A report on acute uncomplicated appendicitis: antibiotic therapy versus appendectomy for Universitätsklinikum Schleswig-Holstein/Campus Kiel

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LIST OF ABBREVIATIONS

ABT	Antibiotic therapy
AEs	Adverse effects
AUA	Acute uncomplicated appendicitis
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CCT	Controlled clinical trial
CPG	Clinical practice guideline
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
FAQ	Frequently asked question
KSR	Kleijnen Systematic Reviews
MA	Meta-analysis
MD	Mean difference
N/A	Not applicable
NR	Not reported
Obs. studies	Observational studies
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Transparent Reporting of Systematic Reviews and Meta-Analyses
QoL	Quality of life
RCT	Randomised controlled trial
RD	Risk difference
RR	Risk ratio
SDM	Shared decision making
SMD	Standardised mean difference
SUR	Surgery
SR	Systematic review
UKSH	Universitätsklinikum Schleswig-Holstein
VAS	Visual Analogue Scale

1. PROJECT OBJECTIVES

The overarching aim of the research project "Making SDM a reality" is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews Ltd (KSR) prepared this report synthesising relevant clinical evidence of treatment options for acute uncomplicated appendicitis in children, namely antibiotic therapy versus appendectomy.

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) which underpin the literature searches were built in collaboration with clinicians at the Universitätsklinikum Schleswig-Holstein (UKSH)/Campus Kiel. These FAQs pertain to the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Systematic reviews (SRs), clinical practice guidelines (CPGs) evaluated herein aim to inform paediatric patients/their parents, clinicians, or health policy makers researchers on relevant evidence pertaining to acute uncomplicated appendicitis in children: antibiotic therapy versus appendectomy.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Patients ≤ 18 years with acute uncomplicated appendicitis, i.e., without signs of perforation, peritonitis, abscess, or coprolite.	Perforated appendicitis; presentation with appendix mass; major anaesthetic risk precluding appendicectomy / known antibiotic allergy preventing non-operative treatment; cystic fibrosis; a positive pregnancy test or current treatment for malignancy. Adult patients >18 years.
Intervention/ comparator	1. Antibiotic therapy 2. Surgical therapy	Transvaginal surgical therapy
Outcomes	• Resolution of symptoms • Time to recovery • Remission of symptoms • Quality of life • Mortality rate • Short and long-term risks/complications • Reoperation rates • Length of hospital stay	N/A
Study design	Systematic reviews, clinical practice guidelines	Narrative reviews; expert opinions; letters' overviews of reviews
N/A = not applicable		

2.2 FREQUENTLY ASKED QUESTIONS

The following FAQs were identified:

1. What does the treatment involve?
2. Will it help my symptoms?
3. How long will treatment effect last? Will it help maintain remission of my disease?
4. How will treatment impact my quality of life?
5. Will the treatment prolong my life?
6. & 7. What are the risks or side effects? Are there long-term negative effects of treatment to be expected?

2.3 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews and evidence-based guidelines regarding acute uncomplicated appendicitis. To inform frequently asked questions (FAQs) a second targeted database search on appendicitis/appendectomy and shared decision making was also undertaken.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2016-2021. The targeted searches on shared decision-making were also limited to 2016-2021 as current and up-to-date evidence in this area was considered to be most relevant. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

2.4.1 Systematic reviews and guidelines

The following systematic review specific databases were searched from 2016 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2021/03/Iss3
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): up to 2018/03
- INAHTA International HTA database (https://database.inahta.org/): up to 2021/03/17
- KSR Evidence (Internet) (https://ksrevidence.com/): up to 2021/03/17
- Epistemonikos (Internet) (https://www.epistemonikos.org/): up to 2021/03/17

The following guidelines resources were searched from 2016 to present:":

- NICE Guidance (Internet) (https://www.nice.org.uk/guidance): up to 2021/03/17
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): up to 2021/03/17
- NHS Evidence (Internet) (www.evidence.nhs.uk/): up to 2021/03/17
- Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): up to 2021/03/17
- Trip Database (Internet) (https://www.tripdatabase.com/): up to 2021/03/17

Full details of all search strategies are presented in Appendix 1.

2.4.2 Targeted searches

To identify questions relevant to shared decision making, targeted searches were undertaken in the following databases from 2016 to present:

- EMBASE (Ovid): 1974-2021/03/16
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2021/03/16

- Cochrane Central Register of Controlled Trials (CENTRAL): up to 2021/03/Iss3

Full details of all search strategies are presented in Appendix 1.

2.4.3 Handling of citations

Identified references from the electronic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.4.4 Supplementary searches

Reference lists of all included studies were checked for relevant studies.

2.5 STUDY SELECTION AND DATA EXTRACTION

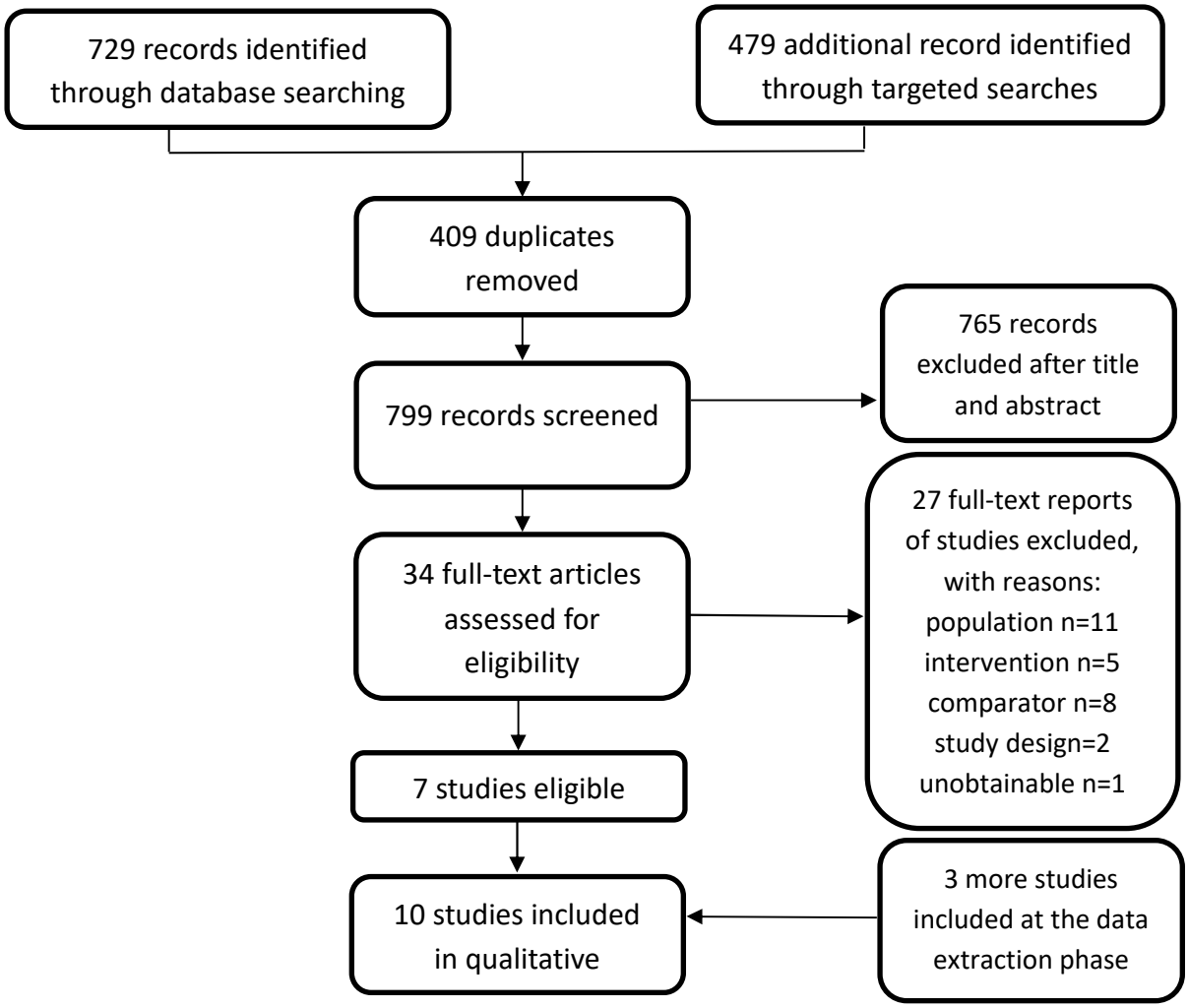
Two independent reviewers screened titles and abstracts of all records identified by the electronic searches and any disagreements were resolved through consensus. Full-text versions were obtained for all potentially eligible studies and screened by these same two reviewers independently against the pre-specified eligibility criteria. For each study, one reviewer extracted the data whereas another validated the entries. Any disagreements were settled through discussion.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Searches were conducted in March 2021 to identify all relevant SRs or CPGs. A total of 729 records were retrieved from the electronic literature searches; and 479 identified through targeted searches. Seven hundred and ninety-nine titles and abstracts were independently screened by two reviewers after removing duplicate records. After screening of 34 full-text papers, seven met the inclusion criteria. Three more studies were included at the data extraction phase. A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[1]

Figure 1: Study selection process



3.2 OVERVIEW OF INCLUDED STUDIES

Eight systematic reviews (SRs) and two clinical practice guidelines (CPGs) were eligible for inclusion. Table 2 below summarises the sources of evidence used to answer the respective seven FAQs. These SRs included evidence from randomised controlled trials (RCTs), controlled clinical trials (CCTs) and observational studies. Quantitative evidence was available to answer the FAQs 2 to 7.

Table 2: Evidence sources

Study/year	Evidence source	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will it help my symptoms?	FAQ3: How long will treatment effect last? Will it help maintain remission of my disease?	FAQ4: How will treatment impact my quality of life?	FAQ5: Will the treatment prolong my life?	FAQ6 & 7: What are the risks or side effects? Are there long-term negative effects of treatment to be expected?
Andric 2020[2]	CPG	ABT	✓					
		SUR						
Bi 2019[3]	SR/MA	ABT		✓				✓
		SUR						
Di Saveiro 2020[4]	CPG	ABT	✓					
		SUR						
Georgiou 2017[5]	SR/MA	ABT	✓					✓
		SUR						
Gorter 2017[6]	SR	ABT						✓
		SUR						
Huang 2017[7]	SR/MA	ABT		✓	✓			✓
		SUR						
Kessler 2017[8]	SR/MA	ABT		✓				✓
		SUR						
Maita 2020[9]	SR/MA	ABT						✓
		SUR						
Podda 2019[10]	SR	ABT		✓		✓		✓
		SUR						
Rollins 2016[11]	SR	ABT		✓				
		SUR						

ABT = antibiotic therapy; CPG = clinical practice guideline; MA= meta-analysis; SR = systematic review; SUR = surgery

3.3 FAQ 1: WHAT DOES THE TREATMENT INVOLVE?

This section describes the treatment options of acute uncomplicated appendicitis (AUA): antibiotic therapy (ABT) versus appendectomy/surgery (SUR). These options are briefly described in Table 3.

Table 3: Description of treatments

Antibiotic therapy (ABT)
Antibiotic therapy (ABT) is considered to be an alternative to surgery in children with uncomplicated acute appendicitis (AUA) in the absence of an appendicolith (calcified deposit within the appendix), no signs of perforation (infection of the appendix that can cause a hole allowing the bacteria to spread to the rest of the abdomen) or peritonitis (inflammation of the tissue that lines the inner wall of the abdomen and covers and supports most of abdominal organs).[2, 12, 13] ABT may be administered intravenously or orally after the diagnosis of AUA is made.[5] Type (e.g., amoxicillin+clavulanic acid, cefotaxime, fluoroquinolone, metronidazole, tinidazole), duration and intensity of ABT treatment can differ e.g., intravenous in the first 24-48 hours, followed by oral administration for a further 8-15 days. Sometimes ABT can be continued beyond the initial course of treatment in some children with no clinical improvement.[12, 14] Paediatric patients and their parents need to be advised of the possibility of ABT failure following misdiagnosed complicated appendicitis.[4] Here a reassessment is advised, potentially preventing the need for appendectomies and reducing morbidity. Oral antibiotics can be continued after discharge, allowing potentially shorter lengths of stay (currently an average of two days).[12] Patients who wish to avoid surgery (described below) should be aware of a risk of recurrence - about one in five patients is likely to be readmitted to hospital after initial successful treatment with ABT, and of those readmitted - one in five may have complicated appendicitis.[12] Other risks involve ABT-specific allergies, interactions (with other drugs), however unlikely if taken under medical supervision.
Surgery (SUR)
Appendectomy, herein also referred to as surgery (SUR) involves a surgical removal of the vermiform appendix (a portion of the large intestine) and is often considered as a first-line treatment for acute uncomplicated appendicitis (AUA).[2] SUR typically requires general anaesthesia, which, although a relatively safe intervention, carries some risks in children including unusual heart rhythms (arrhythmias), breathing difficulties, allergic reactions to medications, and in rare occasions deaths.[5] Other risks involve morbidity including ileus, adhesions, and infections which represent a substantial source of both direct healthcare expenditures and indirect social costs.[4] In general, there are two types of SUR: 1. open laparotomy (open surgery) through a limited right lower quadrant incisions (McBurney's, Lanz, Rutherford-Morison approach) or 2. via laparoscopy (minimally invasive approach i.e., classic three-port technique, single incision laparoscopy, transumbilical laparoscopic assisted laparoscopy).[4] In recent years, laparoscopic appendectomy is considered a 'gold standard' (performed almost routinely) as it is associated with lower postoperative pain,

lower incidence of surgical site infections and higher quality of life as well as less visible scars in children.[4] There is no need for postoperative ABT after SUR for AUA in children. The average length of hospital stay for children with AUA is two days.

3.4 FAQ 2: WILL IT HELP MY SYMPTOMS?

This section explains whether the children' symptoms measured with success rate is higher following different treatment options i.e. ABT or SUR. Three SRs were included under this FAQ.[3, 8, 10] All three studies consistently favoured SUR compared to ABT in improving symptoms of paediatric patients i.e., lower-right abdominal pain, nausea, loss of appetite, constipation or diarrhoea, a high temperature. Quality of the evidence was low for this outcome. The details of their findings are summarised in Table 4. One additional SR was also included under this FAQ.[11] The authors measured pain (and temperature) following the two treatment options.

3.4.1 Success rate

One included study found that there were higher chances of success rate (defined differently in different studies and differently for ABT and SUR, please refer to Table 5 for more details) following SUR when compared with ABT (Table 4). The SR and MA by Bi et al. 2019 searched three databases (MEDLINE, EMBASE and the Cochrane Library) for studies published until September 2018; and included randomised trials (RCTs) and observational studies.[3] For this outcome, the authors reported greater improvement in symptoms following SUR when compared with ABT (odds ratio (OR) = 0.12; 95% confidence interval (CI) 0.04 to 0.36; six studies; and OR = 0.028; 95% CI 0.001 to 0.980; nine studies) at one month and 12 months follow-ups respectively. The certainty of the evidence was ranked as low for this outcome due to data of unclear quality and imprecision and inconsistency, respectively.

The SR and MA by Kessler et al. 2017 searched the same three databases (MEDLINE, EMBASE and the Cochrane Library) for studies published from 1950 to 18 February 2017; and included randomised trials (RCTs) and observational studies.[8] For this outcome, the authors found four cohort studies and one RCT comparing SUR with ABT. The authors reported higher treatment efficacy (improvement in symptoms) following SUR when compared with ABT (risk ratio (RR) = 0.77; 95% CI 0.71 to 0.84).[8] The certainty of the evidence was ranked as low for this outcome due to data of unclear quality and imprecision.

The SR and MA by Podda et al. 2019 searched these same three databases (MEDLINE, EMBASE and the Cochrane Library) for studies published until August 2018; and included randomised trials (RCTs) and observational studies.[10] For this outcome, the authors found nine studies (cohort studies and RCTs). The authors reported higher complication-free treatment success following SUR when compared with ABT (OR = 0.08; 95% CI 0.04 to 0.16) at 12 months follow-up.[10] The certainty of the evidence was ranked as low for this outcome due to data of low quality and inconsistency.

3.4.2 Pain

The SR by Rollins et al. 2016 compared outcomes of ABT with SUR for uncomplicated acute appendicitis in adults (≥16 years old).[11] The authors searched PubMed, MEDLINE, Web of Science, Google Scholar and the Cochrane Controlled Trials Register for RCTs published between January 1966 and 31 July 2015.[11] The authors found four studies for this outcome; and their results are reported narratively.[11] For instance, compared with SUR, two trials favoured ABT in reducing pain measured with Visual Analogue Scale (VAS) and analgesics consumption at approximately one-week follow-up. One trial showed no between groups difference in pain score; and one trial favoured SUR in shortening the duration of pain following commencement of intervention.

Table 4: FAQ 2 – Success rate

Author	No. of studies (type of study)	Average follow up time	n ABT	N ABT	n SUR	N SUR	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Success rate (symptoms improvement)									
Bi 2019[3]	6 RCTs and obs. studies	1 month	175	194	260	262	OR = 0.12; 95% CI 0.04 to 0.36	Low (data of low quality, imprecision)	Benefit of SUR ⇗ but imprecise data of low quality
			90 per 100		99 per 100				
Bi 2019[3]	9 RCTs and obs. studies	12 months	1400	2498	61829	61847	OR = 0.028; 95% CI 0.001 to 0.980	Low (data of low quality, inconsistency)	Benefit of SUR ⇗ but inconsistent data of low quality
			56 per 100		99 per 100				
Kessler 2017[8]	5 RCTs and obs. studies	NR	140	189	249	253	RR = 0.77; 95% CI 0.71 to 0.84	Low (data of low quality, imprecision)	Benefit of SUR ⇗ but imprecise data of low quality
			74 per 100		98 per 100				
Podda 2019[10]	9 RCTs and CCTs	NR	170	282	289	325	OR = 0.21; 95% CI 0.10 to 0.44	Low (data of low quality, inconsistency)	Benefit of SUR ⇗ but inconsistent data of low quality
			60 per 100		89 per 100				
Podda 2019[10]	9 RCTs and CCTs	12 months	192	282	319	325	OR = 0.08; 95% CI 0.04 to 0.16	Low (data of low quality, inconsistency)	Benefit of SUR ⇗ but inconsistent data of low quality
			68 per 100		98 per 100				

ABT = antibiotic therapy; CCT = controlled clinical trial; CI = confidence interval; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; SUR = surgery

Table 5: Definitions of success rate (symptoms improvement)

Author	Definition of the outcome (quote)
Bi 2019[3]	Efficacy of ABT and/or SUR: "improvement of symptoms with no need for SUR and without recurrence within 1 month to 1 year"
Kessler 2017[8]	Efficacy of ABT: "the absence of any of the following: failure of antibiotic treatment or recurrence of appendicitis requiring appendicectomy, development of major post-therapeutic or postoperative complications, including readmission" Efficacy of SUR: "the absence of development of post-therapeutic or postoperative complications, including readmission"
Podda 2019[10]	Efficacy of ABT: "achieving a definitive improvement without requiring surgery within a median follow-up of 1 year" Efficacy of SUR: "uncomplicated appendicitis confirmed at the time of the surgical operation or histological verification of appendicitis, and resolution of symptoms after surgical treatment"
Georgiou 2017[5]	Efficacy of ABT: "discharge from hospital without appendectomy during the initial hospital episode"
Huang 2017[7]	Efficacy of ABT and/or SUR: "no complications and no recurrences within 1 month after hospital discharge"
Rollins 2016[11]	Efficacy of ABT: "treated successfully with ABT only and had none of the following: failure of antibiotic therapy or symptom recurrence needing appendicectomy, and/or developing any post-therapeutic and postoperative complications" Efficacy of SUR: "patients who were successfully treated with SUR and had none of the following: no appendicitis on histology and/or developing any post-therapeutic and postoperative complications including readmissions"
Maita 2020[9]	Efficacy of ABT and/or SUR: "no need of appendectomy during the initial hospital stay"
ABT = antibiotic therapy; SUR = surgery	

3.5 FAQ 3: How long will treatment effect last? Will it help maintain remission of my disease?

This section explains duration of the treatment effect and whether ABT or SUR results in a greater failure. Two systematic reviews were included under this FAQ; and consistently reported benefit SUR compared with ABT.[7, 10]

3.5.1 Failure rate

The SR and MA by Huang et al. 2017 searched these same three databases (MEDLINE, EMBASE and the Cochrane Library) for studies published until April 2017; and RCTs and non-randomised studies.[7] For patients without appendicolith, the authors found three studies and reported lower failure rate following SUR when compared with ABT (OR = 0.12; 95% CI 0.02 to 0.54).[7] In the ABT group, the failure rate was defined as a lack of resolution of symptoms without the need for surgery within 48 hours or recurrence of appendicitis within one month after treatment initiation. In the SUR group, it was defined as a treatment with negative appendectomy findings and/or need for reoperation.[7] The certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision (Table 5).

3.5.2 Recurrence of appendicitis

Also, of the 168 patients allocated to the ABT group, 45 patients (26.8%) had recurrence of appendicitis within 12 months post-surgery (and had to be operated on as a result) compared to none of the patients 236 patients in the SUR (OR = 0.01; 95% CI 0.00 to 0.09).[7] The SR and MA by Podda et al. 2019 reported the overall rate of recurrence of 19.2% at 1-year follow-up (there was no comparison group for this outcome).[10] The certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision or indirectness as per the GRADE guidelines.[15] The details of their findings are summarised in Table 5.

Table 6: FAQ 3 – How long will treatment effect last

Author	No. of studies (type of study)	Average follow up time	n ABT	N ABT	n SUR	N SUR	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Failure rate (without appendicolith)									
Huang 2017[7]	4 RCTs and CCTs	12 months	9	138	1	217	OR = 0.12; 95% CI 0.02 to 0.54*	Low (data of low quality, imprecision)	Benefit of SUR ⇗ but imprecise data of low quality
			7 per 100		1 per 100				
Recurrence of appendicitis within one year									
Huang 2017[7]	5 RCTs and CCTs	12 months	45	168	0	236	OR = 0.01; 95% CI 0.00 to 0.09*	Low (data of low quality, imprecision)	Benefit of SUR ⇗ but imprecise data of low quality
			27 per 100		0 per 100				
Podda 2019[10]	9 RCTs and CCTs	NR	ABT 19.2%	Inestimable	Inestimable	Inestimable	Inestimable	Low (data of low quality, indirectness)	Benefit of SUR ⇗ but inconsistent data of low quality

* = own calculation with RevMan 5.4.1. (please refer to the appendix 2)
ABT = antibiotic therapy; CCT = controlled clinical trial; CI = confidence interval; RCT = randomised controlled trial; OR = odds ratio; SUR = surgery.

3.6 FAQ 4: How will treatment impact my quality of life?

This section explains whether the selection of treatments i.e., ABT or SUR will impact quality of life (QoL) of children. Quality of life was measured with different scales to quantify physical or mental components. One systematic review was included under this FAQ; and the quality of the evidence was low.[10] Based on two studies, Podda et al. 2019 found no differences between ABT and SUR in improving QoL measured with Paediatric Quality of Life Inventory at one month follow-up.[10] The certainty of the evidence was ranked as very low for this outcome due to data of low quality, inconsistency and imprecision. The details of their findings are summarised in Table 6.

Table 7: FAQ 4 – How will treatment impact my quality of life

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimates with 95% CI	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Quality of life							
Podda 2019[10]	2 studies	1 month	n/N NR (Median = 95.7 (ABT)*	n/N NR (Median = 91.3 (SUR)*	NR	Very low (data of low quality, inconsistency, imprecision)	No difference shown ⇔

* = measured with Paediatric Quality of Life Inventory
ABT = antibiotic therapy; NR = not reported; SUR = surgery

3.7 FAQ 5: WILL THE TREATMENT PROLONG MY LIFE?

No quantitative data were found to contribute to evidence on the effects of ABT or surgery on mortality rate.

3.8 FAQs 6&7: What are the risks or side effects; Are there long-term negative effects of treatment to be expected?

This section explains what the both short- and long-term side effects of the treatments are. The following outcomes are evaluated: complications, total length of stay (including readmissions), initial length of stay and hospital readmissions. Seven SRs and CPGs evaluated these outcomes.[3, 5-10] Findings consistently showed no differences between SUR and ABT in reducing complications or total length of stay (including readmissions). For initial length of stay and hospital readmissions studies tend to favour SUR over ABT. Please refer to Table 8.

3.8.1 Complications

Bi et al. 2019 reported lower complication rate (including perforation, abscess, gangrene and/or postoperative complications after the appendectomy) following ABT compared with SUR, however there was uncertainty around the effect (OR = 0.56; 95% CI 0.27 to 1.17).[3] The certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision. The SR and MA by Georgiou et al. 2017 searched three databases (PubMed, Embase and the Cochrane Library) for studies published from the databases inception up to December 2015; and included RCTs and non-randomised studies.[5] The authors reported no differences between ABT and SUR for complication rate (not further specified, but excluding recurrent appendicitis) (risk difference (RD) = -0.02; 95% CI -0.05 to 0.00). Similarly, the certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision (Table 8). The SR and MA by Gorter et al. 2017 searched two databases (PubMed, Embase) for studies published from the databases inception up to 7 January 2017; and included RCTs and non-randomised studies.[6] The authors reported no differences between ABT and SUR for complication rate measured with Clavien-Dindo Scale (range: 1 to 5) (2% versus 2.3%, respectively) at 12 months follow-up. For this outcome, Huang et al. 2017 also reported no differences between ABT and SUR for reducing complication rate (defined as perforation, abscess, gangrene, and/or postoperative complications after the interval appendectomy in ABT group and as postoperative complications, including ileus, surgical site infection, or other postoperative readmissions in the SUR group respectively) (RR = 0.65; 95% CI 0.18 to 2.37) at a follow-up that was not reported.[7] The certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision. Similarly, Kessler et al. 2017 reported no differences between ABT and SUR for reducing complication rate defined as the onset of complicated (perforated or gangrenous) appendicitis or peritonitis occurring after the primary intervention (RR = 1.07; 95% CI 0.26 to 4.46) at a follow-up that was not reported.[8] The certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision. The SR and MA by Maita et al. 2020 searched four databases (MEDLINE, EMBASE, Cochrane and Web of Science) in May 2019; and included RCTs and non-randomised studies.[9] For this outcome, the authors reported no differences between ABT and SUR for reducing complication rate defined as conditions requiring general anaesthesia; perforated appendicitis or peritonitis after ABT or SUR-related complications

requiring invasive intervention (OR = 0.64; 95% CI 0.29 to 1.39) at a follow-up that was not reported.[9] The certainty of the evidence was low for this outcome due to data of low quality and imprecision. Based on six studies, Podda et al. 2019 reported lower complication rate (defined as postoperative abscesses, surgical site infections, incisional hernias, obstructive symptoms, and other general complications, including adverse reaction to antibiotics, anaesthesiology complications, cardiovascular and pulmonary adverse events) following ABT compared with SUR, however there was uncertainty around the effect (OR = 0.57; 95% CI 0.28 to 1.16) at a follow-up that was not reported.[10] Analogically, the certainty of the evidence was ranked as low for this outcome due to data of low quality and imprecision. The details of their findings are summarised in Table 8. However, it is wort stating that SUR and ABT are two dissimilar treatment modalities; complications or/and AEs are distinct i.e., prolonged ileus, pneumonia, and both superficial and deep wound infection after appendectomy are not applicable to ABT.

3.8.2 Total length of stay (including readmissions)

Georgiou et al. 2017 reported no differences between ABT and SUR in reducing total length of stay (including readmissions) in days (the shorter duration, the better) (mean difference (MD) = -1.13; 95% CI -3.49 to 1.22; two studies).[5] The certainty of the evidence was ranked as low for this outcome due to data of low quality and inconsistency (Table 8). For this outcome, Maita et al. 2020 also reported no differences between ABT and SUR (standardised mean difference (SMD) = 0.00; 95% CI -0.71 to 0.71 in days).[9] The certainty of the evidence was low for this outcome due to data of low quality and inconsistency.

3.8.3 Initial length of stay

Georgiou et al. 2017 reported shorter initial length of hospital stay in hours (the shorter duration, the better) following SUR when compared with ABT (MD = 0.48; 95% CI 0.18 to 0.78; four studies).[5] The certainty of the evidence was ranked as low for this outcome due to data of low quality and inconsistency (Table 8). For this outcome, Huang et al. 2017 also reported shorter initial length of hospital stay in hours following SUR when compared with ABT (MD = 14.32; 95% CI 7.49 to 21.15).[7] However, Maita et al. 2020 reported no differences between ABT and SUR for reducing initial length of hospital stay in days (-0.07; 95% CI -0.80 to 0.66 in days).[9] The certainty of the evidence was low for this outcome due to data of low quality and inconsistency. Based on four studies, Podda et al. 2019 found no differences between ABT and SUR in reducing initial length of hospital stay in days (SMD = -1.40; 95% CI -3.71 to 0.92).[10] Similarly, the certainty of the evidence was downgraded to low for this outcome due to data of low quality and inconsistency.

3.8.4 Hospital readmissions

For this outcome, Kessler et al. 2017 reported a higher risk of hospital readmissions following ABT compared with SUR (RR = 6.98; 95% CI 2.07 to 23.60; five studies).[8] The certainty of the evidence was ranked as low for this outcome due to data of unclear quality and imprecision.

3.8.5 Long-term side effects

There was no comparative evidence for long-term side effects of SUR versus ABT. One study suggested that the appendix has an important role in maintaining homeostasis of the gut flora (reservoir of beneficial bacteria residing in the gut).[16, 17] Hence it is believed that through its links with the lymphatic and immune systems, the appendix regulates pathogens (harmful bacteria, viruses), and might prevent diseases.[18] Thus, hypothetically, removing the appendix may have negative long-term consequences.

Table 8: FAQs 6 & 7– What are the risks or side effects

Author	No. of studies (type of study)	Average follow up time	n ABT	N ABT	n SUR	N SUR	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Complications									
Bi 2019[3]	6 RCTs	NR	18	265	25	316	OR = 0.567; 95% CI 0.273 to 1.176	Low (data of low quality, imprecision)	Difference in favour of ABT but imprecise data of low quality ⇗
			7 per 100		8 per 100				
Georgiou 2017[5]	5 non-RCTs or RCTs	NR	1	175	9	239	RD = -0.02; 95% CI -0.05 to 0.00	Low (data of low quality, imprecision)	No difference shown ⇔
			1 per 100		4 per 100				
Gorter 2017[6]	5 RCTs and obs. studies	12 months	3	147	4	173	OR = 1.14; 95% CI 0.25 to 5.16*	Low (data of low quality)	No difference shown ⇔
			2 per 100		2 per 100				
Huang 2017[7]	3 RCTs and CCTs	NR	3	168	7	236	RR = 0.65; 95% CI 0.18 to 2.37	Low (data of low quality, imprecision)	No difference shown ⇔
			2 per 100		3 per 100				
Kessler 2017[8]	4 RCTs and obs. studies	NR	3	189	4	253	RR = 1.07; 95% CI 0.26 to 4.46	Low (data of low quality, imprecision)	No difference shown ⇔
			2 per 100		2 per 100				
Maita 2020[9]	8 RCTs, CCTs and obs. studies	NR	13	264	21	295	OR = 0.64; 95% CI 0.29 to 1.39	Low (data of low quality, imprecision)	No difference shown ⇔
			5 per 100		7 per 100				
Podda 2019[10]	6 RCTs and CCTs	NR	22	229	30	240	OR = 0.57; 95% CI 0.28 to 1.16	Low (data of low quality, imprecision)	Difference in favour of ABT but imprecise data of low quality ⇗
			10 per 100		13per 100				

Author	No. of studies (type of study)	Average follow up time	n ABT	N ABT	n SUR	N SUR	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Total length of stay (including readmissions)									
Georgiou 2017[5]	2 non-RCTs or RCTs	NR (range: 8 weeks to 4 years)	Inestimable	142	Inestimable	126	MD = -1.13; 95% CI -3.49 to 1.22 in days	Low (data of low quality, inconsistency)	No difference shown ⇔
Maita 2020[9]	2 CCTs	NR	Inestimable	63	Inestimable	44	SMD = 0.00; 95% CI -0.71 to 0.71 in days	Low (data of low quality, inconsistency)	No difference shown ⇔
Initial length of stay									
Georgiou 2017[5]	4 non-RCTs or RCTs	NR	Inestimable	151	Inestimable	189	MD = 0.48; 95% CI 0.18 to 0.78 in days	Low (data of low quality, inconsistency)	Difference in favour of SUR; inconsistent data of low quality ⇗
Huang 2017[7]	3 RCTs and CCTs	NR	Inestimable	139	Inestimable	177	MD = 14.32; 95% CI 7.49 to 21.15 in hours	Low (data of low quality, imprecision)	Difference in favour of SUR; imprecise data of low quality ⇗
Maita 2020[9]	7 RCTs, CCTs and obs. studies	NR	Inestimable	4517	Inestimable	61857	SMD = -0.07; 95% CI -0.80 to 0.66 in days	Low (data of low quality, inconsistency)	No difference shown ⇔
Podda 2019[10]	4 RCTs and CCTs	NR	Inestimable	151	Inestimable	189	SMD = -1.40; 95% CI -3.71 to 0.92	Low (data of low quality, inconsistency)	No difference shown ⇔
Hospital readmissions									
Kessler 2017[8]	5 RCTs and obs. studies	NR	Inestimable	Inestimable	Inestimable	Inestimable	RR = 6.98; 95% CI 2.07 to 23.60	Low (data of low quality, imprecision)	Difference in favour of SUR; imprecise data of

Author	No. of studies (type of study)	Average follow up time	n ABT	N ABT	n SUR	N SUR	Effect estimates with 95% CIs	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
									low quality ⇗

* = own calculation with RevMan 5.4.1. ABT = antibiotic therapy; CCT = controlled clinical trial; CI = confidence interval; MD = mean difference; NR = not reported; obs. studies = observational studies; OR = odds ratio; RCT = randomised controlled trial; RD = risk difference; RR = risk ratio; SUR = surgery.

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

Overall, nine papers were included in this review. The certainty of the evidence was low for all FAQs/outcomes (except for QoL where it was downgraded to very low); and findings were often inconsistent or imprecise.

For instance, for FAQ 2 findings consistently showed benefit of SUR when compared with ABT in improving symptoms in children. However, this success rate was not always defined uniformly. For example, Podda et al. 2019 used the term "complication-free treatment" whereas in Huang et al. 2017 it was a composite outcome of "no complications and no recurrences within 1 month after hospital discharge".[7, 10] The follow-ups ranged from one month to 12 months; and the certainty of the evidence was predominantly low. In addition, the findings for pain were inconsistent.[11]

For FAQ 3, findings consistently showed benefit of SUR when compared with ABT in reducing recurrence of appendicitis in children, i.e., over one fourth of the patients initially allocated to the ABT group, underwent SUR within one year follow-up (compared to none in the SUR group).[7]

Only one SR contributed low certainty evidence for FAQ 4.[10] Podda et al. 2019 found no differences between ABT and SUR in improving QoL measured with Paediatric Quality of Life Inventory.[10] The quality of the evidence was low for this outcome due to data of low quality, inconsistency and imprecision.

No quantitative data were found to contribute to evidence for FAQ 5.For FAQs 6 & 7, there were different and often heterogeneous definitions of complications or AEs depending on the treatment options. For example, complication in the ABT group was sometimes defined as "perforation, abscess, gangrene, and/or postoperative complications after the interval appendectomy"; whereas in the SUR group complications were defined as "postoperative complications including ileus, surgical site infection, or other postoperative readmissions".[7] It is worth emphasising that SUR and ABT are two distinct treatment options; complications or/and AEs are disparate i.e., those of SUR are not applicable to ABT and vice versa. Also, findings were inconsistent for FAQ 6. For example two studies reported shorter initial length of hospital stay in days (or hours) following SUR when compared with ABT.[5, 7] However two studies reported no differences [9, 10] For this outcome, the certainty of the evidence was low; with low quality data, inconsistency and imprecision being reasons for downgrading.

4.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

This report has several strengths including comprehensive searches. Evidence from high quality SRs and CPGs was utilised when preparing this report. Nevertheless, several limitations of this report should be acknowledged too. These include an unequal distribution of findings for FAQs 2, 6 & 7 compared with FAQs 3,4; or lack of evidence for FAQ 5. Several uncertainties exist in the area. For instance, the quality of the evidence was predominantly

low; and so was the quality of the primary studies (one of them being retracted owing to plagiarism).[19, 20] Heterogeneity of populations, diversity of interventions i.e., doses, intensities of ABT and types of SUR, comparators, outcomes and follow-up periods and study designs further limit applicability of the findings. In order to reduce the existing uncertainties, future studies in this field should be of higher quality (preferably RCTs) and employ uniform outcome measures.

5. REFERENCES

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APPENDIX 1: SEARCH STRATEGIES

Systematic reviews and guideline search results

Database	Dates	Results
CDSR & CDSR Protocols	2016 – 2021/03/Iss3	8
HTA	2016 – 2018/03	0
INAHTA	2016 – 2021/03/17	8
KSR Evidence	2016 – 2021/03/17	228
Epistemonikos	2016 – 2021/03/17	307
NHS Evidence	2016 - 2021/03/17	168
NICE	2016 - 2021/03/17	5
GIN	2016 - 2021/03/17	0
ECRI	2016 - 2021/03/17	1
TRIP	2016 - 2021/03/17	4
Total		**729**

SDM database searches

Database	Dates	Results
Embase	2016-2021/03/16	147
MEDLINE & PreMedline	2016-2021/03/16	160
CENTRAL	2016 – 2021/03/Iss3	172
Total		**479**

SR/Guidelines searches

Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2021/03/Iss3
Searched: 17.3.21

#1 MeSH descriptor: [Appendicitis] explode all trees 593
#2 MeSH descriptor: [Appendectomy] explode all trees 499
#3 (appendic* or appendec*):ti,ab,kw 2714
#4 #1 or #2 or #3 with Cochrane Library publication date Between Jan 2016 and Mar 2021 1534

CDSR retrieved 7 records
CDSR protocols retrieved 1 record

Health Technology Assessment (HTA) database (CRD): up to 2018/03
Searched: 17.3.21

1 MeSH DESCRIPTOR Appendicitis EXPLODE ALL TREES 153
2 MeSH DESCRIPTOR Appendectomy EXPLODE ALL TREES 147
3 ((appendic* or appendec*)) 380

4 #1 OR #2 OR #3 380
5 (#1 OR #2 OR #3) FROM 2016 TO 2021 0

INAHTA (https://database.inahta.org/): up to 2021/03/17
Searched: 17.3.21
(Appendectomy)[mh] OR (Appendicitis)[mh] OR (appendic* or appendec*) FROM 2016 TO 2021

INAHTA retrieved 8 results

KSR Evidence: up to 2021/03/17
Searched: 17.3.21
1 (appendic* or appendec*) in Title or Abstract **228 results**
Filtered by: PUBLICATION DATE 2021, 2020, 2019, 2018, 2017, 2016

Epistemonikos (https://www.epistemonikos.org/): up to 2021/03/17
Searched: 17.3.21
(advanced_title_en:((appendic* OR appendec*)) OR advanced_abstract_en:((appendic* OR appendec*))) [Filters: classification=systematic-review, protocol=no, cochrane=missing, min_year=2016, max_year=2021]

Search retrieved 307 results

NHS Evidence (www.evidence.nhs.uk): up to 21/03/17
Searched: 17.3.21

Search terms – limited to guidance/systematic reviews, 01/01/2016-17/03/2021	**Hits**
appendicitis or appendectomy	168 (G=65, SR=103)
Total	**168**

National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/guidance): up to 2021/03/17
Searched 17.3.21

Limited to (Published) Guidelines/ Nice Advice

Keywords	**Hits**
Appendicitis	4
Appendectomy	1
Total	**5**

Guidelines International Network (GIN) Library (http://www.g-i-n.net): up to 2021/03/17

Searched: 17.3.21

Limited 2016-C

Search terms	Hits
Appendicitis	0
Appendectomy	0

ECRI (www.guidelines.ecri.org): up to 2021/03/17
Searched 17.3.21

Search terms	Hits
appendicitis or appendectomy	1
Total restricted to 2016 onwards	**1**

TRIP database (https://www.tripdatabase.com/): up to 2021/03/17
Searched: 17.3.21

Limited to guidelines

(Title: appendicitis or appendectomy) from:2016

TRIP retrieved 4 records

SDM Searches

Embase (Ovid): 1974-2021/03/16
Searched 17.3.21

1 exp appendicitis/ or exp appendectomy/ (36835)
2 (appendic$ or appendec$).ti,ab,ot,hw. (54088)
3 or/1-2 (54088)
4 limit 3 to yr="2016 -Current" (16295)
5 *patient decision making/ or *shared decision making/ (4814)
6 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (55540)
7 sdm.ti,ab. (3781)
8 (decision$ adj2 aid$).ti,ab. (9305)
9 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (102397)
10 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (9675)
11 (person centred or person centered).ti,ab. (7201)
12 or/5-11 (181135)
13 4 and 12 (147)

MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid): 1946-2021/03/16
Searched: 17.3.21

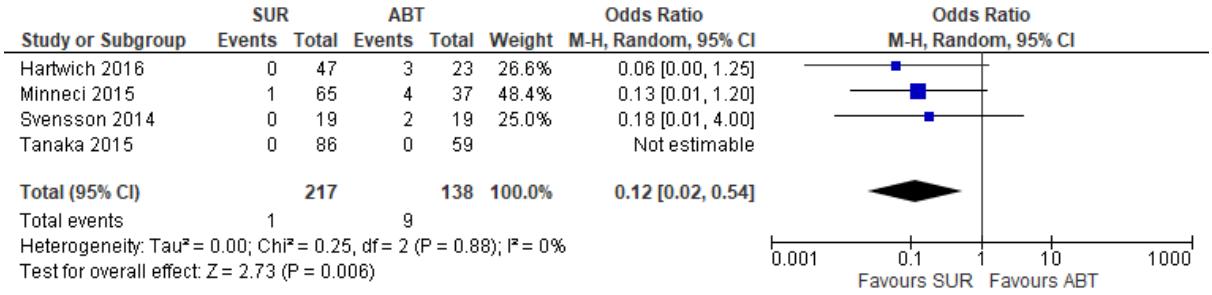
1 appendicitis/ or appendectomy/ (24132)
2 (appendic$ or appendec$).ti,ab,ot,hw. (43179)
3 or/1-2 (43179)
4 limit 3 to yr="2016 -Current" (8762)
5 exp Decision Making/ (208840)
6 exp decision support techniques/ (78895)
7 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (40102)
8 (decision$ adj2 aid$).ti,ab. (6341)
9 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (64933)
10 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (6963)
11 (person centred or person centered).ti,ab. (5861)
12 sdm.ti,ab. (2903)
13 or/5-12 (391120)
14 4 and 13 (160)

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2021/03/Iss3
Searched 17.3.21

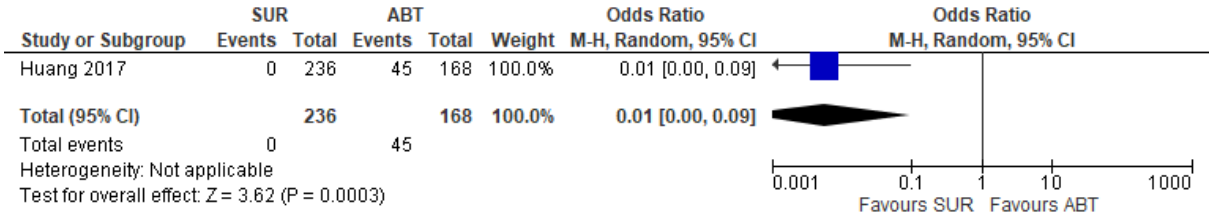
#1 MeSH descriptor: [Appendicitis] explode all trees 593
#2 MeSH descriptor: [Appendectomy] explode all trees 499
#3 (appendic* or appendec*):ti,ab,kw 2714
#4 #1 or #2 or #3 with Cochrane Library publication date Between Jan 2016 and Mar 2021 1534
#5 MeSH descriptor: [Decision Making] explode all trees 3988
#6 MeSH descriptor: [Decision Support Techniques] explode all trees 2478
#7 MeSH descriptor: [Decision Theory] explode all trees 166
#8 ((share* or sharing* or inform*) NEAR/3 (decision* or deciding* or choice*)):ti,ab 4397
#9 (decision* NEAR/2 aid*):ti,ab 1666
#10 ((decision* or choice*) NEAR/3 (making* or support* or behaviour* or behavior*)):ti,ab 12854
#11 ((patient* or consumer*) NEAR/2 (involve* or involving or participat*)):ti,ab 15733
#12 ((patient-centred or patient centred or patient-centered or patient centered) NEAR/2 care):ti,ab 6402
#13 (person centred or person centered):ti,ab 1118
#14 sdm:ti,ab 421
#15 MeSH descriptor: [Informed Consent] explode all trees 731
#16 (informed NEAR/3 (consent* or agree* or assent*)):ti,ab 63260
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 102055
#18 #4 and #17 172

Central retrieved 172 records

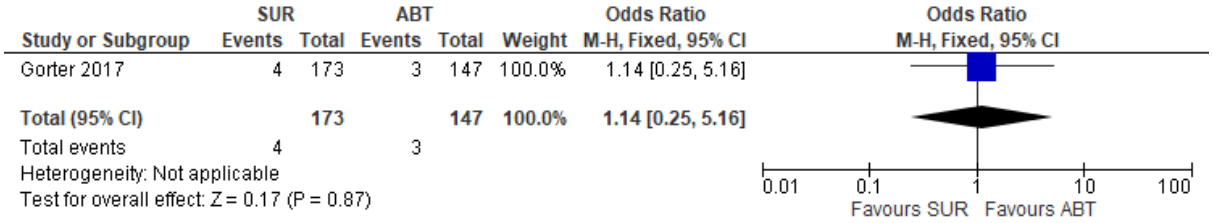
APPENDIX 2: OWN CALCULATIONS WITH REVIEW MANAGER 5.4.1



Outcome: Failure rate without appendicolith (please also refer to table 6)



Outcome: Recurrence of appendicitis (please also refer to table 6)



Outcome: complications (please also refer to table 8)