) at induction of general anesthesia • Postoperative antibiotics if complicated appendicitis was diagnosed during surgery.	• Peritonitis within 30 days of initial treatment.
		disorders on day 15 prompted appendicectomy without an additional CT scan. All patients were seen systematically in consultations on days 15, 30, 90, 180, and 360.		
Eriksson S, Granström L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg*. 1995;82(2):166-169. doi:10.1002/bjs.1800820207	• **Adult patients with a typical history of abdominal pain of less than 72hrs and clinical signs of acute appendicitis.** • **Radiological confirmation was done by positive findings at ultrasonography** • **Laboratory confirmation was done by estimation of total white cell count(WBC) and C-reactive protein(CRP) . One of the diagnostic criteria for acute appendicitis was the presence of elevated WBC and CRP levels, or elevated CRP or WBC levels on two separate occasions within a four-hour time frame.**	• **Cefotaxime 2gm 12 hourly and tinidazole 800 mg IV daily for 2 days.** • **Intravenous fluid for 2 days .** • **During discharge after 2 days , oral treatment with ofloxacin 200 mg twice daily and tinidazole 500 mg twice daily for 8 days were given.** • **All patients were evaluated at 6,10 and 30 days after admission and laboratory tests for determination of WBC and CRP levels were done.** • **During follow-up, pain was registered by visual analogue scale scores and oral temperature was also measured . Abdominal and rectal examination was done on days 6 & 10. Ultrasonography was**	• **Appendicectomy was done with those patients who developed peritonitis due to perforated appendicitis after 12 hrs of their acute presentation. And followed by antibiotics.**	• **Recurrence rate of appendicitis** • **Intensity of pain** • **Effectiveness of antibiotic treatment as compared to surgery among patients with acute appendicitis.**
		done on days 10 and 30. • **Stool was examined for Clostridium difficile to exclude pseudomembranous colitis**		

Systematic Review Terms

Systematic Review Search Terms

Embase Research Terms

- ('appendicitis'/exp OR appendicitis:ab,ti,kw) AND ('antibiotic agent'/exp OR 'antibiotic agent' OR 'ciprofloxacin'/exp OR 'ciprofloxacin' OR antibiotic*:ab,ti,kw OR 'anti biotic*:ab,ti,kw' OR quinolone:ab,ti,kw OR '(piperacillin near/3 tazobactam):ab,ti,kw' OR aztreonam:ab,ti,kw OR ceftriaxone:ab,ti,kw OR '(ampicillin near/3 sulbactam):ab,ti,kw' OR cefoxitin:ab,ti,kw OR cefotetan:ab,ti,kw OR cefazolin:ab,ti,kw OR clyndamicin:ab,ti,kw OR gentamicin:ab,ti,kw OR erythromycin:ab,ti,kw OR neomycin:ab,ti,kw OR levofloxacin:ab,ti,kw) AND [embase]/lim AND ('randomized controlled trial' OR 'controlled clinical trial:ab,ti,kw' OR randomized:ab,ti,kw OR placebo:ab,ti,kw OR randomly:ab,ti,kw OR trial:ab,ti,kw)

PUBMED Research Terms

("Appendicitis"[Mesh] OR appendicitis[tiab]) AND (non-surgical therap*[tiab] OR medical therap*[tiab] OR "Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action] OR antibiotic*[tiab] OR anti biotic*[tiab] OR cephalosporin*[tiab] OR ciproflox*[tiab] OR fluoroquinolone*[tiab] OR penicillin*[tiab] OR Piperacillin/tazobactam*[tiab] OR ceftriaxone*[tiab] OR meropenem*[tiab] OR AMPICILLIN/SULBACTAM*[tiab] OR aztreonam*[tiab] OR cefazolin*[tiab] OR clindamycin*[tiab] OR gentamicin*[tiab] OR tobramycin*[tiab] OR levofloxacin*[tiab] OR erythromycin*[tiab] OR neomycin*[tiab]) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab])

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Do-file Commands

```
** Non operative X operative management of acute appendicitis **
** analysis run by Rodrigo Moises de Almeida Leite, november 2 2021, stata version 17 **


 **  the APPAC trial, JAMA, 2015. The overall complication rate of 2.8% (95% CI, 1.0%- 6.0%) was significantly lower in the antibiotic group (6/216 pa- tients) than the overall rate of 20.5% (95% CI, 15.3%-26.4%) in the surgical group (45/220 patients). There was a difference be- tween groups of 17.7% (95% CI, 11.9%-23.4%) for the overall complication rate (P < .001)
 csi 7 56 250 217

 ** Styrud et al, they claim 16 patients among 128 in antibiotics group had complications in 1 year follow up, and 17 among 124 in surgery group.
 csi 16 17 112 107

 **  COMMA trial. The authors report a 74.4% percentage treatment success at 12 months at the antibiotics group ( 72 among 91 ) and report 5 cases of treatment failure ( 4 patients developed postoperative collection, 1 patient developed imbilical port site infection) among  89 patients

 csi 84 72 5 19

  **  CODDA colaborative trial . The authors claim that the rate for treatment success at 30 days was 462/676(68) in the antibiotics group and 466/663(70) in the surgery group.
  csi 462 466 214 197

 ** Vons et al. The primary endopoint ( rate of peritonitis at 30 days follow up ) was for 9 in 120 ( antibiotic group)  and 2 in 117 in the surgery group.
 csi 9 2 111 117

 ** Eriksson et al. Rates of complication were 7 in 20 ( antibiotic group) and 1 in 20 in surgery group
 csi 7 1 13 19

 **:ASAA trial, Ceresoli et al. The primary outcome ( sucess of treatment) was 16 in 19 for antibiotics group and 22 in 22 in surgety group.
 csi 16 22 3 0

 **Hansson et al. Major complications within a median of 1 year were 11 in 202 in antibiotic group and 18 in 167 in surgery group

 **Logaritimc transformation of the Risk Ratios
 gen logrr = log(rr)
 gen selogrr = (log(ci_u)-log(ci_l))/3.92


 ** Random-effects meta analysis
 metan logrr selogrr, eform effect(Risk Ratio) label(namevar=study) xlabel(.1 .5 1 5 10) random
```

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** Funnel PLot
metafunnel logrr selogrr, eform

** Egger's test and PLot
metabias logrr selogrr, egger graph

** MEta Regression : we conducted a metaregression using the follow up times, year of study publication and number of study participants, and found no evidence of heterogeinty due to these variables.
gen logrr1 = log(RR1)
(2 missing values generated)

gen selogrr1 = (log(ci_u1)-log(ci_l1))/3.92
(2 missing values generated)
metareg log_rr followuptime year N, wsse(se_log_rr) graph

** Secondary Outcome : Rate of Serious Adverse Effects

New england Journal of medicine trial : the authors claim total rate of serious adverse effects was 27 in 676 in the antibiotics group, and 19 in 656 in surgery group.
csi 27 19 649 637

ASAA trial : the authors claim that sencodary negative outcomes happened in 1 in 26 patients in antibiotic group and in 5 of 22 patients in surgery group.
csi 1 5 15 17

Vons et al : the authors claim there were 12 cases of complication in the antibiotics group (2 wound infection, 1 intestinal adhesion and 9 cases of peritonitis) in 119 patients. In surgery group there were 3 cases of complications (1 wound infection and 2 peritonitis).
csi 12 3 107 117

Eriksson et al : the authors did not report the rate of serious adverse effects.

Hansson et al : the authors reply that the rate of major complications at 1 year in the intention to treat population were 11 202 in antibiotics group and 18 in 167 in surgery group
csi 11 18 191 149

The Comma trial : the authors did not report the rate of serious adverse effects.

The APPAC trial : the authors report a complication rate of 6 in 216 in the antibiotic group and 45 in 220 in the surgical group
csi 6 45 210 175

Styrud et al : the authors report that complications ocurred in 31 patients in 128 in the antibiotic group (15 need for operation and 16 recurrence) and in 17 in 124 patients in surgery groups (mainly wound infections)
csi 31 17 97 107

forest plot for secondary outcome :

metan logrr1 selogrr1, eform effect(Risk Ratio) label(namevar=study) xlabel(.1 .5 1 5 10) random

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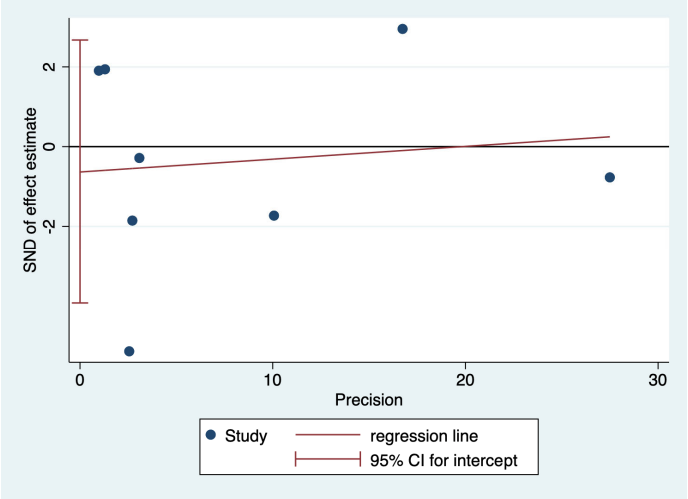
```
Egger's test for small-study effects:
Regress standard normal deviate of intervention
  effect estimate against its standard error

.
Number of studies =  8                                  Root MSE      =    2.83
```

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	.0321305	.1121481	0.29	0.784	-.242286	.306547
bias	-.6357234	1.352513	-0.47	0.655	-3.945203	2.673756

```
Test of H0: no small-study effects          P =  0.655
```

Publication Bias Analysis



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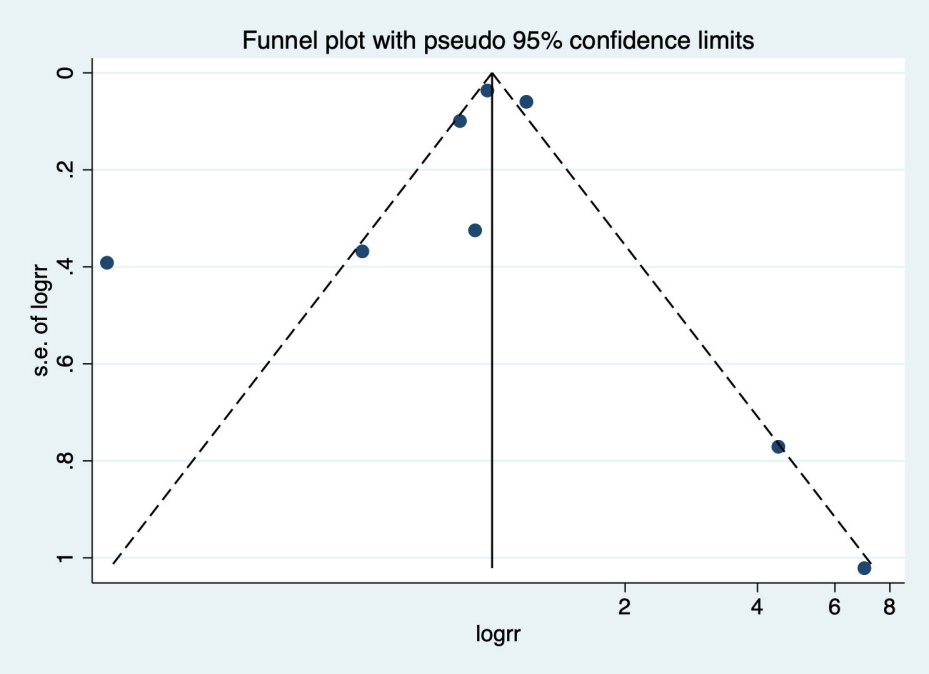

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Heterogeneity - Meta Regression

```
. metareg log_rr followuptime year N, wsse(se_log_rr) graph

Meta-regression                                         Number of obs  =         8
REML estimate of between-study variance                 tau2           =    .8855
% residual variation due to heterogeneity               I-squared_res  =   90.38%
Proportion of between-study variance explained          Adj R-squared  =  -11.01%
Joint test for all covariates                           Model F(3,4)   =    1.44
With Knapp-Hartung modification                         Prob > F       =  0.3566
```

log_rr	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
followuptime	-.1285903	.0709715	-1.81	0.144	-.3256388	.0684581
year	-.035917	.0559212	-0.64	0.556	-.1911791	.1193452
N	-.0007838	.0009498	-0.83	0.456	-.0034208	.0018532
_cons	73.49358	112.3436	0.65	0.549	-238.4222	385.4094

graph option works only with a single *indepvar*

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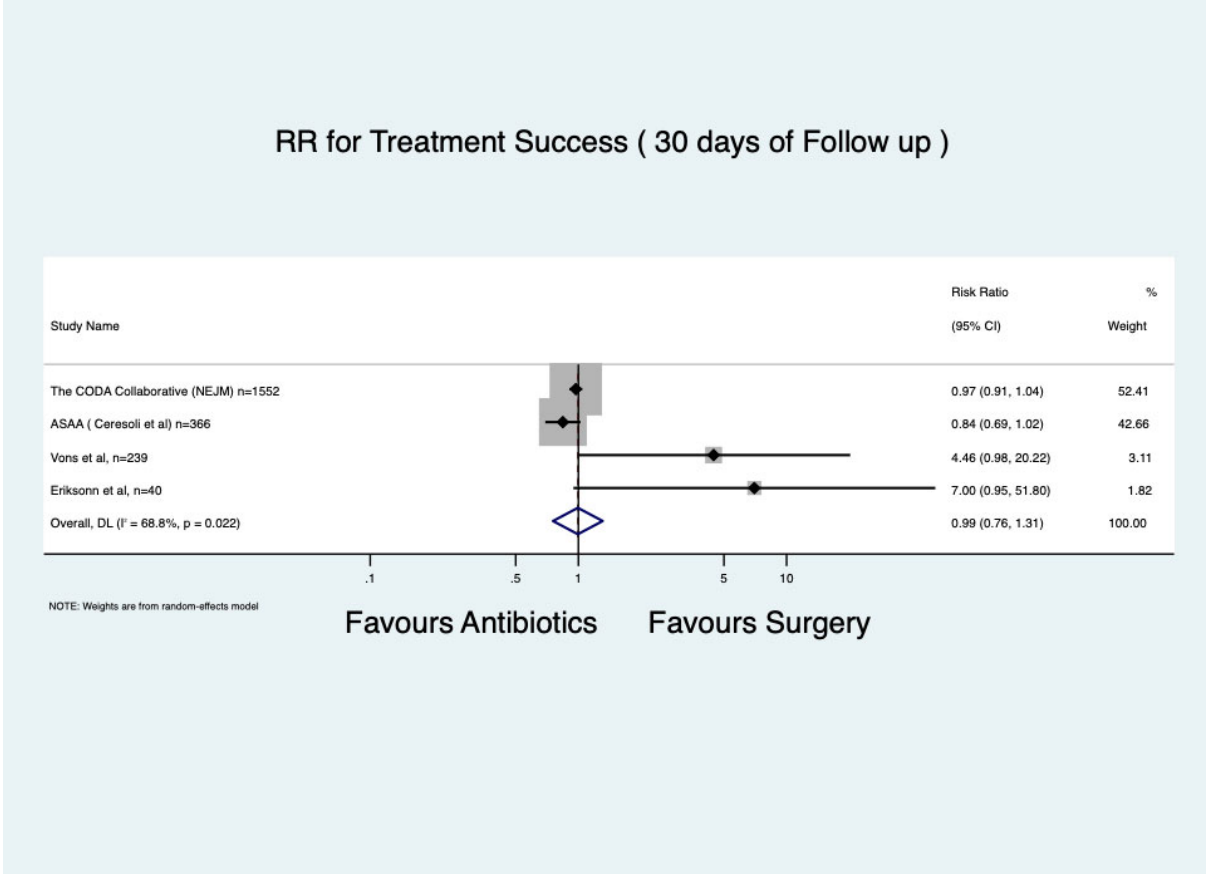
eFigure1. RR for Treatment Success (30 days of Follow-up)



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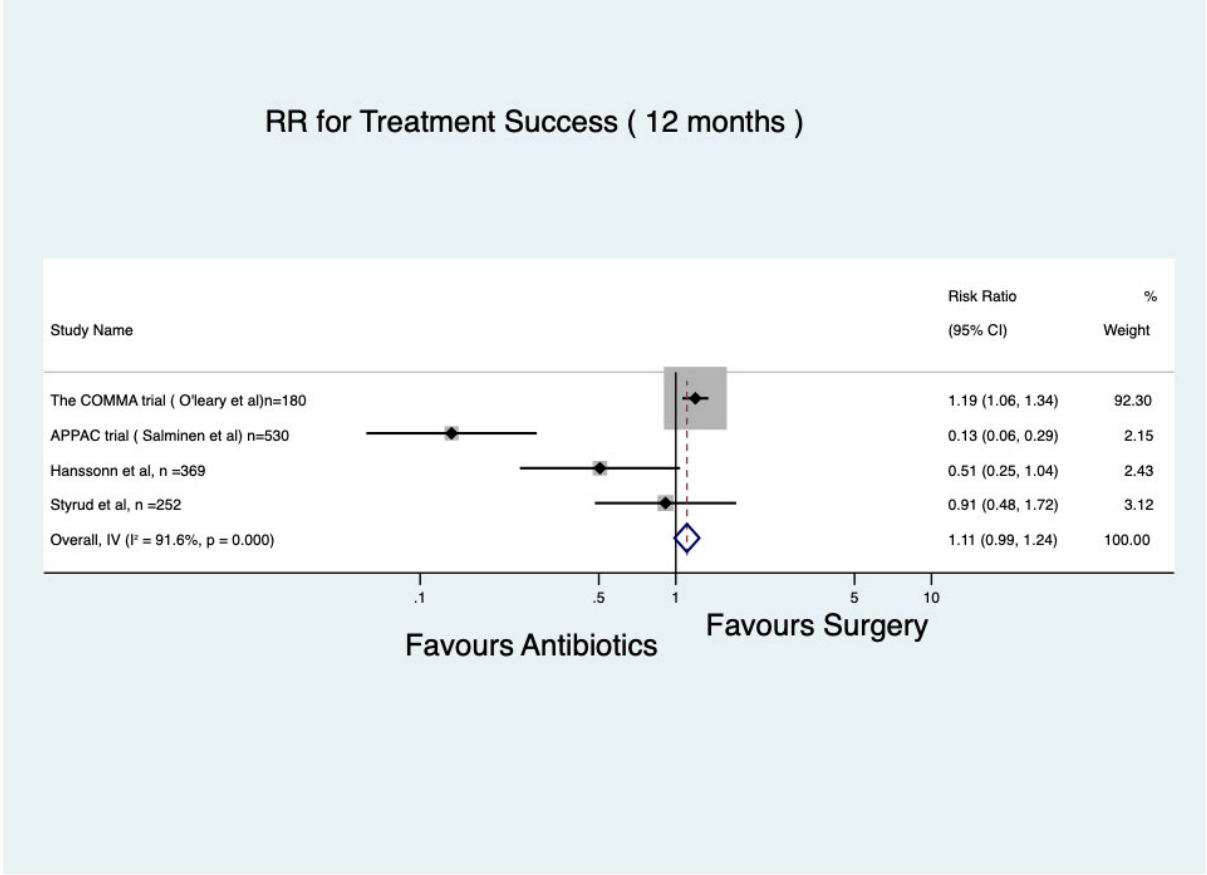
eFigure 2. RR for Treatment Success (12 months)



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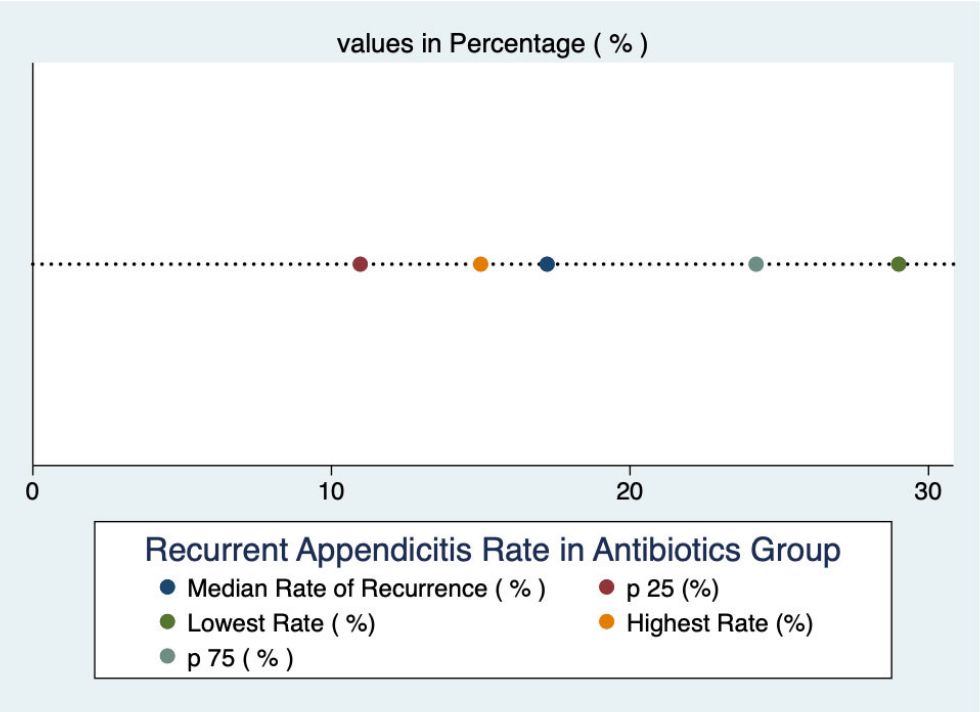
eFigure 3. Recurrent Appendicitis Rate in Antibiotics Group



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eTable 1. Bias Table

	Selection of Participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (Detection bias)	Blinding of outcomes assessment (detection bias)	Incomplete outcome data (attrition bias)
The CODA Collaborative	Low	Low	Low	Low	Low
ASAA (Ceresoli et al)	Low	Low	Low	Unkonwn	Low
The COMMA trial (O'Leary et al)	Low	Low	Low	Low	Low
APPAC trial (Salminen et al)	Low	Low	Low	Low	Low
Hansson et al	Low	Low	Low	Unkonwn	Low
Styrud et al	Low	Low	Low	Unkonwn	High
Vons et al	Low	Low	Low	High	Low
Ericksson et al	Low	Low	Low	Unkonwn	High

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