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SUMMARY WITH CRITICAL APPRAISAL

Fluoroquinolones for the Treatment of Other Respiratory Tract Infections: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AGREE II	Appraisal of Guidelines for Research and Evaluation II
AMSTAR-2	A MeaSurement Tool to Assess systematic Reviews
BTS	British Thoracic Society
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRD	Centre for Reviews and Dissemination
CSLD	Chronic Suppurative Lung Disease
FDA	Food and Drug Administration
FQs	Fluoroquinolones
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HTA	Health Technology Assessment
LRTI	Lower respiratory tract infection
MA	Meta-analysis
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-analysis
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SR	Systematic Review
SUCRA	Surface under the cumulative ranking

Context and Policy Issues

Fluoroquinolones (FQs) are a common class of antibiotic used for the treatment of infections, including those of the respiratory tract. However, the use of FQs has been controversial as certain types are associated with antibiotic resistance and adverse events.

Antibiotic resistance is of significant concern due to the broad-spectrum nature and common use of FQs, and FQ resistance occurs through a number of potential individual or combined mechanisms.[1] Recent global surveillance studies have found increasing rates of FQ resistance among almost all species of bacteria, and this has been demonstrated in urinary tract infection, respiratory tract infections, intraabdominal infections, skin and skin structure infections, and sexually transmitted infections.[2,3] FQ resistance has likely been driven by the widespread use of the antibiotic, and adjustments clinical practice guidelines may be warranted to limit misuse of FQs.

Common adverse events include gastrointestinal and central nervous system toxicities, while other adverse events include rashes and other allergic reactions, tendinitis and tendon rupture, QT prolongation, hypoglycemia and hyperglycemia, and hematologic toxicity. Several FQs have been withdrawn from the market due to adverse events.[4] In the United States, examples include the withdrawal of grepafloxacin in 1999 due to fatal cardiovascular events, temafloxacin in 1992 due to severe adverse reactions (e.g. hemolytic anemia, acute renal failure, hepatotoxicity, and death), and alatrofloxacin in 2006 due to liver toxicity and death.[5]

The association of FQ use with serious adverse events has led to reevaluations of the use of FQs for uncomplicated infections in several jurisdictions. In 2016, the United Sates Food and Drug Administration (FDA) released a statement advising the restriction of FQ use in patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections

who have other treatment options, because the risk of serious side effects generally outweighed the benefits.[6] As a result, Health Canada undertook a review of FQs and associated adverse events, and posted the results in their Summary Safety Review in January 2017. The review concluded that adverse events associated with FQ use may be persistent and disabling in rare cases, and that Health Canada would collaborate with drug manufacturers to update product safety information to reflect this potential risk.[7] There remains uncertainty in the use of FQs for the treatment of infections.

This report is an extension of a previous Rapid Response report,[8] which identified evidence for the clinical effectiveness, cost-effectiveness, and guidelines for FQs in pneumonia and chronic obstructive pulmonary disease (COPD). The report found inconsistent results in the systematic reviews of the clinical effectiveness of FQ use in pneumonia, while there was a limited volume of evidence in the clinical effectiveness in COPD, and cost-effectiveness of FQ use in pneumonia. The current report aims to identify and synthesize the evidence describing the clinical effectiveness, cost-effectiveness and guidelines for the use of FQs in other respiratory tract infections (excluding COPD, pneumonia, cystic fibrosis and tuberculosis).

Research Questions

1. What is the clinical effectiveness of fluoroquinolones for the treatment of 'other' respiratory tract infections?
2. What is the cost-effectiveness of fluoroquinolones for the treatment of 'other' respiratory tract infections?
3. What are the evidence-based guidelines for the use of fluoroquinolones for the treatment of 'other' respiratory tract infections?

Key Findings

Overall, six publications met the eligibility criteria and were included in this report. Two of the included publications were systematic reviews; one systematic review which examined antibiotic use (including fluoroquinolones) in patients with acute rhinosinusitis, and one systematic review with a meta-analysis and a network meta-analysis which examined anti-bacterial agents (including fluoroquinolones) for patients with bronchitis. In the treatment of bronchitis, no significant differences in treatment efficacy for total pathogen eradication were noted in the meta-analysis or network meta-analysis, however, based on the surface under the cumulative ranking curve, the authors reported that gemifloxacin and levofloxacin were found to be high ranking in total pathogen eradication efficacy. In the systematic review of the treatment of acute rhinosinusitis, levofloxacin was found to be the most effective treatment.

One non-randomized study was included, which retrospectively analyzed patients with lower respiratory tract infections who had been treated with ceftriaxone sodium, ceftizoxime sodium, levofloxacin or azithromycin. The authors reported no statistically significant differences in the effectiveness rates of the antibiotics compared, but found levofloxacin had the lowest treatment costs.

No evidence related to the cost-effectiveness of fluoroquinolones for the treatment of lower respiratory tract infections was identified.

Three guidelines were identified; one informing the treatment of acute exacerbations of bronchiectasis (non-cystic fibrosis) from the National Institute for Health Care and

Excellence, one informing the treatment of bronchiectasis in adults from the British Thoracic Society, and one informing the treatment of chronic suppurative lung disease and bronchiectasis from the Thoracic Society of Australia and New Zealand. The British Thoracic Society and the Thoracic Society of Australia and New Zealand guidelines recommends ciprofloxacin as a first line treatment for patients with Pseudomonas aeruginosa. The National Institute for Health Care and Excellent recommends levofloxacin for adults and ciprofloxacin (on specialist advice) for children as second line oral treatments for patients at high risk of treatment failure or as first line intravenous treatment.

While the three guidelines provided similar recommendations for the use of fluoroquinolones in the treatment of bronchiectasis (non-cystic fibrosis), the variable findings and methodological limitations in the body of evidence identified for other conditions, including bronchitis and acute rhinosinusitis, to inform this report limit generalizability and warrant caution in its interpretation for the clinical effectiveness and cost-effectiveness of fluoroquinolones for the treatment of respiratory tract infections.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including MEDLINE, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses (MA), randomized controlled trials (RCT), non-randomized studies, economic studies, and guidelines. For randomized control trials and non-randomized studies, the search was focused to main concepts appearing in the title or subject heading. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and March 28, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with respiratory tract infections (e.g., bronchitis, rhinosinusitis) excluding COPD, pneumonia, cystic fibrosis and tuberculosis
Intervention	Fluoroquinolones as monotherapy
Comparator	Q1-Q2: Any antibiotic comparator Q3: No comparator
Outcomes	Q1: Clinical effectiveness; harms (e.g., Clostridium difficile infections) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	HTA/Systematic Reviews/Meta-Analyses; RCTs; Non-Randomized Studies; Economic Evaluations; Guidelines

COPD = chronic obstructive pulmonary disease; HTA = health technology assessment; RCT = randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded. Studies with patient populations for COPD, pneumonia, cystic fibrosis, and tuberculosis were excluded. Additionally, only studies with FQs used as monotherapy were included; studies utilizing combination therapies (e.g. beta-lactam/FQ combinations) were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2),[9] the non-randomized study was assessed using the Critical Appraisal Skills Programme (CASP) checklist,[10] and guidelines were assessed with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 497 citations were identified in the literature search. Following screening of titles and abstracts, 430 citations were excluded and 67 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 64 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised two SRs, one non-randomized studies, and three evidence-based guidelines. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.Appendix 2

Summary of Study Characteristics

Overall, six publications met the eligibility criteria and were included in this report: two SR,[13,14] one non-randomized study,[15] and three guidelines.[16-18]

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Systematic Reviews & Meta-Analysis

Two SRs were eligible for inclusion in this report, published in 2017,[13] and 2015.[14] The disease areas included bronchitits[13] and acute rhinosinusitis.[14]

The 2017 SR examined the efficacy and safety of anti-bacterial agents, including FQs, for the treatment of bronchitis. The authors conducted a SR after searching Embase, Cochrane Library and PubMed for articles published in the last two decades (exact search dates were not provided). The review included 27 RCTs, published from 1991 to 2007. The authors conducted a pair-wise MA using a random-effects or fixed-effects model, as well as a

network-meta-analysis (NMA) using a Bayesian framework. In order to rank the medications, the authors produced the surface under the cumulative ranking curve (SUCRA).[13] Thirteen of these studies were relevant to the current report.

The 2015 SR examined the use of common antibiotics, including FQs, in the treatment of acute rhinosinusitis. The authors performed a literature search in PubMed and included 31 RCTs in their review. The authors did not provide information on the dates used in their search or the years the included RCTs were published.[14] Eleven of the 31 studies were relevant to the current report.

There was no overlap of included studies between the SRs, as detailed in **Error! Reference source not found.**.

Non-Randomized Studies

One non-randomized study, which utilized a retrospective cohort design, examined lower-respiratory tract infections (LRTIs) and compared four antibiotics in terms of therapeutic effect.[15]

Guidelines

Three guidelines were eligible for inclusion in this report: one informing the treatment of bronchiectasis in adults from the British Thoracic Society (BTS),[16] one informing the treatment of acute exacerbations of bronchiectasis (non-cystic fibrosis) from the National Institute for Health Care and Excellence (NICE),[17] and one informing the treatment of chronic suppurative lung disease (CSLD) and bronchiectasis from the Thoracic Society of Australia and New Zealand.[18]

The *British Thoracic Society Guideline for Bronchiectasis in Adults* was developed in accordance with the methodology and criteria set by the AGREE collaboration. The scope of the guideline and literature search were informed by clinical questions structured by patient, intervention, control, and outcomes. Literature searches were completed in Ovid MEDLINE (including MEDLINE In Process), Ovid EMBASE, and the Cochrane Library, and were run in June 2014 and updated in June 2016. Selected papers were critically appraised using the Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal checklists. The Guideline Development Group used evidence tables to judge the body of evidence, and recommendations were graded from A to D based on the strength of the evidence. The draft guideline was reviewed by the BTS Standards of Care Committee and was then made available for public consultation and circulated to all the relevant stakeholders, and the Guideline will be reviewed within five years from the publication date.[16]

The NICE Guideline *Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial prescribing* sets out an antimicrobial prescribing strategy for managing and preventing acute exacerbations of bronchiectasis (non-cystic fibrosis) and aims to optimise antibiotic use and reduce antibiotic resistance. Systematic literature searches were undertaken according to the NICE guidelines manual 2012, only one RCT was identified for antimicrobial interventions and no evidence in children or young people was identified. Included studies were critically appraised and, where appropriate, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence assessments were applied.[17]

The Thoracic Society of Australia and New Zealand *Chronic Suppurative Lung Disease and Bronchiectasis in Children and Adults in Australia and New Zealand Clinical Practice*

Guideline provides guidelines for managing CSLD and bronchiectasis, and is based on systematic reviews, multi-disciplinary meetings and a modified Delphi process. Recommendations were categorized as strong, weak, or no specific recommendations using the principles of evidence based medicine and the reviews GRADE approach.[18]

Country of Origin

The SRs were published by authors in China,[13] and Singapore.[14] The non-randomized primary clinical study was published by authors in China.[15]

Two of the included guidelines are intended for practice in the United Kingdom,[16,17] and the remaining guideline is intended for practice in Australia and New Zealand.[18]

Patient Population

Systematic Reviews & Meta-Analysis

In the SR of bronchitis patients, the authors noted that 9,414 patients with bronchitis (including acute bronchitis, chronic bronchitis, and acute bacterial exacerbation of chronic bronchitis) were enrolled in the 27 eligible RCTs included. Of note, the data from an RCT not relevant to the current review contributes to the indirect comparison (the study included patients with COPD, asthma, emphysema, bronchiectasis and acute exacerbations of chronic bronchitis, and it's interventions were not within the scope of the current review).[13]

One SR included RCTs of patients with clinical diagnosis of acute rhinosinusitis. The study setting and baseline characteristics of acute rhinosinusitis patients (e.g. age) of the included studies were not reported. Relevant to the current report, the authors reported the inclusion of six studies for levofloxacin (capturing 1,050 study patients) and five studies for moxifloxacin (capturing 937 patients).[14]

Non-Randomized Studies

One non-randomized study retrospectively analyzed data from 200 patients with LRTI who had been treated in the Department of Respiratory Medicine of Dongying People's Hospital, in Dongying, China between February 2015 and May 2017. Among the four groups of patients, Group A included 21 males and 29 females, aged 16 to 59 years (mean age: 35.44 ± 16 years); Group B included 23 males and 27 females aged 18 to 65 years (mean age: 35.14 ± 2.01 years); Group C included 19 males and 31 females aged 20 to 63 years (mean age: 34.52 ± 2.35 years); and Group D included 24 males and 26 females aged 19 to 66 years (mean age: 34.68 ± 2.46 years).[15]

Guidelines

The BTS guideline was developed for healthcare practitioners who are involved in the care of adult patients with bronchiectasis (e.g. primary care clinicians, hospital specialist teams in infectious disease, respiratory medicine, microbiologists, and radiologists).[16] The NICE guideline is intended for health professionals as well as people with bronchiectasis, their families and carers.[17] The Thoracic Society of Australia and New Zealand guideline is intended for the management of children and adults in Australia and New Zealand with CSLD and bronchiectasis, including urban and rural-remote indigenous people.[18]

Only the recommendations related to antibiotic treatment, and specifically treatment with FQs, are relevant to this Rapid Response.

Interventions and Comparators

Systematic Reviews & Meta-Analysis

Both of the included SRs compared efficacy and/or safety of various antibiotic treatments; the following section outlines the comparisons relevant to the current report.

The SR of antibiotic treatments for bronchitis examined the efficacy and safety of various antibiotic monotherapies (no placebo studies were included in the review). The FQ antibiotics studied varied (type, dosage, durations), and included: levofloxacin versus amoxicillin-clavulanate, moxifloxacin versus amoxicillin-clavulanate (two RCTs), gemifloxacin versus amoxicillin-clavulanate (one RCT), gatifloxacin versus amoxicillin-clavulanate (one RCT), levofloxacin versus azithromycin (two RCTs), moxifloxacin versus azithromycin (two RCT), gemifloxacin versus clarithromycin (one RCT), moxifloxacin versus clarithromycin (two RCTs), gatifloxacin versus clarithromycin (one RCT), and levofloxacin versus gemifloxacin (two RCTs). The route of treatment (e.g. oral or IV) and the length of follow-up was not reported for any RCTs.[13]

One SR compared the clinical efficacy and safety profile of placebo or antibiotics (including levofloxacin and moxifloxacin) in the treatment of acute rhinosinusitis. Six RCTs on levofloxacin (500 to 750 mg once a day, 5 to 10 days) and five RCTs on moxifloxacin 400 mg once a day, 5 to 10 days) were included in this SR; however, the route of administration (e.g. oral, inhaled, IV) was not reported.[14] The current report will focus only on the comparisons of antibiotics, not comparisons with placebo.

Non-Randomized Studies

The non-randomized study compared four groups of patients: Group A was treated with intravenous infusion of 2.0 g ceftriaxone sodium injection + 100 ml 9% sodium chloride injection (two times/day), Group B was treated with intravenous infusion of 2.0 g ceftizoxime sodium + 100 ml 9% sodium chloride injection (two times/day), Group C was treated with intravenous infusion of 0.3 g levofloxacin + 100 ml 9% sodium chloride injection (two times/day), and Group D was treated with intravenous infusion of 1.0 g azithromycin + 100 ml 9% sodium chloride injection (two times/day); all patients were treated for one week as one course of treatment.[15]

Guidelines

The BTS guideline examined what treatments improved outcomes for patients with stable bronchiectasis as well as the use of antibiotic therapy to improve outcomes in patients with exacerbations of bronchiectasis (non-cystic fibrosis).[16] The NICE guideline examined antibiotic treatment for the management of acute exacerbation of bronchiectasis (non-cystic fibrosis), including antibiotic choice.[17] Similarly, the Thoracic Society of Australia and New Zealand guideline examined management of CSLD and bronchiectasis through antibiotics for acute exacerbations, Pseudomonas aeruginosa eradication, and long-term suppression.[18]

Outcomes

Systematic Reviews & Meta-Analysis

The SR of bronchitis patients included six outcomes: the main outcomes were total pathogen eradications and the total incidence of adverse events, while secondary outcomes included the pathogen eradication of H. influenzae, M. catarrhalis, or S.

pneumonia, as well as diarrhoea; no further details regarding the definitions of these outcomes were provided by the authors.[13]

The SR of acute rhinosinusitis utilized clinical cure rate (based on symptoms, and signs detected in physical and/or endoscopic exam) at test-of-cure visit as the primary outcome, and secondary outcomes included radiological and/or microbiologic response rate and adverse events. The diagnosis and evaluation of cure of acute rhinosinusitis was made by clinical and/ or radiological (n = eight RCTs) criteria and/or bacteriological criteria (n =four RCTs) in patients with symptoms of acute rhinosinusitis. The included FQ studies had study endpoints measured at five or 10 days.[14]

Non-Randomized Studies

The non-randomized study sought to compare the effects of different antibiotic regimens in the treatment of LRTI. After patients were treated for seven days, the therapeutic effect was evaluated and scored. The authors categorized patients as 'cured' if lesions and clinical symptoms had completely disappeared according to x-ray examination, there were no adverse reactions and quality of life had returned to normal; 'effective' if lesions and clinical symptoms were greatly improved according to x-ray examination, there were no adverse reactions and quality of life was obviously improved; or 'ineffective' if lesions and clinical symptoms were not improved or exacerbated according to x-ray examination, there were adverse reactions and quality of life was poor. The authors calculated the Total Effective Rate as follows: total effective rate = (cured cases + effective cases)/number of cases x 100%.[15]

Guidelines

The BTS guideline considered clinical outcomes such as lung function capacity, sputum production, severity of disease, exacerbation frequency, side effects, as well as microbiological and quality of life outcomes.[16]

The NICE guideline considered outcomes such as reduction in symptoms (duration or severity), time to clinical cure, rate of complications (including mortality), health and social care utilization as well as thresholds or indications for antimicrobial treatment.[17]

The Thoracic Society of Australia and New Zealand guideline considered symptom control, preserve lung function, quality of life, exacerbation frequency and survival.[18]

Summary of Critical Appraisal

Critical appraisal was completed for each of the included publications in this report. Additional details regarding the strengths and limitations of included publications are provided Appendix 3.

Systematic Reviews

A number of strengths of the SR were identified through the critical appraisal process. The research questions and inclusion criteria were clearly stated in all studies,[13,14] and study selection and data extraction were performed in duplicate.[13,14] The authors of both SRs reported no conflicts of interest.[13,14] In one SR, the authors described the populations, interventions (including dosage), comparators and research designs for the included studies.[13] The authors also provided methodological details for the MA and used appropriate techniques to combine the study results, as well as assessed and explained heterogeneity.[13]

The following limitations were noted: neither SR provided an explicit statement that the review protocol was established prior to the conduct of the review, the search strategies were limited in one SR in that authors did not search trial registries or sources of grey literature, and no date range for the search was provided,[13] and the other SR only searched one online database.[14] Neither SR explained their selection of study designs for inclusion in the review, provided a list of excluded studies, assessed the risk of bias of the included studies, reported the sources of funding for included studies, or carried out an investigation of publication bias.[13,14] The SR of patients with acute rhinosinusitis did not describe the populations or comparators used in the studies pooled for each intervention.[14] The SR of patients with bronchitis provided limited details on the methodology of the NMA performed; specifically, the authors did not provide adequate details regarding the assessment of consistency of trials (e.g. what baseline characteristics were considered), nor did the authors state whether a random or fixed-effects model was utilized for the NMA, and no sensitivity or subgroup analyses (e.g. age, gender, severity of disease or smoking history/exposure) were reported.[13] It should also be highlighted that there were some reporting inconsistencies in one of the included SRs. This review had discrepancies between a study table and the text: the table reported a range of side effects of 16.9% to 38.2% for moxifloxacin while the text reported a range of 24.3% to 38.2%.[14] Additionally, while the authors noted that six RCTs of levofloxacin were included in the SR, the relevant figure suggested that one study was counted as separate trials (each of the 500 mg and 750 mg levofloxacin arms of the study are counted as a separate trial).[14] Furthermore, while the authors reported the pooled average efficacy for the study arms, they did not report the pooled efficacy of the control arms of those same studies.[14]

Non-Randomized Studies

A number of strengths were identified for the included non-randomized study. The study addressed a clearly focused issue, with a well-defined population and outcomes, and the study groups were recruited in an acceptable way. Additionally, baseline characteristics did not differ between groups, outcomes were measured objectively, and the follow-up of subjects was sufficiently long. However, the authors did not address or account for potential confounding factors and the authors identified that a further limitation was the lack of drug susceptibility testing in patients.[15]

Guidelines

Overall, the guidelines were conducted and reported well, and a number of strengths and limitations were identified through critical appraisal. All of the included guidelines described the objectives and populations of interest,[16-18] and two of the guidelines clearly described the health questions covered by the guideline.[16,17] Additionally, all three guidelines clearly defined the target users of the guideline, included the views of the target population as well as relevant professionals in the guideline development process, and the recommendations provided by all the guidelines were specific, and clearly identifiable.[16-18] The development of the guidelines was generally well reported. For instance, the search methods, selection criteria, and strengths and limitations of the evidence were well reported, however, the NICE 2018 guideline did not describe methods for formulating recommendations,[17] and none of the guidelines explicitly described updating procedures.[16-18] The facilitators and barriers to the application of recommendations in the BTS guideline was not described, and all guidelines lacked a description of resource implications and monitoring and/or auditing criteria.[16-18]

Summary of Findings

The summary of findings below are presented according to the research questions posed by this report. Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Fluoroquinolones

Two SRs were identified which assessed the clinical efficacy and safety of FQs, these examined antibiotic use in patients with bronchitis[13] and in patients with acute rhinosinusitis.[14]

In the MA and NMA of antibiotics in patients with bronchitis, the authors reported no significant differences across the included medications for total pathogen eradication. However, the results showed that patients treated with gemifloxacin had a lower risk of adverse events when compared to patients treated with amoxicillian + clavulanate (odds ratio (OR) = 0.58, 95% confidence interval (CI): 0.36 to 0.91). Furthermore, patients treated with FQs compared to amoxicillin + clavulanate had a reduced risk of diarrhea, including moxifloxacin (OR 0.39, 95% CI: 0.18 to 0.82), gemifloxacin (OR 0.22, 95% CI: 0.09 to 0.50) and gatifloxacin (OR 0.31, 95% CI: 0.13 to 0.85); this reduction was also observed among patients treated with levofloxacin compared to those treated with azithromycin (OR 0.41, 95% CI: 0.17–0.96). In the NMA, gatifloxacin and moxifloxacin performed better than clarithromycin with respect to pathogen eradication-H. influenzae (OR 21.37, 95% credible interval:1.22 to 541.28; and OR 7.43, 95% credible interval:1.79 to 30.50, respectively). Finally, the authors ranked medications using SUCRA values. For the FQs, the authors reported that gemifloxacin and levofloxacin had a relatively high ranking in total pathogen eradication efficacy. Though moxifloxacin revealed good performance in total pathogen eradication and pathogen eradication of H. influenzae, it was accompanied with a poor performance in pathogen eradication of S. pneumonia and all adverse effects.[13]

In the SR examining the efficacy and safety of antibiotics used in the treatment of acute rhinosinusitis, the FQs levofloxacin and moxifloxacin were included. Six RCTs of levofloxacin were identified by the SR, which reported efficacies (clinical success, resolution of ≥3 acute rhinosinusitis symptoms) over 86% (median efficacy 91.4%, range: 23.4 to 93.9%), though one study reported an efficacy of only 23.4%. Overall, four of the RCTs of levofloxacin showed minor side effect occurrences to be less than 22.5% (n = four), although two RCTs showed it to be around 40%; no major side effects were reported. For moxifloxacin, the majority of the included RCTs showed an efficacy (defined as clinical cure rates at test-of-cure visit) close to or above 90% (median efficacy 86%, range: not reported). The minor side effect profile of moxifloxacin ranged from 24.3% to 38.2% and no major side effects were observed. The authors noted that with the exception of one RCT, levofloxacin was shown to be the most effective medication.

The clinical effectiveness of FQs was retrospectively analyzed in one non-randomized study which compared patients treated with ceftriaxone sodium, ceftizoxime sodium, levofloxacin or azithromycin. The authors concluded that ceftriaxone sodium, ceftizoxime sodium, levofloxacin and azithromycin all had a good antimicrobial efficacy, with no statistically significant differences among the four groups in terms of the total effective rate (P>0.05). The total effective rate was 94%, 92%, 96% and 90%, for Group A (ceftriaxone sodium), Group B (ceftizoxime sodium), Group C (levofloxacin) and Group D (azithromycin), respectively. No adverse reactions occurred to patients in the four groups during treatment.[15]

Cost-Effectiveness

Though no cost-effectiveness analyses were identified, the non-randomized study of patients with LRTI reported some cost data. The authors reported that the treatment cost of levofloxacin was the lowest, noting that treatment expenses of patients in Group A (ceftriaxone sodium), Group B (ceftizoxime sodium) and Group D (azithromycin) were significantly increased compared with those in Group C (levofloxacin; $P<0.01$).[15]

Guidelines

The three included guidelines examined bronchiectasis (non-cystic fibrosis). The BTS guidelines recommends offering patients with bronchiectasis associated with clinical deterioration and a new growth of Pseudomonas aeruginosa eradication antibiotic treatment and suggests first line treatment with ciprofloxacin (500 to 750 mg bd for two weeks). The guideline noted that there was insufficient evidence to evaluate the efficacy of antibiotics in exacerbations in adults with bronchiectasis, but as 'good practice points' they highlight first and second line treatments for common pathogens implicated in exacerbations of bronchiectasis: ciprofloxacin is recommended as a first line treatment for Coliforms for example, Klebsiella, Enterobacter and Pseudomonas aeruginosa, as well as a second line treatment for Haemophilus influenzae- beta lactamase negative, Haemophilus influenzae- beta lactamase positive, Moraxella catarrhalis.[16]

For adults aged 18 years and older, in choosing an antibiotic for treating an acute exacerbation of bronchiectasis, NICE recommends levofloxacin (500mg twice a day for seven to 14 days) as an alternative choice oral antibiotic if the patient is at higher risk of treatment failure for empirical treatment in the absence of current susceptibility data. Levofloaxin (500mg once or twice a day) is recommended as a first-choice intravenous antibiotic if the patient is unable to take oral antibiotics or is severely unwell. For children and young people younger than 18 years, NICE recommends ciprofloxacin, on specialist advice, as an alternative choice of oral antibiotic or as a first-choice intravenous antibiotic if the patient is unable to take oral antibiotics or is severely unwell. It was noted that the Guideline Committee was aware of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommendation to restrict the use of FQ antibiotics for the treatment of mild or moderately severe infections unless other antibiotics cannot be used. The committee discussed that FQs are appropriate as an alternative option for people who may be at a higher risk of treatment failure, and that FQ safety concerns should be taken into account on an individual patient basis.[17]

The Thoracic Society of Australia and New Zealand guideline recommends that base antibiotic selection for exacerbations of CSLD/bronchiectasis be made based on lower airway culture results or bronchoalveolar lavage when available, as well as considerations regarding local antibiotic susceptibility patterns, clinical severity and patient tolerance. Ciprofloxacin is recommended for initial empiric therapy in children and adults with mild to moderate exacerbations, if Pseudomonas aeruginosa was in recent cultures.[18]

Limitations

There are several limitations that should be noted. Among the evidence identified related to the clinical effectiveness of FQs for other respiratory tract infections, it should be noted that a variety of indications are addressed. For instance, one study was identified for bronchitis, acute rhinosinusitis, and LRTIs respectively. The limited volume, and diverse outcomes of interest reported limits the interpretation of these study findings. Additionally, the

methodological concerns identified through critical appraisal of the included studies warrant further caution. In terms of the cost-effectiveness of FQs for other respiratory tract infections, no evidence was identified, and this remains an area for further research. While the included guidelines were generally well developed methodologically and produced similar recommendations for patients with bronchiectasis, the identified guidelines are intended for practice in the UK, Australia and New Zealand, and thus the recommendations may not be generalizable to the Canadian population.

Due to limitations in terms of volume of evidence, methodological concerns, and generalizability, caution should be used when interpreting the findings of this report.

Conclusions and Implications for Decision or Policy Making

Six publications describing clinical effectiveness, cost-effectiveness, and evidence-based guidelines for the use of FQs in patients with respiratory tract infections (excluding COPD, pneumonia, cystic fibrosis and tuberculosis) were identified in this report; of these, two are systematic reviews, one is a non-randomized study, and three are evidence-based guidelines. Specific findings were as follows:

Two SRs were identified and included in the current report, examining antibiotic use for the treatment of bronchitis[13] and acute rhinosinusitis.[14] The SR of bronchitis examined several FQs, such as gemifloxacin, moxifloxacin, gatifloxacin, and levofloxacin. While no significant differences in total pathogen eradication between antibiotics were shown in the MA or NMA, the authors used SUCRA values to rank the medications, which demonstrated that gemifloxacin and levofloxacin had a relatively high ranking in total pathogen eradication efficacy.[13] The SR examining the efficacy and safety of antibiotics used in the treatment of acute rhinosinusitis, included two FQs: levofloxacin and moxifloxacin. The authors reported that levofloxacin was shown to be an effective treatment option.[14] Finally, a retrospective analysis of patients with LRTI treated with ceftriaxone sodium, ceftizoxime sodium, levofloxacin or azithromycin found no statistically significant differences among the four groups in terms of the total effective rate; no adverse reactions during the treatment period occurred.[15]

No cost-effectiveness analyses were identified for inclusion in this report.

The three included guidelines examined bronchiectasis (non-cystic fibrosis) and provided similar recommendations; overall, the guidelines recommended the use of FQs for limited populations. Both the BTS and Thoracic Society of Australia and New Zealand guidelines recommend ciprofloxacin for the first line treatment of patients with bronchiectasis associated with Pseudomonas aeruginosa.[16,18] NICE recommends FQs as an alternative choice oral antibiotic for patients at higher risk of treatment failure and as a first-choice intravenous antibiotic if the patient is unable to take oral antibiotics of is severely unwell; recommending levofloxacin for adult patients and ciprofloxacin for people younger than 18 years, on specialist advice.[17]

While the three guidelines provided similar recommendations for the use of FQs in the treatment of bronchiectasis (non-cystic fibrosis), the variable findings and methodological limitations in the body of evidence identified for other conditions, including bronchitis and acute rhinosinusitis, to inform this report limit generalizability and warrant caution in its interpretation for the clinical effectiveness and cost-effectiveness of FQs for the treatment of respiratory tract infections. Further evidence regarding the clinical efficacy, safety and cost-effectiveness of FQs in treating respiratory tract infections, particularly in the Canadian

context, is needed to provide guidance on the appropriate use of FQs for the treatment of respiratory tract infections.

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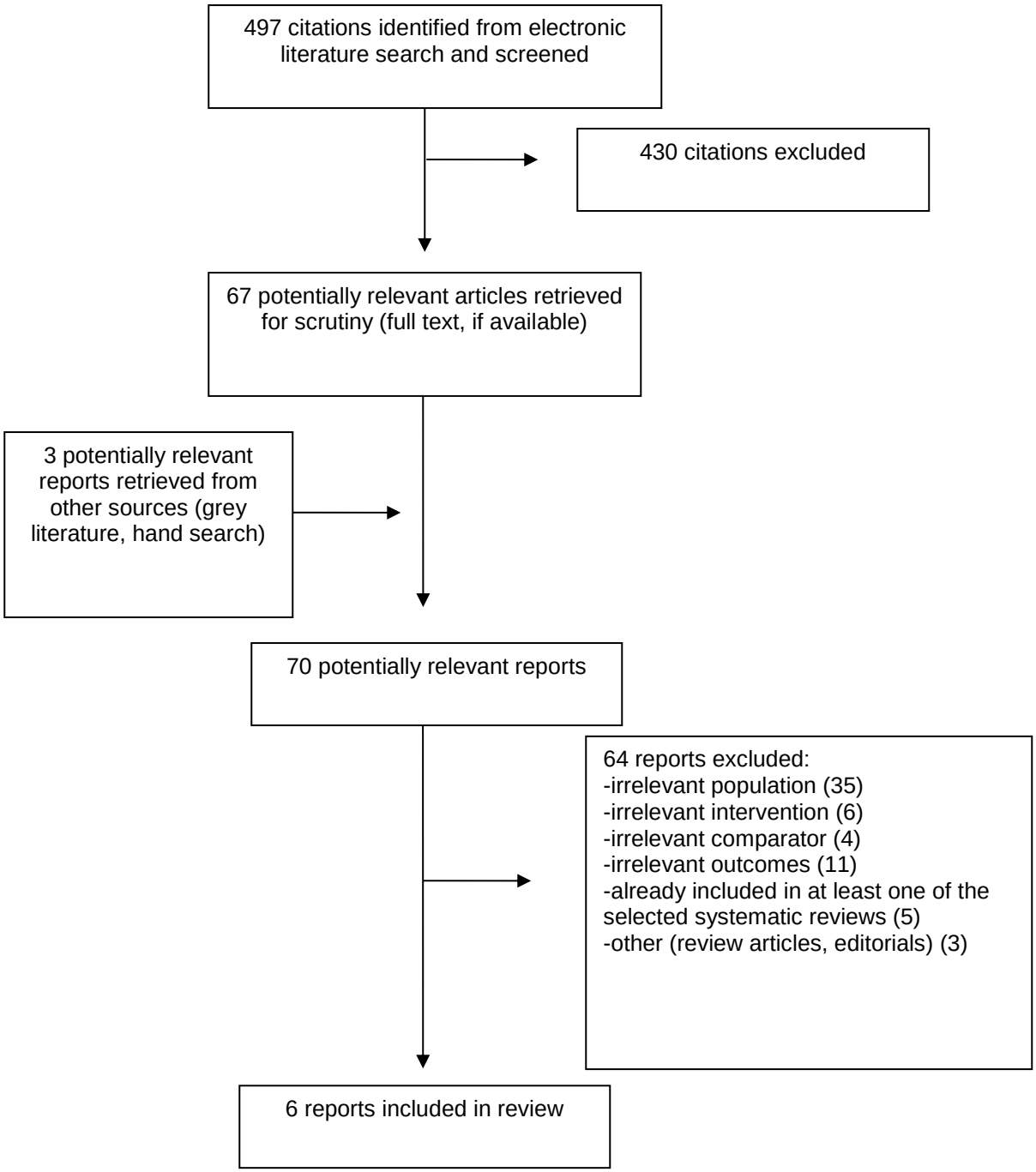
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wang et al., 2017, China[13]	• 27 RCTs included • RCTs relevant to this report, n= 13	Adults diagnosed with bronchitis	Various bronchitis anti-bacterial therapies: ampicillin, azithromycin, amoxicillin-clavulanate, clarithromycin, dirithromycin, telithromycin and FQs (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin)	Primary Outcomes • Efficacy: total pathogen eradication • Safety: total incidence of adverse effects Secondary Outcomes • Efficacy: pathogen eradication of: H. influenzae, M. catarrhalis, S. pneumonia • Safety: incidence of diarrhea Length of follow-up: Not reported
Sng et al., 2015, Singapore[14]	• 31 RCTs included • RCTs relevant to this report, n=10	Symptomatic patients with clinical and/or radiological and/or bacteriological diagnosis of ARS	Common antibiotics used for ARS: (cefuroxime axetil, telithromycin, amoxicillin/potassium clavulanate, clarithromycin, and FQs (levofloxacin, moxifloxacin)) or placebo (Antibiotics with at least 5 independent studies or more were included)	Primary outcome • Clinical cure rate (based on clinical symptoms and physical and/or endoscopic exam findings) at test-of cure visit Secondary outcomes • Radiological or bacteriological cure rate • Adverse events Length of follow-up: Not reported

ARS = acute rhinosinusitis; FQ = fluoroquinolone; RCT = randomized controlled trial

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Zhang, 2018, China[15]	Retrospective cohort study	Patients with LRTI treated in the Department of Respiratory Medicine of Dongying People's	Group A: ceftriaxone sodium (IV infusion of 2.0 g ceftriaxone sodium injection + 100 ml 9% sodium chloride	• White blood cells of venous blood pre and post treatment • C-reactive protein

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Hospital between February 2015-May 2017 Group A: 21 males, 29 females, mean age of 35.44±16 years Group B: 23 males, 27 females, mean age of 35.14±2.01 years Group C: 19 males, 26 females, mean age 34.52±2.35 years Group D: 24 males, 26 females, mean age of 34.68±2.46 years	injection; 2 times/day) Group B: ceftizoxime sodium (IV infusion of 2.0 g ceftizoxime sodium + 100 ml 9% sodium chloride injection; 2 times/day) Group C: levofloxacin (IV infusion of 0.3 g levofloxacin + 100 ml 9% sodium chloride injection; 2 times/ day) Group D: azithromycin (IV infusion of 1.0 g azithromycin + 100 ml 9% sodium chloride injection; 2 times/day).	<u>Therapeutic effect</u>: • Cured: symptom disappearance, no adverse reactions, normal QoL • Effective: improved symptoms, no adverse reactions, improved QoL • Ineffective: symptoms not improved, adverse reactions, poor QoL

IV = intravenous; LRTI = lower respiratory tract infection; QoL = quality of life; RCT = randomized controlled trial

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Hill, 2019, UK[16]						
This guideline is aimed at all healthcare practitioners who are involved in the care of patients with bronchiectasis including: primary care clinicians (GPs, practice and district nurses), hospital specialist teams (infectious disease and respiratory medicine), microbiologists, and radiologists Target population: adults (>15 years) with non-CF bronchiectasis)	A stepwise management plan including diagnostic (e.g., imaging, microbiology and lab tests), therapeutic approaches (e.g., airway clearance techniques, pulmonary rehabilitation, anti-inflammatory drugs, mucoactives, antibiotics, and surgery) and monitoring of bronchiectasis based on severity and stability of symptoms *Outside the scope of report:* It also presents applicable recommendations for bronchiectasis associated with CF, ABPA, common variable immune deficiency, NTM, coexistent asthma, COPD, and ILD	Clinical (e.g., lung function capacity, sputum production, severity of disease, exacerbation frequency, side effects), microbiological (e.g., sputum cultures), and QOL. (Appendix 8)	A systematic search of electronic databases (Ovid MEDLINE, Ovid EMBASE, and the Cochrane Library) from inception up to June 2016 was carried out to address the predefined clinical questions. Titles and abstracts were screened (3 reviewers); potentially relevant citations were allocated to proper sections of the guideline and were subjected to full-text review (2 reviewers). Synthesis was based on available evidence and/or expert consensus	The two reviewers for each section independently appraised and graded their assigned papers using the SIGN critical appraisal checklist. The body of evidence for each recommendation was summarized into evidence statements and graded using the SIGN grading system. "Appraisal was performed to be compliant with the AGREE collaboration" (p.10)	Recommendations were formulated based on body of evidence (evidence tables). When evidence was not available, expert consensus was obtained. Grading of recommendations was based on the strength, volume, applicability to the target audience, generalizability, and consistency of evidence plus deliverability in clinical practice: grades A – D, and √ for good clinical practice points (no evidence)	Peer review by the BTS Standards of Care Committee Public and stakeholders consultation
NICE, 2018, England[17]						
This guideline is intended for health professionals, people with bronchiectasis, their families and care	The guideline sets out an antimicrobial prescribing strategy for managing and	Critical outcomes: • Reduction in	A systematic literature search of online databases (Cochrane Central Register of	The GRADE approach was utilized; however, the strength of	As limited evidence base for antibiotic therapy in acute exacerbation of	Consultation with stakeholders

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
givers The target population are people with non-CF bronchiectasis	preventing acute exacerbations of non-CF bronchiectasis	symptoms (duration or severity) • Time to clinical cure • Rate of complications (including mortality) • Health and social care utilization • Thresholds or indications for antimicrobial treatment	Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Effectiveness, Embase via Ovid, Health Technology Assessment (HTA) via Wiley, MEDLINE via Ovid, MEDLINE-in-Process via Ovid) was conducted. Titles and abstracts followed by full text references were assessed for relevance in duplicate (10% of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%) The methods for evidence synthesis are not explained in the main guideline or the evidence review document (according to interim process guide 2017)	recommendations is not presented in the guideline. (The online "Evidence review" document presents the GRADE profiles for the included studies).	bronchiectasis exists (e.g. choice and length of therapy) all recommendations were informed by committee consensus (based on experience)	
Thoracic Society of Australia and New Zealand, 2014[18]						
The guideline is intended for primary and secondary care practitioners (not intended for individualized specialist care)	The guideline provides recommendations on: • Diagnostic	• Symptom control (e.g., reduced sputum volume and purulence,	An updated* systematic search for assigned recommendations was conducted by a member of the writing group (PubMed and	The quality of evidence was assessed using GRADE and rated as:	Recommendations were updated based on available evidence and by complete agreement within the writing group	External independent review and feedback to writing group

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Target population includes children and adults with chronic non-CF CSLD and bronchiectasis in Australia and New Zealand	investigations • Management (e.g., pharmacological interventions, airway clearance techniques, pulmonary rehabilitation, life-style changes, immunisations) • Health care delivery (e.g. indigenous populations in rural areas)	improved cough character (wet to dry or cessation of cough) • Preserve lung function • Optimize the Quality of life • Reduce exacerbation frequency • Enhance survival	Cochrane Central Library databases, up to Oct 2013). Only full-text English papers were retrieved. *This guideline presents an update from previous recommendations published in 2008 and 2010.	• High: further research is very unlikely to change our confidence in the estimate of effect. •Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • Very low: any estimate of effect is very uncertain.	(modified Delphi method). Strength of recommendations based on GRADE were assigned by voting (agreement by >75% of the writing group was defined as consensus) and categorized into: “strong”, “weak”, or “no specific recommendation”	

ABPA = allergic bronchopulmonary aspergillosis; AGREE = Appraisal of Guidelines for Research and Evaluation II; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; CSLD = chronic suppurative lung disease; GP = General Practitioner; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ILD = interstitial lung disease; NTM = nontuberculous mycobacteria; QoL = quality of life; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR-2[9]

Strengths	Limitations
Wang, 2017[13]	
• The research question and inclusion criteria of the review included population, intervention, comparator, and outcomes of interest • The authors provided key search terms and searched at least two databases, and references of selected studies were searched. • Study selection and data extraction was performed in duplicate • The authors described the populations, interventions (including dosage), comparators, outcomes and research designs of included studies and mentioned the majority of studies were multicenter • The authors provided methodological details for the meta-analysis and used an appropriate techniques to combine study results and to adjust for heterogeneity if present • The authors explained the potential impact of heterogeneity in evidence on the results of meta-analysis • The authors reported no conflicts of interests	• The review did not provide an explicit statement that the review methods/protocol were established prior to the conduct of the review • The authors did not explain their selection of study designs for inclusion in the review • The authors didn't search the trial registries and sources of grey literature and the search date was not defined • A list of excluded studies was not provided • The authors didn't assess the risk of bias in included studies • The authors did not report the sources of funding for the included studies • The authors did not assess the potential impact of risk of bias in individual studies on the results of meta-analysis (no regression or subset analysis) • The authors did not account for the risk of bias in the individual studies when interpreting/discussing the results • The authors did not carry out an investigation of publication bias • The authors did not provide details regarding the assessment of consistency of trials (e.g. what baseline characteristics were considered), • The authors not state whether a random or fixed-effects model was utilized for the NMA, • No sensitivity or subgroup analyses (e.g. age, gender, severity of disease or smoking history/exposure) for the NMA were reported. •
Sng, 2015[14]	
• The research question and inclusion criteria of the review included population, intervention, comparator, and outcomes of interest. • The authors provided their search key words • Study selection and data extraction was performed in duplicate. • The authors reported no conflicts of interests.	• The review did not provide an explicit statement that the review methods/protocol were established prior to the conduct of the review. • The authors did not explain their selection of study designs for inclusion in the review. • The authors searched only one online database (PubMed) and no other sources. • Non-English language articles were excluded • Antibiotics with less than 5 independent studies retrieved were excluded • A list of excluded studies was not provided. • The authors didn't describe the populations and comparators of the studies pooled for each intervention. • The authors didn't assess the risk of bias in included studies • The authors did not report the sources of funding for the included studies.

	• The authors did not account for the risk of bias in the individual studies when interpreting/discussing the results • The authors noted heterogeneity in the population (different definitions of acute rhinosinusitis) but did not provide an explanation or discussion of the heterogeneity. • The authors did not carry out an investigation of publication bias.

RCT = abbreviation,

Table 6: Strengths and Limitations of Clinical Studies using CASP[10]

Strengths	Limitations
Zhang, 2018[15]	
• The study addressed a clearly focused issue, with a focused population and outcomes • The study cohorts were recruited acceptably, with eligible patients randomly assigned to treatment groups • Baseline characteristics did not differ between groups • The outcomes were objectively measured, and methods with similar across groups • The follow-up of subjects was sufficient	• The authors did not address or account for confounding factors • Drug resistance mechanisms were not conducted

Table 7: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline		
	HILL, 2019[16]	NICE, 2018[17]	Thoracic Society of Australia and New Zealand 2014[18]
Domain 1: Scope and Purpose			
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Unclear
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes
Domain 2: Stakeholder Involvement			
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes

Table 7: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline		
Domain 3: Rigour of Development			
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	No	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Unclear	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes	Yes
14. A procedure for updating the guideline is provided.	No	No	Yes
Domain 4: Clarity of Presentation			
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes
Domain 5: Applicability			
18. The guideline describes facilitators and barriers to its application.	No	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	Unclear
20. The potential resource implications of applying the recommendations have been considered.	No	No	No
21. The guideline presents monitoring and/or auditing criteria.	No	No	No
Domain 6: Editorial Independence			
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Wang, 2017[13]	
Pairwise meta-analysis: Among all direct comparisons of FQs vs other antibiotics, no significant difference was observed for any pathogen eradication outcomes: **Total pathogen eradication: OR (95% CI)** • Levofloxacin vs. Amoxicillin-Clavulanate: 1.02 (0.65, 1.59) • Moxifloxacin vs. Amoxicillin-Clavulanate: 0.98 (0.64, 1.50) • Gemifloxacin vs. Amoxicillin-Clavulanate: 1.14 (0.61, 2.11) • Gatifloxacin vs. Amoxicillin-Clavulanate: 1.10 (0.71, 1.71) • Levofloxacin vs. Azithromycin: 1.07 (0.72, 1.60) • Moxifloxacin vs. Azithromycin: 1.00 (0.74, 1.37) • Gemifloxacin vs. Clarithromycin: 1.14 (0.64, 2.03) • Moxifloxacin vs. Clarithromycin: 1.11 (0.87, 1.41) • Gatifloxacin vs. Clarithromycin: 0.98 (0.67, 1.41) • Levofloxacin vs. Gemifloxacin: 1.07 (0.61, 1.85) **Pathogen eradication--H.influenzae: OR (95% CI)** • Levofloxacin vs. Amoxicillin-Clavulanate: 0.84 (0.37, 1.89) • Moxifloxacin vs. Amoxicillin-Clavulanate: - • Gemifloxacin vs. Amoxicillin-Clavulanate: 1.19 (0.34, 4.13) • Gatifloxacin vs. Amoxicillin-Clavulanate: 1.10 (0.55, 2.20) • Levofloxacin vs. Azithromycin: 1.04 (0.52, 2.08) • Moxifloxacin vs. Azithromycin: 1.03 (0.59, 1.79) • Gemifloxacin vs. Clarithromycin: - • Moxifloxacin vs. Clarithromycin: 1.40 (0.91, 2.16) • Gatifloxacin vs. Clarithromycin: - • Levofloxacin vs. Gemifloxacin: 0.91 (0.27, 3.04) **Pathogen eradication-M.Catarrhalis: OR (95% CI)** • Levofloxacin vs. Amoxicillin-Clavulanate: 0.99 (0.33, 2.88) • Moxifloxacin vs. Amoxicillin-Clavulanate: - • Gemifloxacin vs. Amoxicillin-Clavulanate: 0.95 (0.34, 2.65) • Gatifloxacin vs. Amoxicillin-Clavulanate: 0.88 (0.22, 3.49) • Levofloxacin vs. Azithromycin: 1.03 (0.47, 2.26) • Moxifloxacin vs. Azithromycin: 1.05 (0.54, 2.05) • Gemifloxacin vs. Clarithromycin: - • Moxifloxacin vs. Clarithromycin: 0.97 (0.56, 1.67) • Gatifloxacin vs. Clarithromycin: - • Levofloxacin vs. Gemifloxacin: 1.31 (0.34, 5.00) **Pathogen eradication-S.Pneumonia: OR (95% CI)** • Levofloxacin vs. Amoxicillin-Clavulanate: 0.99 (0.33, 2.88) • Moxifloxacin vs. Amoxicillin-Clavulanate: - • Gemifloxacin vs. Amoxicillin-Clavulanate: 0.98 (0.26, 3.66) • Gatifloxacin vs. Amoxicillin-Clavulanate: 0.86 (0.31, 2.32)	"In conclusion gemifloxacin and levofloxacin are more preferable than others for lowering respiratory tract inflammation and infections considering their balanced performance between pathogen eradication and adverse effects". (p.3181)

- Levofloxacin vs. Azithromycin: 1.04 (0.34, 3.15)
- Moxifloxacin vs. Azithromycin: 0.95 (0.42, 2.12)
- Gemifloxacin vs. Clarithromycin: -
- Moxifloxacin vs. Clarithromycin: 0.96 (0.59, 5.86)
- Gatifloxacin vs. Clarithromycin: -
- Levofloxacin vs. Gemifloxacin: 1.06 (0.14, 7.82)

Total adverse effects OR (95% CI)

- Levofloxacin vs. Amoxicillin-Clavulanate: 0.97 (0.47, 2.01)
  Moxifloxacin vs. Amoxicillin-Clavulanate: 0.86 (0.56, 1.33
- Gemifloxacin vs Amoxicillin-Clavulanate: 0.58 (0.36, 0.91)
- Gatifloxacin vs. Amoxicillin-Clavulanate: 0.75 (0.43, 1.30)
- Levofloxacin vs. Azithromycin: 0.96 (0.58, 1.57)
- Moxifloxacin vs. Azithromycin: 1.09 (0.77, 1.53)
- Gemifloxacin vs. Clarithromycin: 0.74 (0.52, 1.06)
- Moxifloxacin vs. Clarithromycin: 1.32 (0.72, 2.42)
- Gatifloxacin vs. Clarithromycin: -
- Levofloxacin vs. Gemifloxacin: 0.82 (0.55, 1.22)

Diarrhea OR (95% CI)

- Levofloxacin vs. Amoxicillin-Clavulanate: 0.71 (0.31,1.59)
- Moxifloxacin vs Amoxicillin-clavulanate: 0.39 (0.18, 0.82)
- Gemifloxacin vs Amoxicillin-clavulanate: 0.22 (0.09, 0.50)
- Gatifloxacin vs Amoxicillin-clavulanate: 0.33 (0.13, 0.85)
- Levofloxacin vs Azithromycin: 0.41 (0.17, 0.96)
- Moxifloxacin vs. Azithromycin: 0.68 (0.33,1.41)
- Gemifloxacin vs. Clarithromycin: 0.73 (0.39,1.37)
- Moxifloxacin vs. Clarithromycin: 0.94 (0.57,1.53)
- Gatifloxacin vs. Clarithromycin: -
- Levofloxacin vs. Gemifloxacin: 0.51 (0.17,1.52)

NMA results: (based on Bayesian framework and Markov Chain Monte Carlo (MCMC) simulations)

Indirect comparisons

- There was no significant difference in the relative efficacy of antibacterial medications for total, M. catarrhalis and S. pneumonia pathogen eradication outcomes.

Pathogen eradication-H.influenzae (OR, 95% Credible Interval (Crl))

- Gatifloxacin and Moxifloxacin exhibited better performance than Clarithromycin: (OR=21.37, CrI: 1.22–541.28; OR=7.43, CrI: 1.79–30.50, respectively)
- Telithromycin showed worse performance vs Gatifloxacin and Moxifloxacin (OR=0.03 CrI: 0.01–0.65; OR=0.07, CrI: 0.01–0.73, respectively)
- The results for other indirect comparison of FQs were not significantly different.

Total adverse effects

- Telithromycin was safer than moxifloxacin (OR=0.41, CrI: 0.17–0.96)
- The results for other indirect comparison of FQs were not significantly different.

Diarrhea (OR, 95% CrI) • Levofloxacin vs. Amoxicillin-Clavulanate: 0.38 (0.18, 0.77) • Moxifloxacin vs. Amoxicillin-Clavulanate: 0.44 (0.23, 0.78) • Gemifloxacin vs. Amoxicillin-Clavulanate: 0.31 (0.16, 0.63) • Gatifloxacin vs. Amoxicillin-Clavulanate: 0.31 (0.10, 0.99) • Levofloxacin vs. Azithromycin: 0.38 (0.17, 0.79) • Moxifloxacin vs. Azithromycin: 0.44 (0.20, 0.86) • Gemifloxacin, vs. Azithromycin: 0.32 (0.13, 0.74) • The results for other indirect comparison of FQs were not significantly different. • The node-splitting forest plots showed consistency between direct and indirect evidence was overall satisfactory among the majority of comparisons (except for clarithromycin vs azithromycin in total pathogen eradication) • Ranking of treatments based on SUCRA probability scores found that Gemifloxacin (76%) and Levofloxacin (72%) had a relatively high ranking in terms of total pathogen eradication. • Though moxifloxacin revealed good performance in total pathogen eradication (0.59%) and pathogen eradication of H. influenza (073%), it was accompanied with a poor performance in pathogen eradication of S. pneumonia (0.33) and all adverse effects (0.24%) • According to SUCRA cluster analysis Gemifloxacin and Levofloxacin were recommended as the first-line treatments for bronchitis (with respect to high total pathogen eradication and low rate of adverse effects)	
Sng, 2015[14]	
Levofloxacin (500-750 mg/day, 5-10 days): 6 RCTs, n=1050 Efficacy • The median clinical success rate among studies (resolution of > or = 3 ARS symptoms) was reported as 91.4% (range: 23.4%-93.9%) Adverse effects • The range of minor side effects was reported as 15.3%-39.8% among the studies • No major side effects reported **Moxifloxacin (400 mg/day, 5-10 days):** 5 RCTs, n=937 Efficacy • The median clinical cure rate (at test-of cure visits) was reported as 86% Adverse effects • The range of minor side effects was reported as 16.9% - 38.2% among the studies • No major side effects reported	"Clinical studies have found that while antibiotics are efficacious in treating ARS, there is a large placebo effect present as well, which may be due in part to the natural course of the disease. The side effects of antibiotics to treat ARS must be balanced against the therapeutic effect of antibiotics. Larger double-blind placebo controlled studies should be performed to effectively evaluate the true efficacy of antibiotics in the treatment of ARS". (p.8) Relevant to the scope of this report: "Levofloxacin has been shown to have a high efficacy in the treatment of ARS with a high safety profile, and side effect being minor and predominantly gastrointestinal in nature. More research should be done to assess its viability as a first line antibiotic of choice in the treatment of ARS". (p.7)

Note: No results regarding any comparison between antibiotics and/or placebo was presented.	

ARS=Acute Rhinosinusitis; CI = confidence interval; CrL = credible interval; FQ = fluoroquinolone; OR = odds ratio; NMA = network meta-analysis; RCT = randomized controlled trial; SUCRA = surface under the cumulative ranking curve

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Zhang, 2018[15]	
WBC counts in the 4 groups of patients before and after treatment: No statistically significant differences were found in the WBC count in patients among the 4 groups at 1 day before treatment and at 1, 4 and 7 days after treatment (*P*>0.05). **CRP in the 4 groups of patients before and after treatment:** There were no statistically significant differences in the CRP measured value in patients among the 4 groups at 1 day before treatment and at 1, 4 and 7 days after treatment (*P*>0.05). **Therapeutic effects in the 4 groups of patients:** • Group A, ceftriaxone sodium: ○ 21 cured cases (42.00%), 26 effective cases (52.00%), 3 ineffective cases (6.00%) ○ Total effective rate of 94.00% • Group B, ceftizoxime sodium: ○ 19 cured cases (38.00%), 27 effective cases (54.00%), 4 ineffective cases (8.00%) ○ Total effective rate of 92.00% • Group C, levofloxacin: ○ 24 cured cases (48.00%), 24 effective cases (48.00%), 2 ineffective case (4.00%) ○ Total effective rate of 96.00% • Group D, azithromycin: ○ 20 cured cases (40.00%), 25 effective cases (50.00%), 5 ineffective cases (10.00%) ○ Total effective rate of 90.00% • The total effective rate indicated no statistically significant difference among the 4 groups of patients (P>0.05) • No adverse reactions occurred in the 4 groups of patients during treatment. **Treatment costs in the 4 groups of patients:** • Treatment Costs ○ Group A, ceftriaxone sodium: 1037.15±126.51 yuan ○ Group B, ceftizoxime sodium: 1451.38±134.55 yuan ○ Group C, levofloxacin: 983.67±86.37 yuan ○ Group D, azithromycin: 1537.45±146.59 yuan • Compared with that in Group C, treatment costs of patients were significantly increased in Group A, Group B and Group D (*P*<0.01). • Compared with that in Group A, treatment costs of patients	"In conclusion, ceftriaxone sodium, ceftizoxime sodium, levofloxacin, and azithromycin have excellent antibacterial efficacy. WBC and CRP can be used to dynamically monitor the treatment of LRTI and accurately observe the disease evolution and treatment effect on patients. The treatment cost of levofloxacin is the lowest in economic terms; thus, it is worthy of clinical promotion and application." (p. 2373)

were remarkably increased in Group B and Group D (P<0.01). • Compared with that in Group B, the treatment cost of patients in Group D was increased obviously (P<0.01)	

CRP = C-reactive protein, LRTI = lower respiratory tract infection, WBC = while blood cells

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Hill, 2019[16]	
Clinical question: "**Does eradication of potentially pathogenic microorganisms improve outcomes in patients with stable bronchiectasis**? **Recommendation:** • Offer patients with bronchiectasis associated with clinical deterioration and a new growth of P. aeruginosa (first isolation or regrowth in the context of intermittently positive cultures) eradication antibiotic treatment (first-line treatment: ciprofloxacin 500–750 mg twice per day for 2 weeks…)" (p 6) • "Discuss with patients the potential risks and benefits of starting eradication antibiotic treatment versus clinical observation following a new growth of P. aeruginosa in the context of stable bronchiectasis. This will include consideration of the likelihood of achieving sustained eradication, the risk of developing chronic infection, and the risk of adverse events with each management approach" (p 6, 7)	• **Grade D recommendations** • The **level of evidence** regarding first-line ciprofloxacin therapy: 2 RCTs, level **1+** 1 retrospective study, level **2+**
Clinical question: Does antibiotic therapy improve outcomes in patients with an exacerbation of bronchiectasis? **Good practice points:** ✓ Prompt antibiotic therapy based on previous sputum bacteriology: • Ciprofloxacin 500 mg or 750 mg twice a day for 14 days as second line therapy for Haemophilus influenzae—beta lactamase negative and positive, and Moraxella catarrhalis • Oral ciprofloxacin 500 mg or 750 mg twice a day for 14 days as first line therapy for Coliforms, e.g., Klebsiella, Enterobacter • Oral ciprofloxacin 500 mg twice a day (750 mg twice a day in more severe infections) for 14 days as first line for Pseudomonas aeruginosa	**Grade ✓ recommendation (Good practice points)** **Evidence statement**: There is insufficient evidence to evaluate the efficacy of antibiotics in exacerbations in adults with bronchiectasis **(Level 2-)**
Good practice points ✓ Where possible, treatment should be guided by antibiotic sensitivity results but is often empirical based on previous sputum bacteriology.	**Evidence statement**: there is no evidence to show that antibiotic treatment guided by sensitivity results improves clinical outcomes for patients. Acute antibiotic treatment only occasionally results in the development of resistance. (1-)

NICE, 2018[17]	
Choice of antibiotic for treating an acute exacerbation <u>Adults aged 18 years and over</u> • **Empirical treatment** • Levofloxacin* 500 mg once or twice a day for 7 to 14 days is recommended as an "alternative choice oral antibiotic" • Levofloxacin* 500 mg once or twice a day is recommended as a "first choice intravenous antibiotics" (if unable to take oral antibiotics or severely unwell). • Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible for a total antibiotic course of 7 to 14 days. • **When current susceptibility data available, choose antibiotics accordingly** <u>Children and young people (1 to 17 years)</u> • **Empirical treatment** • Ciprofloxacin* 20 mg/kg twice daily (maximum 750 mg per dose) for 7 to 14 days is recommended as an "alternative choice oral antibiotic" (on specialist advice) • Ciprofloxacin* 10 mg/kg three times a day (maximum 400 mg per dose) is recommended on specialist advice as a "first choice intravenous antibiotics" (if unable to take oral antibiotics or severely unwell) • Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics • where possible for a total antibiotic course of 7 to 14 days. • **When current susceptibility data available, choose antibiotics accordingly** *The committee was aware of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommendation to restrict the use of fluoroquinolone antibiotics following a review of disabling and potentially long-lasting side effects mainly involving muscles, tendons and bones and the nervous system (press release October 2018). This includes a recommendation to not use them for mild or moderately severe infections unless other antibiotics cannot be used. The committee discussed that fluoroquinolones are appropriate as an alternative option for people who may be at a higher risk of treatment failure. However, the committee was keen to point out that fluoroquinolone safety concerns should be taken into account on an individual patient basis" (p.19) **Choice of antibiotic for prophylaxis of acute exacerbations** "Based on evidence and experience, the committee agreed that people should not routinely be offered antibiotic prophylaxis to	"Very limited evidence was identified to guide the choice of antibiotic for treating an acute exacerbation of bronchiectasis" (p.15) "Very limited evidence was identified to guide the duration of antibiotics for treating an acute exacerbation of bronchiectasis" (p.16) The Grading and strength of recommendations are not reported; however, they were all made based on the committee's "experience"

prevent acute exacerbations, because of the balance of risks and benefits in the overall population" (p.17) "The committee were unable to make specific recommendations on the choice of antibiotic for prophylaxis, because this will be an individualised decision based on the clinical needs of the person, their preferences and advice from a specialist" (p.18)	
Thoracic Society of Australia and New Zealand, 2014[18]	

Mild-moderate exacerbation of CSLD/bronchiectasis, Oral therapy:
 	
• **Initial (empiric) antibiotic therapy in children and adults:**
  ○ Ciprofloxacin if P. aeruginosa positive in *recent* cultures (children and adults)*
• **For P. aeruginosa positive cultures:**
  • Oral Ciprofloxacin (max 14 days)
 	
* Aminoglycosides, macrolides and fluoroquinolones in particular should be used with care in the elderly (page 9, box 3, footnote)
 	
Long term antibiotic suppression therapy:
 	
"New inhaled antibiotic formulations (e.g. ciprofloxacin, amikacin) are currently undergoing clinical trials to determine if they have a role in managing non-CF bronchiectasis" in long term suppression (p. 6)
	GRADE of recommendation: Strong;
	Level of evidence: Moderate
	
	Evidence: One double blind RCT (42 adults with Pa, mixture of liposomal and free ciprofloxacin, alternating 28-day cycles on and off therapy for 6 months reduced the odds of an antibiotic treated exacerbation by 80%. (Table 3, p.14)

CF = cystic fibrosis; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Wang 2017[13]	Sng 2015[14]
Aldons 1991	X	
Bachand 1991	X	
Guay and Craft 1992	X	
Bradbury 1993	X	
Pozzi 1994	X	
Beghi 1995	X	
Gris 1996	X	
Hoepelman 1998	X	
Cazzola 1999	X	
Wilson 1999	X	
Wilson 2002	X	
Chodosh 2000	X	
DeAbate 2000	X	
File 2000	X	
Anzueto 2001	X	
Gotfried 2001	X	
Martinot 2001	X	
Schaberg 2001	X	
Aubier 2002	X	
Amsden 2003	X	
Soler et al 2003	X	
Sethi 2004	X	
Starakis 2004	X	
Fogarty 2005	X	
Martinez 2005	X	
Zervos 2007	X	
Upchurch 2006		X
Tellier 2005		X
Gehanno 2004		X
Buchanan 2003		X

Siegert 2003		X
Siegert 2009		X
Burke 1999		X
Henry 1999		X
Gehanno 1996		X
Kristo 2005		X
Ferguson 2004		X
Luterman 2003		X
Roos 2002		X
Henry 2003		X
Wald 2009		X
Seggev 1998		X
Marple 2007		X
Poole 2006		X
Murray 2005		X
Henry 2004		X
Lasko 1998		X
Klossek 2003		X
Clifford 1999		X
Murray 2000		X
Wald 1986		X
Lindbaek 1996		X
Stalman 1997		X
Hansen 2000		X
Varonen 2003		X
Hadley 2010		X

Appendix 6: Additional References of Potential Interest

Related CADTH Reports

1. Fluoroquinolone prescribing and use in Canadian primary care practice. *(CADTH Technology review no. 5)*. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/fluoroquinolone-prescribing-and-use-canadian-primary-care-practice-0. Accessed 2019 May 6.

2. Colistin for prophylactic use in non-cystic fibrosis bronchiectasis or COPD with exacerbations: a review of clinical and cost-effectiveness and guidelines. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/colistin-prophylactic-use-non-cystic-fibrosis-bronchiectasis-or-copd-exacerbations-review-clinical . Accessed 2019 May 6.

3. The new fluoroquinolones in community-acquired pneumonia: clinical and economic perspectives. *(CCOHTA Health technology assessment)* Ottawa (ON): CCOHTA; 2001: https://www.cadth.ca/new-fluoroquinolones-community-acquired-pneumonia-clinical-and-economic-evaluation-0. Accessed 2019 May 6.

4. Clinical and economic considerations in the use of fluoroquinolones. *(CCOHTA Technology overview).* Ottawa (ON): CCOHTA. 1997: https://www.cadth.ca/clinical-and-economic-considerations-use-fluoroquinolones-0. Accessed 2019 May 6.

5. Fluoroquinolones for the treatment of otitis media: a review of clinical effectiveness, cost-effectiveness, and guidelines. *(CADTH Rapid response report: summary with critical appraisal).* Ottawa (ON): CADTH; 2019: https://www.cadth.ca/fluoroquinolones-treatment-otitis-media-review-clinical-effectiveness-cost-effectiveness-and-0. Accessed 2019 May 6.

6. Fluoroquinolones for the treatment of intra-abdominal infections: a review of clinical effectiveness, cost-effectiveness, and guidelines. *(CADTH Rapid response report: summary with critical appraisal).* Ottawa (ON): CADTH; 2019: https://www.cadth.ca/fluoroquinolones-treatment-intra-abdominal-infections-review-clinical-effectiveness-cost. Accessed 2019 May 6.