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Shorter Versus Longer Duration of Antibiotic Therapy in Patients With Community-Acquired Pneumonia: A Rapid Review

M Ghazipura

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Evidence Development and Standards Branch at Health Quality Ontario

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Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards 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 (SRs), health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. SRs are evaluated using a rating scale developed for this purpose. If the SR 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 SR has not evaluated the primary studies using GRADE, the primary studies included in the SR are retrieved and a maximum of two outcomes are graded. If no well-conducted SRs are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

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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. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—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 policymakers.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are 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, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario 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 can 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 Systematic Reviews
CAP	Community-acquired pneumonia
CI	Confidence interval
HQO	Health Quality Ontario
LOS	Length of stay
RCT	Randomized controlled trial
SR	Systematic review

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

The aim of this rapid review is to determine the optimal duration for administering antibiotics to patients presenting with community-acquired pneumonia (CAP).

Clinical Need and Target Population

Several studies suggest that prolonged duration of antibiotic therapy is unnecessary. (1) Overuse of antibiotics has been associated with increased risk of antimicrobial resistance, increased adverse events, and overall increase in costs. (2)

The international guidelines on the diagnosis and management of adults with CAP are inconsistent with regard to the duration of antibacterial therapy. The guidelines all recommend treating patients for a minimum of 7 days; however, they do not all recommend a maximum duration. Including a maximum duration would contribute to reducing the risk of antibiotic overexposure (see Table 1).

Table 1. Guideline Recommendations for Early Administration of Antibiotics for Patients Hospitalized With Community-Acquired Pneumonia

BTS (GB) (3)	IDSA/ATS (US) (4)	ACEP (US) (5)	SWAB/NVALT (NL) (6)	SSID (SE) (7)	ERS/ESCMID (Europe) (8)
7 days	Minimum 5 days	Average of 7–14 days; minimum of 5 days	5–7 days	7 days	≥ 8 days

Abbreviations: ACEP, American College of Emergency Physicians; ATS, American Thoracic Society; BTS, British Thoracic Society; CAP, community-acquired pneumonia; ERS, European Respiratory Society; ESCMID, European Society for Clinical Microbiology and Infection Diseases; GB, Great Britain; IDSA, Infectious Disease Society of America; NL, The Netherlands; NVALT, Dutch Association of Chest Physicians; SE, Sweden; SSID, Swedish Society of Infectious Diseases; SWAB, Dutch Working Party on Antibiotic Policy; US, United States.

Rapid Review

Research Question

What is the optimal duration of antibacterial therapy in patients with community-acquired pneumonia (CAP)?

Research Methods

Literature Search

A literature search was performed on May 30, 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 30, 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 30, 2013
- health technology assessments, systematic reviews (SRs), and meta-analyses
- hospitalized adult patients with CAP
- studies comparing ≤ 7 days with > 7 days of antibiotic therapy

Exclusion Criteria

- primary studies (randomized controlled trials [RCTs], observational studies, case series, etc.)
- children (patients aged < 18 years)
- outpatients with CAP
- patients with hospital-acquired and ventilator-associated pneumonia
- studies where outcomes of interest cannot be extracted

Outcomes of Interest

- mortality
- length of stay (LOS) in hospital

Expert Panel

In April 2013, an Expert Advisory Panel on Episodes of Care for Pneumonia 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 Expert Advisory Panel on Episodes of Care for Pneumonia was to contextualize the evidence produced by Health Quality Ontario (HQO) and provide advice on the appropriate clinical

pathway for a patient with pneumonia in the Ontario health care setting. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to assess the quality of the final selection of the SR. (9) Details on the outcomes of interest were abstracted from the selected review, and primary studies were referenced as needed.

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (10) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural method.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 factors that could raise the quality of evidence were considered: large magnitude of effect, dose-response gradient, and accounting for all residual factors. (10) For more detailed information, please refer to the latest series of GRADE articles. (10)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to the estimate of the effect;
Moderate	Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low	Confidence in the effect estimate is limited—the true effect could be substantially different from the estimate of the effect;
Very Low	Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect.

Results of Literature Search

The database search yielded 691 citations published between January 1, 2008, and May 30, 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 retrieved for further assessment.

Two SRs met the inclusion criteria. (11;12) Both report on the outcome of mortality, but neither report on the outcome of length of stay. AMSTAR was used to review them both (Appendix 2, Table A1). The 2007 SR by Li et al (12) received an AMSTAR rating of 8. It includes studies that compare different antibiotics for the short-duration and extended-duration arms. The 2008 SR by Dimopoulos et al (11) received an AMSTAR rating of 10, and it compares the same antibiotic in both study arms. Thus, because the SR by Dimopoulos et al (11) received a higher AMSTAR score, was more recently published, and compares the same drugs in both study arms, this SR was selected for inclusion in this review. It is summarized in Table 2.

Table 2. Summary of Systematic Review Included in This Rapid Review

Author, Year	Review Type	Search Dates	Inclusion Criteria	No. of Studies	AMSTAR Score
Dimopoulos et al, 2008 (11)	SR	January 1966 to November 2007	RCTs English language only Patients of all ages with a diagnosis of CAP Studies that compare treatment with the same antibacterial regimen in the same doses but different durations	5	10

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAP, community-acquired pneumonia; RCT, randomized controlled trial; SR, systematic review.

The RCTs selected for inclusion in the meta-analysis by Dimopoulos et al (11) are summarized in Table 3.

Table 3. Summary of Randomized Controlled Trials Included in the Systematic Review[a] of Optimal Duration for Antibiotic Therapy

Author, Year	Sample Size	Short-Course (≤ 7 days)	Long-Course (> 7 days)	Results and Conclusion
Siegel et al, 1999 (13)	52	Cefuroxime 750 mg q8h IV for 2 days, plus cefuroxime axetil 500 mg q12h PO for 5 days (7 days total)	Cefuroxime 750mg q8h IV for 2 days, plus cefuroxime axetil 500 mg q12h PO for 8 days (10 days total)	No difference between groups
Leophonte et al, 2002 (14)	244	Ceftriaxone 1 g IV od for 5 days	Ceftriaxone 1 g IV od for 10 days	No difference between groups
Tellier et al, 2004 (15)	378	Telithromycin 800 mg PO od for 5 days	Telithromycin 800 mg PO od for 7 days	No difference between groups
El Moussaoui et al, 2006 (16)	119	Amoxicillin 1 g IV q6h for 3 days	Amoxicillin 1 g IV q6h for 3 days, plus amoxicillin 720 mg PO q8h for 5 days (8 days total)	No cases of death, therefore not estimable
File et al, 2007 (17)	510	Gemifloxacin 320 mg PO od for 5 days	Gemifloxacin 320 mg PO od for 7 days	No difference between groups

Abbreviations: IV, intravenous; od, once daily; PO, oral; qxh, every *x* hours; RCT, randomized controlled trial.
[a]Systematic review by Dimopoulos et al. (11)

Results for Outcomes of Interest

The SR by Dimopoulos et al (11) reports on mortality, but no studies that report on LOS as an outcome were found. Since the SR does not provide the GRADE level of evidence, all primary studies were retrieved and the GRADE for the outcome of mortality was assessed.

Mortality

Dimopoulos et al (11) identifies 5 RCTs that evaluate mortality. Meta-analysis identified no difference in the short-course (≤ 7 days) versus long-course (> 7 days) antibiotic therapy (1,188 patients; odds ratio [OR], 0.60; 95% confidence interval [CI], 0.23–1.58) (Table 3). The GRADE for this outcome was assessed as high (Appendix 2, Table A2 and Table A3).

Table 4. Results from Meta-Analysis Comparing Antibiotic Duration of Less Than Seven Days Versus Greater Than Seven Days

Source Author, Year	No. of RCTs	< 7 Days		> 7 Days		Odds Ratio (95% CI)[a]	*P* [a]	I^2 [a]	GRADE
		No. Of Events	Total	No. Of Events	Total				
Dimopoulos et al, 2008 (11)	5	6	654	10	643	0.60 (0.23–1.58)	0.78	0%	High[b]

Abbreviations: CI, confidence interval; RCT, randomized controlled trial.
[a]Rapid reviews used a Mantel-Haenzel statistical method with a fixed effects analysis.
[b]GRADE was not assessed directly by authors of the SR. Individual studies were pulled and GRADE was separately assessed.

Quality Assessment

The quality assessment was conducted based on details published in the SR by Dimopoulos et al (11). Few sources of bias were identified, with the main one being a lack of blinding in individual RCTs, primarily due to the specific nature of the study question. As a result, the effect estimate for the outcome of mortality is based on high GRADE quality of evidence (Appendix 2, Table A2 and Table A3).

Length of Stay

No literature was found that assessed the outcome of LOS for patients receiving short-course versus long-course antibiotic therapy

Conclusions

On the basis of 1 SR evaluating the optimal duration for antibiotic therapy in patients presenting to the emergency department with signs of community-acquired pneumonia, the following conclusions were reached:

- High quality evidence indicates that there is no significant difference in mortality for patients who received antibiotic therapy for ≥ 7 days compared to those who received antibiotic therapy for < 7 days.
- There was no available evidence assessing the impact of the duration of antibiotic therapy on length of hospital stay.

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Editorial Staff
Joanna Odrowaz, BSc (Hons.)

Medical Information Services
Corinne Holubowich, BEd, MLIS
Kellee Kaulback, BA(H), MISt

HQO's Expert Advisory Panel on Evidence-Based Episodes 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
Dr Mark Soth	McMaster University St. Joseph's Healthcare Hamilton	Associate Professor Chief, Department of Critical Care

Panel Members	Affiliation(s)	Appointment(s)
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
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
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

Search date: May 30, 2013
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED

Q: Optimal Duration for Antibiotics in Community Acquired Pneumonia

Limits: 2008-current; English
Filters: Meta-analyses, systematic reviews, health technology assessments

Databases: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 2013, EBM Reviews - ACP Journal Club 1991 to May 2013, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2013, EBM Reviews - Cochrane Central Register of Controlled Trials April 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, Embase 1980 to 2013 Week 21, Ovid MEDLINE(R) 1946 to May Week 4 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 29, 2013

#	Searches	Results
1	exp Pneumonia/	248413
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	292879
3	or/1-2	405126
4	exp Anti-Bacterial Agents/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp antibiotic agent/ use emez	1412583
5	exp Quinolones/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp quinolone derivative/ use emez	143191
6	exp Macrolides/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp macrolide/ use emez	209479
7	exp Tetracyclines/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp tetracycline derivative/ use emez	155043
8	exp Chloramphenicol/	65618
9	exp Streptogramins/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp streptogramin derivative/ use emez	1899
10	exp Ketolides/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp ketolide/ use emez	3890
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.	635233
12	or/4-11	1707130
13	3 and 12	111685
14	Meta Analysis.pt.	40966
15	Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	49796
16	Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez	82558
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 or ((health technolog* or biomedical technolog*) adj2 assess*)).ti,ab.	355991
18	or/14-17	405320
19	13 and 18	2195
20	limit 19 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	2051
21	limit 20 to yr="2008 -Current" [Limit not valid in DARE; records were retained]	896
22	remove duplicates from 21	691

Appendix 2: Quality-Assessment Tables

Table A1: AMSTAR Score of Systematic Review[a]

Author, Year	AMSTAR score[a]	1) Provided Study Design	2) Duplicate Study Selection	3) Broad Literature Search	4) Considered Status of Publication	5) Listed Excluded Studies	6) Provided Characteristics of Studies	7) Assessed Scientific Quality	8) Considered Quality in Report	9) Methods to Combine Appropriate	10) Assessed Publication Bias	11) Stated Conflict of Interest
Dimopoulos et al, 2008 (11)	10	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Li et al, 2007 (12)	8	✓	✓	✓	✓		✓	✓	✓	✓		

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews.
[a] Details of AMSTAR method are described in Shea et al. (9)

Table A2: Risk of Bias for All Studies included in the Dimopoulos et al (11) Systematic Review of Optimal Duration for Antibiotic Therapy in Patients with Community-Acquired Pneumonia

Source Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Siegel et al, 1999 (13)	No serious limitations	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations
Leophonte et al, 2002 (14)	No serious limitations	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations
Tellier et al, 2004 (15)	No serious limitations	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations
El Moussaoui et al, 2006 (16)	No serious limitations	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations
File et al, 2007 (17)	No serious limitations	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations

[a] Due to the nature of the research question, blinding was not possible in the studies.

Table A3: GRADE Evidence Profile for Optimal Duration of Antibiotic Therapy in Patients with Community-Acquired Pneumonia

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality							
5 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕⊕High

Abbreviation: RCT, randomized controlled trial.

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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