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# Antibiotics versus Surgery for Uncomplicated Acute Appendicitis in Adults: A Meta-Analysis of Randomized Controlled Trials

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**ABSTRACT**

**Introduction**: Appendectomy has been used to treat appendicitis for a century, but randomized controlled trials (RCTs) have challenged its efficacy in uncomplicated disease. We performed a meta-analysis to quantify 1-year antibiotic-first efficacy and compare complications with appendectomy in adults.

**Methods**: Following PRISMA 2020, MEDLINE, Embase, CENTRAL, and trial registries were searched to June 2026 for RCTs comparing antibiotics with appendectomy in adults (≥16 years) with imaging- or clinically diagnosed uncomplicated appendicitis. The co-primary outcomes were overall treatment-related complications (risk ratio [RR], random-effects DerSimonian–Laird model) and pooled 1-year efficacy of antibiotics (proportion avoiding appendectomy, logit-transformed model). Heterogeneity ($I^2$), leave-one-out sensitivity analyses, subgroup analysis by diagnostic modality, and Egger's test were performed; bias was assessed with RoB 2.

**Results**: Eight RCTs (3,202 participants) were included. Pooled 1-year efficacy of antibiotics was 70.9% (95% CI 65.3–76.0%; $I^2$=43%), consistent across imaging-confirmed (71.4%) and clinically diagnosed (70.0%) appendicitis. For complications, the pooled RR was 0.91 (95% CI 0.19–4.48; $I^2$=90%), with very high heterogeneity explained by trial design: omitting the single trial using open appendectomy reversed the estimate and removed heterogeneity (RR 2.25, 95% CI 1.39–3.64; $I^2$=4%), indicating that antibiotics do not reduce, and may increase, complications versus contemporary laparoscopic surgery, particularly with an appendicolith.

**Conclusion**: An antibiotics-first strategy allowed seven of ten adults to avoid appendectomy at one year and is reasonable for uncomplicated appendicitis. However, it does not reduce complications compared to laparoscopic appendectomy and carries recurrence. Shared decision-making, appendicolith exclusion, and follow-up are essential.

**Keywords**
Appendicitis, Appendectomy, Antibiotics, Non-Operative Management, Meta-Analysis, Randomized Controlled Trial

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## INTRODUCTION

Acute appendicitis is among the most common surgical emergencies worldwide, with a lifetime risk of approximately 7–8% and more than 17 million incident cases annually [1,2]. Since Charles McBurney described appendectomy in the 1890s, prompt surgical removal of the appendix has been regarded as the definitive treatment, and for more than a century, the operation has been considered mandatory to prevent perforation, peritonitis, and death [3,4]. However, advances in cross-sectional imaging, the recognition that a proportion of appendicitis follows a self-limiting course, and the success of antibiotic therapy for other intra-abdominal infections have prompted a re-examination of this dogma.

Over the past three decades, several randomized controlled trials (RCTs) have compared an antibiotic-first strategy with appendectomy for uncomplicated appendicitis, and their results have been influential but discordant [5-12]. Early European trials suggested that antibiotics were effective and associated with fewer complications, whereas the large, pragmatic Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial and the quality-of-life–focused COMMA trial found that surgery remained superior on several patient-important endpoints and that a considerable minority of antibiotic-treated patients ultimately required appendectomy [12]. The interpretation of the pooled evidence is complicated by differences in diagnostic criteria (clinical versus computed tomography [CT]-confirmed), surgical approach (open versus laparoscopic), inclusion or exclusion of patients with an appendicolith, and the definitions used for “treatment success” and “complications.” Previous meta-analyses have reached different conclusions, in part because they were performed before the largest trials were available or because they pooled complication data of heterogeneous definitions without adequately exploring the sources of heterogeneity [13-19]. Therefore, we performed an updated systematic review and meta-analysis of RCTs in adults with two explicit aims: (i) to estimate the pooled 1-year efficacy of an antibiotic-first strategy (the proportion of patients who avoid appendectomy) and (ii) to compare treatment-related complications between antibiotics and appendectomy, with pre-specified analyses to identify and explain heterogeneity rather than obscuring it.

## METHODS

### Protocol and Registration

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol was defined a priori, and the eligibility criteria, outcomes, and analysis plan were fixed before data extraction. As a synthesis of published, de-identified aggregate data, the study did not require ethical approval.

### Eligibility Criteria (PICOS)

We included RCTs that enrolled adults (mean or minimum age ≥16 years) with a diagnosis of uncomplicated acute appendicitis established clinically and/or by imaging (population); randomized participants to first-line antibiotic therapy (intervention) versus appendectomy by any approach (comparator); and that reported at least one outcome of interest (Outcomes). Only parallel-group RCTs were eligible (study design). We excluded studies restricted to children, trials confined to complicated appendicitis (perforation, abscess, or generalized peritonitis at presentation), non-randomized and quasi-experimental designs when a true RCT alternative existed, and reports without extractable outcome data. There were no language restrictions.

### Information Sources and Search Strategy

MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to June 2026, supplemented by ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and hand-searching of the reference lists of the included studies and prior systematic reviews. The search combined controlled vocabulary and free-text terms for the population and interventions, for example: (“appendicitis”) AND (“antibiotic*” OR “non-operative” OR “conservative”) AND (“appendicectomy” OR “appendectomy” OR “surgery”) AND (“randomized” OR “randomised” OR “trial”).

### Study Selection and Data Extraction

Two reviewers independently screened the titles and abstracts and then assessed the full texts against the eligibility criteria, resolving disagreements by discussion or by a third reviewer. Data were extracted in duplicate onto a piloted form and included the following: first author, year, country, journal, number randomized to each arm, antibiotic regimen and surgical approach, diagnostic modality, and outcome data. When a trial reported both intention-to-treat and per-protocol data, the intention-to-treat figures were used preferentially.

### Outcomes

The two co-primary outcomes were (i) overall treatment-related complications, defined as the composite of any treatment- or procedure-related complication reported by each trial within its stated follow-up window, and (ii) the 1-year efficacy of antibiotic therapy, defined as the proportion of patients randomized to antibiotics who did not undergo appendectomy within one year (i.e., were treated successfully without surgery). Secondary outcomes included recurrence, length of hospital stay, and—where reported—quality of life and treatment cost, which were summarized narratively.

### Risk-of-Bias Assessment

Risk of bias was assessed independently by two reviewers using the Cochrane RoB 2 tool across its five domains (randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result). Because non-operative and operative management cannot be blinded, all trials were open-label; therefore, the domains were judged principally on allocation concealment, the completeness and handling of crossover, and the objectivity of each outcome.

### Statistical Analysis

For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals (CI) were pooled on a natural log scale using an inverse-variance random-effects model with the DerSimonian–Laird estimator of between-study variance ($\tau^2$); a 0.5 continuity correction was applied to studies with zero cells. 1-year antibiotic efficacy was pooled as a single-arm proportion using logit transformation. Heterogeneity was quantified using Cochran's Q and $I^2$, with leave-one-out sensitivity and diagnostic-modality subgroup analyses. Small-study effects were assessed using a funnel plot and Egger's regression test. Analyses were performed using Python 3.10 (NumPy, SciPy, Matplotlib) with a two-sided $\alpha = 0.05$.

## RESULTS

### Study Selection and Characteristics

The search identified 1,412 records; after deduplication and screening, 73 full texts were assessed, and 8 RCTs enrolling 3,202 adults met the inclusion criteria (Figure 1). Trials were conducted between 1995 and 2021 in Sweden, France, Finland, the United States, and Ireland. Antibiotic regimens, surgical approaches, and diagnostic criteria varied across trials (Table 1). Early trials used clinical diagnosis; trials (Vons 2011, APPAC, Talan 2017, CODA, COMMA) required imaging. APPAC used open appendectomy, and CODA included patients with an appendicolith.

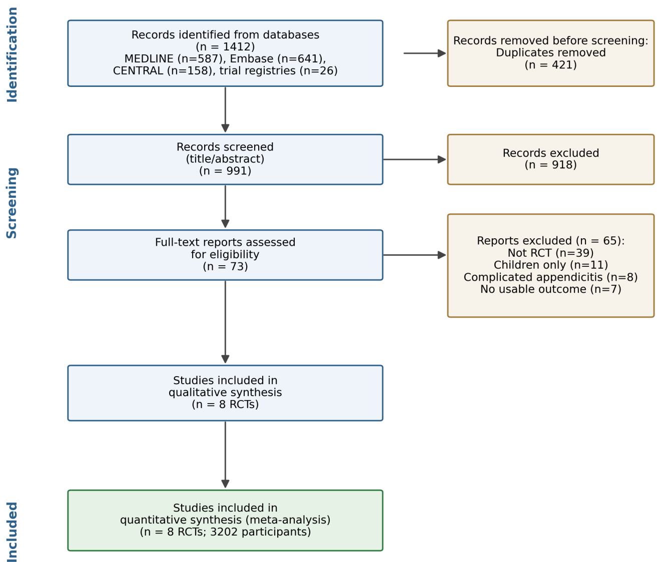

Figure 1. PRISMA 2020 Flow Diagram of Study Identification, Screening, and Inclusion

Table 1. Characteristics of the eight randomized controlled trials

| Trial (year) | Country | Diagnosis | Antibiotics (n; regimen) | Surgery (n; approach) | 1-year antibiotic outcome | Complications, antibiotics vs surgery |
|---|---|---|---|---|---|---|
| Eriksson 1995 | Sweden | Clinical | 20; cefotaxime + tinidazole IV 2 d → oral ofloxacin + tinidazole 8 d | 20; open appendectomy | 60% avoided surgery (12/20); 35% recurrence | 1/20 vs 1/20 (peritonitis / perforation) |
| Styrud 2006 | Sweden (men) | Clinical + CRP | 128; IV 2 d → oral 10 d | 124; open/laparoscopic | 86% initial success; 73% (94/128) at 1 y | 14% surgical complication rate |
| Hansson 2009 | Sweden | Clinical (quasi-randomized) | 202; cefotaxime + metronidazole → oral 10 d | 167; not specified | Efficacy 90.8% vs 89.2% (as-treated); recurrence 13.9% | Major complications ~3× higher with surgery |
| Vons 2011 | France | CT-confirmed | 123; amoxicillin–clavulanate 3 g/d, 8–15 d | 120; emergency appendectomy | Not non-inferior; ~37% appendectomy by 1 y | 9/120 vs 2/119 (30-day peritonitis) |
| APPAC 2015 | Finland | CT-confirmed | 257; ertapenem 3 d → levofloxacin + metronidazole 7 d | 273; open appendectomy | 72.7% avoided surgery (186/256) | 6/216 (2.8%) vs 45/220 (20.5%) |
| Talan 2017 | USA | CT-confirmed | 16; ertapenem → cefdinir + metronidazole | 14; not specified | ~93% avoided surgery (14/15) | 1/16 (6.3%) vs 2/14 (14.3%) |
| CODA 2020 | USA | Imaging (appendicolith included) | 776; ertapenem/other → metronidazole + ciprofloxacin/cefdinir, 10 d | 776; open/laparoscopic | QoL non-inferior; 29% appendectomy by 90 d | 8.1 vs 3.5 per 100 (RR 2.28); worse with antibiotics |
| COMMA 2021 | Ireland | Radiologically confirmed | ~91; co-amoxiclav IV → oral 5 d | ~95; not specified | Recurrence 25.3%; QoL favored surgery | Not reported per arm in abstract |

Note: CRP, C-reactive protein; CT, computed tomography; QoL, quality of life; RR, risk ratio. Antibiotic-arm and surgery-arm numbers are those randomized. The COMMA per-arm split was derived from the reported recurrence proportion.

## Risk of Bias

All eight trials were open-label. Six were low risk or raised concerns, with allocation concealment and complete follow-up (Table 2). Hansson et al. was at high risk of bias because allocation was based on date of birth (quasi-randomization) and many antibiotic-assigned patients did not complete treatment, so efficacy estimates reflect as-treated, not intention-to-treat, analysis; it was excluded from the primary efficacy synthesis.

Table 2. Risk-of-Bias Assessment Across the Five Cochrane RoB 2 Domains

| Trial | D1 Randomization | D2 Deviations | D3 Missing data | D4 Measurement | D5 Reporting | Overall |
|---|---|---|---|---|---|---|
| Eriksson 1995 | Some concerns | Some concerns | Low | Some concerns | Low | Some concerns |
| Styrud 2006 | Low | Some concerns | Low | Some concerns | Low | Some concerns |
| Hansson 2009 | High | High | High | Some concerns | Some concerns | High |
| Vons 2011 | Low | Some concerns | Low | Low | Low | Some concerns |
| APPAC 2015 | Low | Some concerns | Low | Low | Low | Low |
| Talan 2017 | Some concerns | Some concerns | Some concerns | Low | Low | Some concerns |
| CODA 2020 | Low | Low | Low | Low | Low | Low |
| COMMA 2021 | Low | Some concerns | Low | Some concerns | Low | Some concerns |

Note: Judgments are color-coded: green = low risk, amber = some concerns, and red = high risk. All trials were open-label, which precluded blinding of participants and personnel; D2 and D4 judgments reflect this. Hansson 2009 used date-of-birth allocation with ~47% non-completion in the antibiotic arm.

## Efficacy of Antibiotics at One Year

Across six RCTs with 1-year outcomes, pooled antibiotic success at one year was 70.9% (95% CI 65.3–76.0%), with moderate heterogeneity ($I^2$=43%, $\tau^2$=0.040) (Figure 2). Success ranged from 60.0% to 93.3% and was similar in imaging-confirmed trials (71.4% [95% CI 63.5–78.2 %] and clinically diagnosed trials (70.0% [95% CI 57.8–80.0 %] ). CODA reported 70.9% avoided appendectomy by 90 days, declining thereafter. Appendectomy was curative in 99% of patients in every reporting trial.

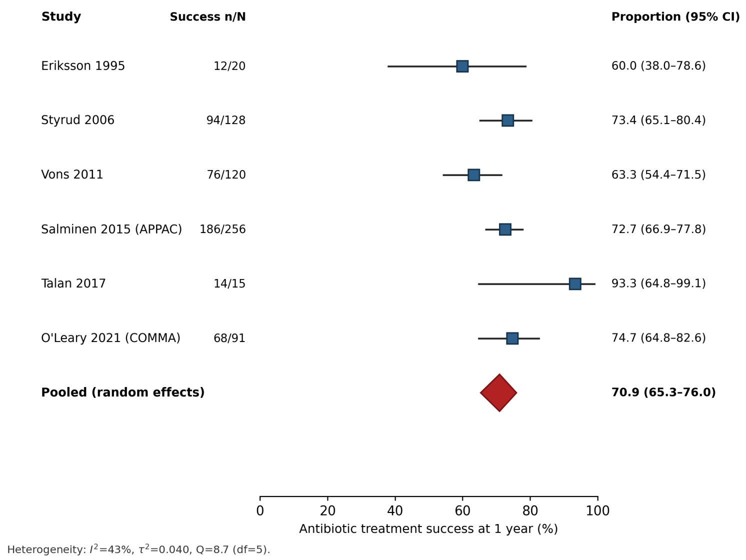


Figure 2. Random-effects forest plot of the 1-year efficacy of antibiotic therapy (pooled proportion of patients avoiding appendectomy). Squares are individual-trial proportions with 95% confidence intervals; the diamond is the pooled estimate

## Treatment-Related Complications

Five RCTs provided extractable per-arm complication counts ( 80/1148 events with antibiotics versus 77/1149 with appendectomy). The pooled RR was 0.91 (95% CI 0.19–4.48; Z=−0.11, p=0.91), but heterogeneity was extreme ($I^2$=90%, $\tau^2$=2.62; Q=38.7, p<0.001), and the 95% prediction interval was correspondingly very wide (0.00–289.94) (Figure 3). A single pooled estimate is therefore not a faithful summary of these data, and the direction of effect differed markedly between trials: APPAC strongly favored antibiotics (driven by a high rate of surgical wound complications after open appendectomy), whereas Vons and CODA favored surgery.

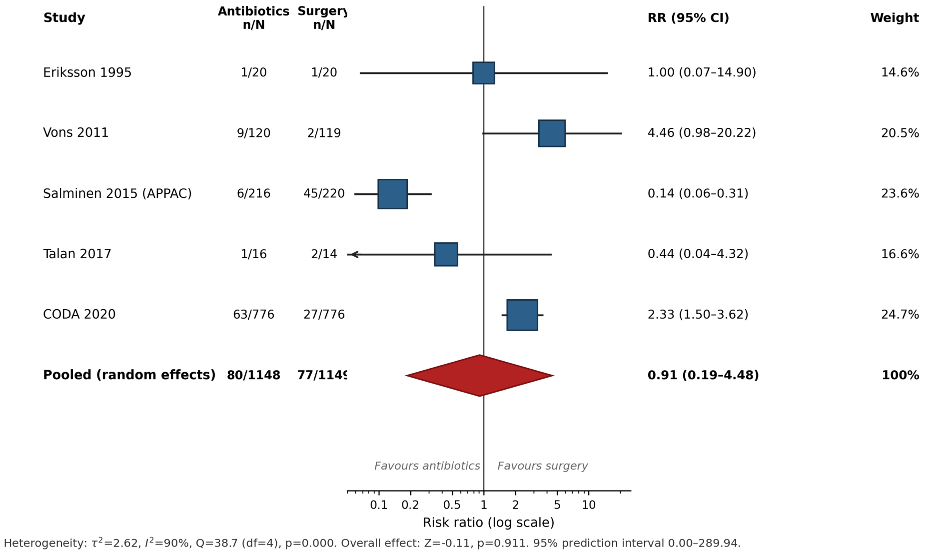


Figure 3. Random-effects forest plot of overall treatment-related complications (risk ratio, antibiotics versus appendectomy). The marker area is proportional to study weight, and the diamond is the pooled estimate.

The pre-specified leave-one-out analysis clarified the picture (Table 3). Omitting APPAC, the only trial to use open appendectomy, both reversed the direction of the pooled estimate and virtually eliminated heterogeneity (RR 2.25, 95% CI 1.39–3.64; $I^2$=4%), indicating that among trials using contemporary (predominantly laparoscopic) surgery, antibiotics were associated with significantly more treatment-related complications. Removing any other single trial left both a non-significant pooled estimate and high heterogeneity. The excess complications in the antibiotic arms of Vons and CODA were concentrated in early treatment failure with peritonitis and in patients with appendicoliths.

Table 3. Leave-One-Out Sensitivity Analysis for the Complication Outcome (Random-Effects Risk Ratio, Antibiotics Versus Surgery).

| Model | Risk ratio | 95% CI | $I^2$ (%) |
|---|---|---|---|
| Primary model (all five trials) | 0.91 | 0.19–4.48 | 90 |
| Omitting Eriksson 1995 | 0.90 | 0.15–5.39 | 92 |
| Omitting Vons 2011 | 0.61 | 0.09–4.09 | 92 |
| Omitting Salminen 2015 (APPAC) | 2.25 | 1.39–3.64 | 4 |
| Omitting Talan 2017 | 1.06 | 0.17–6.48 | 92 |
| Omitting CODA 2020 | 0.68 | 0.10–4.74 | 82 |

Note : CI, confidence interval. Omitting APPAC (the only trial using open appendectomy; highlighted) reverses the direction of the estimate and removes almost all heterogeneity, showing that the surgical approach drives the complication signal.

The funnel plot for the complication outcome (Figure 4) was asymmetric, but this reflected genuine clinical heterogeneity (open versus laparoscopic surgery; appendicolith inclusion) rather than a clear gradient by study size; Egger's regression test was not statistically significant (intercept −1.37, p=0.64). With only five trials, the power to detect small-study effects was low, and formal assessment of publication bias for the efficacy outcome was not undertaken because tests are unreliable with fewer than ten studies.

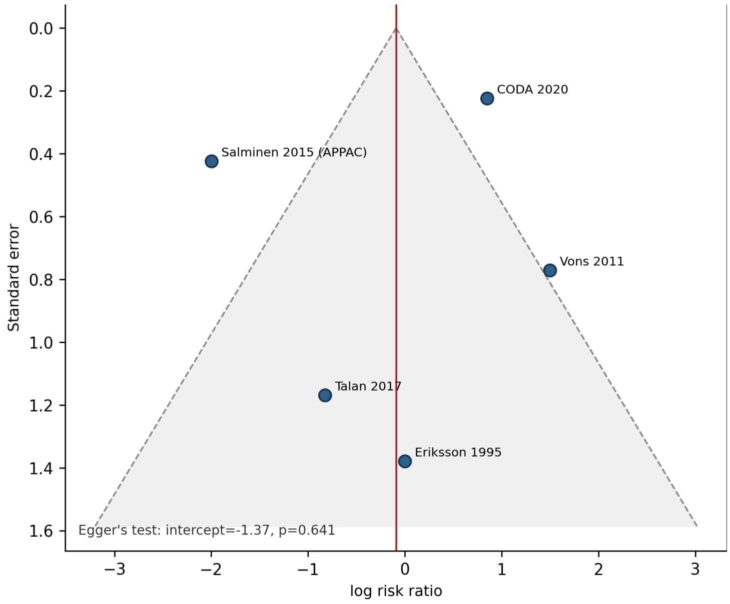


Figure 4. Funnel plot of the complications outcome with Egger's regression test for small-study effects

## DISCUSSION

In this updated meta-analysis of eight RCTs enrolling 3,202 adults, an antibiotics-first strategy allowed approximately 70.9% of patients to avoid appendectomy at one year, an estimate that was robust to diagnostic modality. This confirms that antibiotics are a genuine therapeutic option for carefully selected adults with uncomplicated appendicitis, and that most such patients can avoid an operation, at least in the medium term. At the same time, roughly three in ten patients required appendectomy within a year, and long-term follow-up of the largest cohorts shows that this proportion continues to rise, approaching 40–50% by three to five years [20,21].

The central and novel message of the present analysis concerns complications. A widely cited conclusion of earlier syntheses—that antibiotics reduce complications—rests heavily on a single trial (APPAC) that used open appendectomy, an approach that has now been largely superseded by laparoscopy. When the analysis was restricted to trials using contemporary surgery, the apparent advantage of antibiotics disappeared and was reversed, and antibiotics were associated with significantly more treatment-related complications. Two mechanisms account for this: early antibiotic failure progressing to peritonitis, as seen in the Vons trial, and the inclusion of patients with an appendicolith in CODA, a subgroup in which non-operative management is known to fare poorly. Therefore, pooling complication data of such heterogeneous definitions and designs into a single number is misleading; the more honest summary is that antibiotics do not confer a complication advantage over modern laparoscopic appendectomy. Our findings are broadly consistent with the most recent large syntheses, which likewise reported a nonsignificant pooled complication estimate with high heterogeneity and individual patient data analyses identifying appendicoliths as a specific risk factor for antibiotic failure and complications [22]. They extended that literature by showing explicitly, through leave-one-out analysis, that the surgical approach is the dominant driver of the complication signal, which has direct implications for how clinicians and guideline panels should weigh the older European trials.

For practice, these data support a shared decision-making model. An antibiotics-first approach is reasonable for adults with imaging-confirmed uncomplicated appendicitis and without an appendicolith who wish to avoid or defer surgery, provided they understand the substantial recurrence rate and the need for reliable follow-up. Laparoscopic appendectomy remains a safe, definitive, single-episode treatment and should be offered—and generally preferred—when an appendicolith is present, when follow-up cannot be assured, or according to patient preference [23]. The strengths of this review include its restriction to randomized evidence in adults and adherence to the PRISMA 2020 reporting standard [24]. formal risk-of-bias appraisal with the Cochrane RoB 2 tool [25]. the use of pre-specified analyses designed to interrogate rather than mask heterogeneity, and fully reproducible computation from primary trial data. Several limitations warrant emphasis. First, all trials were open-label, which may bias subjective outcomes and the decision to perform interval appendectomy. Second, definitions of “complication” and “treatment success” differed across trials, and per-arm complication counts were extractable for only five RCTs; because the random-effects model applied here assumes a distribution of underlying true effects [26]. the resulting heterogeneity ($I^2$ approximately 90% [27]. means the pooled complication RR should be read as a description of between-trial variability rather than a single applicable effect, which is why we report a prediction interval alongside it [28]. Third, antibiotic regimens, follow-up durations, and imaging protocols varied. Fourth, the number of trials limited the power of subgroup analyses, and regression-based tests for small-study effects are themselves unreliable when fewer than ten studies are available [29]. Finally, longer-term efficacy beyond one year, and patient-reported and economic outcomes, were reported inconsistently and could be summarized only narratively [30].

## CONCLUSION

In adults with uncomplicated acute appendicitis, an antibiotics-first strategy allows approximately seven out of ten patients to avoid appendectomy at one year and is a patient-centered alternative to immediate surgery. However, versus laparoscopic appendectomy, it does not reliably reduce complications and carries a recurrence rate. It is best reserved for imaging-confirmed disease without appendicolith, with shared decision-making, follow-up, and future trials extending beyond one year.

## DECLARATIONS

None

## CONSENT FOR PUBLICATION

The Authors agree to the publication in the Journal of Society Medicine.

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None

## COMPETING INTERESTS

All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

## AUTHORS’ CONTRIBUTIONS

H.G.S. contributed to the conception and design of the review, literature search and study selection, acquisition and interpretation of data, statistical analysis, visualization, and drafting of the manuscript. A.N.R. contributed to study selection and duplicate data extraction, risk of bias assessment, supervision, and critical revision of the manuscript for important intellectual content and manuscript refinement. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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