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Antibiotic Coverage in Atypical Pathogens for Adults Hospitalized With Community-Acquired Pneumonia: A Rapid Review

Health Quality Ontario

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Evidence Development and Standards Branch at Health Quality Ontario

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http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

Conflict of Interest Statement

All reports prepared by the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Clinical questions are developed by the Evidence Development and Standards branch at Health Quality Ontario in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to a maximum of 2 outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short time frames, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Evidence Development and Standards and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systemic Reviews
CAP	Community-acquired pneumonia
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HQO	Health Quality Ontario
ICU	Intensive Care Unit
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Funding (QBF) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Funding initiative, visit www.hqontario.ca.

Objective of Analysis

This rapid review aims to assess the effectiveness of regimens containing antibiotic coverage for atypical pathogens compared with regimens containing antibiotic coverage for typical pathogens.

Clinical Need and Target Population

Community-acquired pneumonia (CAP) is a common condition worldwide that can sometimes lead to hospitalization. Typically, CAP is caused by a virus or bacterial infection.

The bacteria or pathogens associated with CAP are usually classified as either "atypical" pathogens or "typical" pathogens. Pathogens considered atypical are *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. According to the Public Health Agency of Canada, *Legionella pneumophila* is the cause of 1% to 2% of all pneumonia cases in adults. (1) The primary typical pathogen is *Streptococcus pneumoniae*. Antibiotics that treat atypical pathogens include quinolones and macrolides. Usually coverage for typical pathogens includes ß-lactam antibiotics.

In 2007, Arnold et al (2) published an analysis of the incidence of CAP due to atypical pathogens and treatment of atypical pathogens in 4 regions: North America, Europe, Latin America, and Asia. They found that the incidence of CAP due to atypical pathogens ranged from 20% to 28% in these regions, and the treatment for atypical pathogens ranged from 91% in North America to 10% in Asia. The results of this study showed that approximately 77% of patients globally receive antibiotic coverage for atypical pathogens.

The Cochrane review by Eliakim-Raz et al (3) did not find a significant difference in the adverse events between patients receiving atypical coverage versus typical coverage. However, the randomized controlled trials (RCTs) reported in the Cochrane review were not designed to assess adverse events, nor did they consistently report adverse events in terms of type or severity of the adverse event.

Guidelines

International guidelines on the diagnosis and management of adults with CAP have fairly consistent recommendations regarding use of antibiotics for the coverage of atypical pathogens, although there are some differences (Table 1). The guidelines consistently recommend treating patients with severe CAP (i.e., those in the Intensive Care Unit) with antibiotic coverage for atypical pathogens. The guidelines are less consistent for hospitalized patients with mild or moderate CAP.

Table 1. Recommendations for Antibiotic Coverage to Treat Atypical Pathogens in Patients Hospitalized With Community-Acquired Pneumonia

Guideline	Patients with CAP in ICU	Patients with CAP in Ward (Not ICU)
Canadian Infectious Disease Society/Canadian Thoracic Society (2000) (4)	Respiratory fluoroquinolone[a] and ß-lactam	Respiratory fluoroquinolone[a]
Infectious Diseases Society of America/American Thoracic Society (2007) (5)	ß-lactam and macrolide[a]	Respiratory fluoroquinolone[a] or ß-lactam and macrolide[a]
British Thoracic Society (2009) (6)	Severe: ß-lactam and macrolide[a]	Moderate: ß-lactam and macrolide[a] Mild: ß-lactam
Anti-infective Guidelines for Community-Acquired Infections in Ontario (2013) (7)	Not reported	Not reported
American College of Emergency Physicians (2009) (8)	Not reported	Not reported
Swedish Society of Infectious Diseases (2012) (9)	Macrolide[a] + fluoroquinolone[a] + cephalosporin	ß-lactam with or without cephalosporin (treat with macrolide[a] if atypical pathogen is suspected)
SWAB/NVALT Dutch Guidelines (2011) (10)	Quinolone[a] with or without ß-lactam or macrolide[a] + cephalosporin	ß-lactam
Scottish Intercollegiate Guidelines Network (2002) (11)	Not reported	Not reported
European Respiratory Society (2011) (12)	Macrolide[a] + cephalosporin	Macrolide[a] + cephalosporin or ß-lactam
South African Guidelines (2009) (13)	ß-lactam + cephalosporin + macrolide[a]	ß-lactam with or without cephalosporin (fluoroquinolone[a] if atypical pathogen suspected)

Abbreviations: CAP, community-acquired pneumonia; ICU, intensive care unit.
[a]Antibiotic for atypical pathogen.

Rapid Review

Research Question

What is the effectiveness of regimens containing atypical antibiotic coverage compared with regimens with typical antibiotic coverage, in terms of mortality and treatment failure?

Research Methods

Literature Search

A literature search was performed on May 8, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2008, until May 8, 2013. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full reports
- published between January 1, 2008, and May 8, 2013
- health technology assessments, systematic reviews, and meta-analyses
- hospitalized adults with CAP or nursing home–acquired pneumonia
- comparing atypical antibiotic coverage with typical antibiotic coverage alone

Exclusion Criteria

- primary studies (RCTs, observational studies, case series, etc.)
- children
- outpatients with CAP
- patients with hospital-acquired pneumonia

Outcomes of Interest

- overall mortality
- treatment failure

Expert Panel

In April 2013, the Pneumonia Expert Advisory Panel was struck. Members of the panel included physicians, nurses, allied health professionals, and personnel from the Ministry of Health and Long-Term Care.

The role of the Pneumonia Expert Advisory Panel was to place the evidence produced by Health Quality Ontario into context and to provide advice on the appropriate clinical pathway for a patient with

pneumonia in Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Results of Literature Search

The database search yielded 682 citations published between January 1, 2008, and May 8, 2013 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

One systematic Cochrane review was identified that met the inclusion criteria. This 2012 review by Eliakim-Raz et al (14) was an update of a previous Cochrane review on the use of antibiotic coverage of atypical pathogens from 2008 (which was an update of the original review published in 2005). The Assessment of Multiple Systematic Reviews (AMSTAR) rating for this review was 11, which indicates that this review met all of the criteria outlined by the AMSTAR rating tool.

Results

The Cochrane review by Eliakim-Raz et al (14) looked at two outcomes for patients with CAP: mortality and treatment failure. For the outcome of mortality, the authors grouped the patients by antibiotic type, region of residence (Europe, North America, other), age (>65 years, <65 years), and study design criteria (blinding, allocation concealment). They were unable to find a significant difference in mortality between patients receiving antibiotic coverage for atypical pathogens and patients receiving antibiotic coverage for typical pathogens regardless of subgroup.

The outcome of treatment failure was also stratified by pathogen type in addition to the subgroups used in the mortality outcome. The results were the same, showing no significant difference in the rate of treatment failure among patients receiving antibiotics for atypical pathogens compared with those receiving antibiotics for typical pathogens, with the exception of the subgroup for *Legionella pneumophila*. This subgroup showed significantly reduced treatment failure in patients receiving atypical coverage versus typical coverage. These results are unsurprising because the antibiotics for atypical pathogens are designed to treat *Legionella*.

Some of the results from the Eliakim-Raz et al (14) review are presented in Table 2.

Table 2. Results from Cochrane Systematic Review

Subgroup	Number of Studies (Participants)	Effect Size (95% Confidence Interval)
Mortality		
Quinolone in atypical arm	19 (3698)	0.98 (0.69, 1.39)
Macrolide in atypical arm	4 (540)	1.25 (0.52, 3.01)
Combined quinolone and macrolide in atypical arm	1 (808)	2.29 (0.81, 6.44)
Pristinamycine in atypical arm	1 (398)	1.98 (0.37, 10.69)
All atypical treatments	25 (5444)	1.14 (0.84, 1.55)
Treatment failure		
Quinolone in atypical arm	21 (3704)	0.89 (0.79, 1.02)
Macrolide in atypical arm	5 (536)	1.11 (0.76, 1.62)
Combined quinolone and macrolide in atypical arm	1 (808)	0.93 (0.75, 1.17)
Pristinamycine in atypical arm	1 (371)	1.18 (0.77, 1.81)
All atypical treatments	28 (5419)	0.93 (0.84, 1.04)
Pneumococcal pneumonia	18 (1021)	1.22 (0.88, 1.70)
Atypical pathogens	4 (158)	0.52 (0.24, 1.10)
Legionella pneumophila	5 (43)	0.17 (0.05, 0.63)

Conclusion

Moderate-quality evidence indicates no significant difference in mortality or treatment failure among adults hospitalized with CAP receiving antibiotics for atypical pathogens compared with those receiving antibiotics for typical pathogens.

Acknowledgements

Editorial Staff
Elizabeth Jean Betsch, ELS

Medical Information Services
Corinne Holubowich, BEd, MLIS

HQO's Expert Advisory Panel on Evidence-Based Episode of Care for Pneumonias Presenting to Hospitals

Panel Members	Affiliation(s)	Appointment(s)
Co-Chairs		
Dr Andrew Morris	Mount Sinai Hospital University Health Network University of Toronto	Medical Director, MSH-UHN Antimicrobial Stewardship Program Associate Professor, Division of Infectious Diseases
Dr Howard Ovens	Mount Sinai Hospital University of Toronto	Director, Schwartz-Reisman Emergency Centre Associate Professor, Department of Family and Community Medicine
Respirologist		
Dr Meyer Balter	University of Toronto Mount Sinai Hospital	Professor of Medicine Director, Asthma and COPD Education Clinic
Dr Gerard Cox	St. Joseph's Healthcare Hamilton McMaster University	Head of the Division of Respirology
Dr David Fishbein	Humber River Hospital	Chief of the Department of Medicine, Division of Respirology
Dr Kevin Sanders	North York General Hospital Sunnybrook Health Sciences	Respirologist, Intensive Care Unit, Critical Care Response Team
Intensivist		
Dr Christine Bradley	Hamilton General Hospital McMaster University	Associate Clinical Professor
Dr Niall Ferguson	Mount Sinai Hospital University of Toronto	Director of Critical Care
Dr Cindy Hamielec	McMaster University Hamilton General Hospital	Associate Clinical Professor Past National Chair at Canadian Intensive Care Foundation
Dr Michael Miletin	William Osler Health Centre	Director of Critical Care
Dr John Muscedere	Kingston General Hospital Queen's University	Research Director, Clinical Care Program

Panel Members	Affiliation(s)	Appointment(s)
Dr Mark Soth	McMaster University St. Joseph's Healthcare Hamilton	Associate Professor Chief, Department of Critical Care
Infectious Disease Specialist		
Dr Gary Garber	Ontario Agency for Health Protection and Promotion The Ottawa Hospital Research Institute	Medical Director Infection Prevention and Control
Dr Wayne Gold	Toronto General Hospital University of Toronto	Director of Adult Infectious Diseases Program
Dr Jeff Powis	Toronto East General Hospital University of Toronto	Director of Antimicrobial Stewardship Program
Dr Dan Ricciuto	Lakeridge Health	Physician Lead, IPAC and Antimicrobial Stewardship
Infectious Disease Specialist/Medical Microbiologist		
Dr William Ciccotelli	Grand River Hospital St. Mary's General Hospital	Medical Director Infection Prevention and Control Physician Lead – Antimicrobial Stewardship Program
Medical Microbiologist		
Jonathan Gubbay	Ontario Agency for Health Protection and Promotion University of Toronto The Hospital for Sick Children	Medical Microbiologist and Paediatric Infectious Disease Specialist
Emergency Medicine Specialist		
Dr Gary Mann	Central East LHIN Rouge Valley Health Centre	Central East LHIN/Provincial LHIN Lead Program Chief, Dept. of Emergency Medicine
Dr Shaun Visser	University of Ottawa	Champlain ED LHIN Lead and Medical Director Emergency Department, Montfort Hospital
Family Medicine		
Dr Kenneth Hook	Ontario College of Family Physicians STAR Family Health Team	Past-President Senior Physician
Dr John Jordan	Byron Family Medical Centre Western University	Professor of Family Medicine
Dr Frank Martino	William Osler Health Centre McMaster University Ontario College of Family Physicians	Lead Physician President, OCFP
Hospitalist		
Dr Robert Maloney	Sault Area Hospital	Chief Hospitalist
Dr Cary Shafir	Guelph General Hospital	Chief Hospitalist
Dr Warren Wilkins	Peterborough Regional Health Centre	Medical Director, Internal Medicine Program Acting Lead Hospitalist

Panel Members	Affiliation(s)	Appointment(s)
Hospitalist/Geriatrician		
Dr Mireille Norris	Sunnybrook Health Sciences	Education Director of Hospitalist Training Program
Geriatrician		
Dr Anthony Kerigan	Hamilton Health Sciences	Geriatrician
Clinical Pharmacist		
Anne Marie Bombassaro, PharmD	London Health Sciences Centre	Pharmacy Practice Leader
Mark McIntyre, PharmD	Mount Sinai Hospital	Clinical Pharmacist
Pharmacotherapy Specialist		
Miranda So, PharmD	University Health Network Mount Sinai Antimicrobial Stewardship Program	Pharmacotherapy Specialist
Antimicrobial Pharmacy Specialist		
Rosemary Zvonar	The Ottawa Hospital	Antimicrobial Pharmacy Specialist
Senior Hospital Administrator		
Jocelyn Bennett	Mount Sinai Hospital	Senior Director for Urgent and Critical Care
Registered Nurse		
Fran Izon	Mississauga Halton CCAC	Client Services Manager
Donna Johnson	St. Joseph's Healthcare Hamilton	Director, Clinical Programs
Registered Nurse (Emergency)		
Licina Simoes	Toronto Western Hospital (UHN)	Registered Nurse (Emergency)
Registered Nurse Educator (Emergency)		
Susan Harper	Peterborough Regional Health Centre	Registered Nurse Educator (Emergency)
Nurse Practitioner		
Cheryl Lennox	South West Community CCAC, Intensive Home Care Team	Nurse Practitioner-Primary Health Care Certified Respiratory Educator
Registered Respiratory Therapist		
Carole Madeley	Ontario Lung Association	Certified Respiratory Educator Director of Respiratory Health Programs
Charge Respiratory Therapist		
Vagia T. Campbell	Mount Sinai Hospital	Charge Respiratory Therapist, Urgent & Critical Care
Physiotherapist		
Cathy Relf	Trillium Health Partners – Mississauga Hospital	Physiotherapist

Panel Members	Affiliation(s)	Appointment(s)
Intensive Care Physiotherapist		
Tania Larsen	London Health Sciences	Intensive Care Physiotherapist
Decision Support and Case Costing Specialist		
Linda Welham	Southlake Regional Health Centre	Decision Support and Case Costing Specialist

Appendices

Appendix 1: Literature Search Strategies

Database: EMBASE 1980 to 2013 Week 18, Ovid MEDLINE(R) 1946 to May Week 1 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 08, 2013
Search Strategy:

#	Searches	Results
1	exp Pneumonia/	245279
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	286976
3	or/1-2	398237
4	exp Anti-Bacterial Agents/ use mesz or exp antibiotic agent/ use emez	1390448
5	exp Quinolones/ use mesz or exp quinolone derivative/ use emez	139876
6	exp Macrolides/ use mesz or exp macrolide/ use emez	203840
7	exp Tetracyclines/ use mesz or exp tetracycline derivative/ use emez	152971
8	exp Chloramphenicol/	65246
9	exp Streptogramins/ use mesz or exp streptogramin derivative/ use emez	1877
10	exp Ketolides/ use mesz or exp ketolide/ use emez	3830
11	(((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or macrolid* or doxycyclin* or t etracyclin* or chloramphenicol* or streptogramin* or ketolid* or erythromycin* or roxithromycin* or azithromycin* or clarithro mycin* or ciprofloxacin* or ofloxacin* or levofloxacin* or trovaflox acin* or moxifloxacin* or grepafloxacin* or tigecyclin* or minocyclin* or pristinamycin* or quinupristin* or telithromycin*).ti,ab.	616190
12	or/4-11	1673803
13	3 and 12	109019
14	Meta Analysis.pt.	40231
15	Meta-Analysis/ use mesz or exp Technology Assessment, Biomedical/ use mesz	49071
16	Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez	82034
17	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	317193
18	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	4093
19	or/14-18	368699
20	13 and 19	2114
21	limit 20 to english language	1970
22	limit 21 to yr="2008 -Current"	841
23	remove duplicates from 22	639

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 2013, EBM Reviews - ACP Journal Club 1991 to April 2013, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2013, EBM Reviews - Cochrane Central Register of Controlled Trials March 2013, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 2nd Quarter 2013, EBM Reviews - NHS Economic Evaluation Database 2nd Quarter 2013

#	Searches	Results
1	exp Pneumonia/	2150
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	4868
3	or/1-2	5447
4	exp Anti-Bacterial Agents/ use acp,cctr,coch,clcmr,dare,clhta,cleed	18290
5	exp Quinolones/ use acp,cctr,coch,clcmr,dare,clhta,cleed	2806
6	exp Macrolides/ use acp,cctr,coch,clcmr,dare,clhta,cleed	5073
7	exp Tetracyclines/ use acp,cctr,coch,clcmr,dare,clhta,cleed	1678
8	exp Chloramphenicol/	287
9	exp Streptogramins/ use acp,cctr,coch,clcmr,dare,clhta,cleed	20
10	exp Ketolides/ use acp,cctr,coch,clcmr,dare,clhta,cleed	50
11	(((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or macrolid* or doxycyclin* or t etracyclin* or chloramphenicol* or streptogramin* or ketolid* or erythromycin* or roxithromycin* or azithromycin* or clarithro mycin* or ciprofloxacin* or ofloxacin* or levofloxacin* or trovaflox acin* or moxifloxacin* or grepafloxacin* or tigecyclin* or minocyclin* or pristinamycin* or quinupristin* or telithromycin*).ti,ab.	17008
12	or/4-11	28510
13	3 and 12	2274

14	Meta Analysis.pt.	464
15	Meta-Analysis/ use acp,cctr,coch,clcmr,dare,clhta,cleed	21
16	exp Technology Assessment, Biomedical/ use acp,cctr,coch,clcmr,dare,clhta,cleed	438
17	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	32939
18	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	608
19	or/14-18	33829
20	13 and 19	69
21	limit 20 to yr="2008 -Current" [Limit not valid in DARE; records were retained]	43
22	remove duplicates from 21	43

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Comparison of "Atypical" Antibiotic Coverage and "Typical" Antibiotic Coverage

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Outcome: Mortality (atypical arm: quinolone)							
19 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Mortality (atypical arm: macrolide)							
4 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Mortality (atypical arm: quinolone and macrolide)							
1 (RCT)	No serious limitations	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕⊕ Low
Outcome: Mortality (atypical arm: pristinamycine)							
1 (RCT)	Serious limitations (−1)[d]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕ Very low
Outcome: Mortality (all atypical)							
25 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment failure (atypical arm: quinolone)							
21 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (atypical arm: macrolide)							
5 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (atypical arm: quinolone and macrolide)							
1 (RCT)	No serious limitations	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (atypical arm: pristinamycine)							
1 (RCT)	Serious limitations (−1)[d]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Outcome: Treatment Failure (all atypicals)							
28 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (pneumococcal pneumonia)							
18 (RCTs)	Very serious limitations (−2)[a,e]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Outcome: Treatment Failure (atypical pathogens)							

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
4 (RCTs)	Very serious limitations (−2)[a,e]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Outcome: Treatment Failure (*Legionella pneumophila*)							
5 (RCTs)	Very serious limitations (−2)[a,e]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]There was at least 1 risk of bias criterion with limitations for each study.
[b] There was only 1 study—not possible to assess consistency.
[c]Confidence intervals were wide.
[d]Poor risk of bias rating—maybe variables were unclear, and outcome data were incomplete.
[e] An ad hoc subset of patients was extracted from the study for analysis.

Table A2: Risk of Bias Among Randomized Controlled Trials for Comparison of "Atypical" Antibiotic Coverage and "Typical" Antibiotic Coverage

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Aubier, 1998	Limitations[b]	No limitations	Limitations[c]	No limitations	No limitations
Bohte, 1995	Limitations[b]	Limitations[d]	Limitations[e]	No limitations	Limitations[f,g]
Carbon, 1992	Limitations[b]	No limitations	Limitations[c]	No limitations	Limitations[f,g]
Chuard, 1989	Limitations[b]	Limitations[d]	No limitations	No limitations	No limitations
Feldman, 2001	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Fourrier, 1986	Limitations[b]	Limitations[b]	No limitations	Limitations[h]	No limitations
Genne, 1997	No limitations	Limitations[d]	Limitations[i]	No limitations	No limitations
Gleadhill, 1986	Limitations[b]	Limitations[d]	Limitations[j]	No limitations	No limitations
Hatipoglu, 2010	Limitations[b]	Limitations[b]	Limitations[k]	Limitations[b]	No limitations
Hirate-Dulas, 1991	Limitations[b]	Limitations[d]	No limitations	No limitations	No limitations
Hong-yun, 2007	Limitations[b]	Limitations[b]	Limitations[b]	Limitations[b]	No limitations
Kalbermatter, 2000	Limitations[b]	Limitations[d]	No limitations	No limitations	No limitations
Khan, 1989	No limitations	Limitations[d]	Limitations[j]	No limitations	No limitations
Kobayashi, 1984	Limitations[l]	No limitations	Limitations[c]	No limitations	No limitations
Kohno, 2011	No limitations	Limitations[d]	Limitations[j]	No limitations	No limitations
Lephonte, 2004	Limitations[b]	No limitations	Limitations[j]	No limitations	No limitations
Lode 1995	Limitations[b]	No limitations	No limitations	No limitations	No limitations
Miki, 1984	Limitations[b]	No limitations	Limitations[j]	No limitations	No limitations
Norrby, 1998	No limitations	Limitations[d]	Limitations[j]	No limitations	No limitations
Peterson, 1988	No limitations	Limitations[d]	No limitations	No limitations	No limitations
Petitpretz, 2001	No limitations	No limitations	Limitations[j]	No limitations	No limitations
Rizzato, 1997	Limitations[b]	Limitations[d]	Limitations[j]	No limitations	No limitations
Romanelli, 2002	Limitations[b]	Limitations[d]	Limitations[j]	No limitations	No limitations
Tremolieres, 1998	Limitations[b]	No limitations	Limitations[j]	No limitations	No limitations
Tremolieres, 2005	Limitations[b]	No limitations	Limitations[j]	No limitations	No limitations
Vanderdonckt, 1990	Limitations[b]	Limitations[d]	Limitations[c]	No limitations	No limitations
Vogel, 1991	Limitations[b]	Limitations[d]	Limitations[c]	No limitations	No limitations
Zeluff, 1988	Limitations[b]	No limitations	Limitations[j]	No limitations	No limitations

[a] Data in this table are based solely on the information provided in the Cochrane Systematic Review by Eliakim-Raz et al. (14) No primary studies were retrieved.
[b] Not reported.
[c] Satisfactory data provided for mortality but not for treatment failure.
[d] Open trial, no blinding stated.
[e] Satisfactory data provided for mortality, unclear data for treatment failure.
[f] No intent-to-treat analysis.
[g] Funded by industry.
[h] Data lost by trial investigators.
i Unsatisfactory data provided for mortality, unclear data for treatment failure.
[j] Unsatisfactory data provided for mortality and treatment failure.
[k] Satisfactory data provided for treatment failure, unclear data for mortality.
[l] Inadequate data provided.

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Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca