Clinical Practice Guidelines Management and Prevention of Adult Community Acquired Pneumonia

DISCLAIMER

The recommendations in this guideline are based on careful consideration of the best available evidences at the time of its formulation. These guidelines are not mandatory nor are they meant to restrict physicians from using their sound clinical judgment. It is still the responsibility of the healthcare professional to make appropriate decisions considering the individual patient's risk factors, needs and preferences.

RISK STRATIFICATION FOR COMMUNITY ACQUIRED PNEUMONIA

	Low Risk	Moderate Risk	High Risk
Vital Signs	Stable	Unstable	Unstable
Respiratory rate	< 30/minute	≥ 30/minute	≥ 30/minute
Pulse rate	<125/minute	≥125/minute	≥125/minute
Systolic blood pressure	≥ 90 mmHg	< 90 mmHg	< 90 mmHg
Diastolic blood pressure	> 60 mmHg	≤ 60 mmHg	≤ 60 mmHg
Temperature	> 36°C or < 40°C	≤ 36°C or ≥ 40°C	≤ 36°C or ≥ 40°C
Others			
Altered mental state of acute onset	Absent	Present	Present
With suspected aspiration	No	Yes	Yes
Co-morbid condition	None or stable co-morbid	Unstable or decompensated • Uncontrolled diabetes mellitus • Active malignancies • Neurologic disease in evolution • Congestive heart failure Class II-IV • Unstable coronary artery disease • Renal failure on dialysis • Uncompensated COPD • Decompensated liver disease	Unstable or decompensated • Uncontrolled diabetes mellitus • Active malignancies • Neurologic disease in evolution • Congestive heart failure Class II-IV • Unstable coronary artery disease • Renal failure on dialysis • Uncompensated COPD • Decompensated liver disease
Severe Sepsis and Septic shock	Absent	Absent	Present/Absent[a]
Need for mechanical ventilator	No	No	No/Yes[a]

[a]**High risk CAP**: Any of the clinical feature of moderate risk CAP plus any of the following: Severe sepsis and Septic shock OR need for mechanical ventilator

ABBREVIATION

AGREE II	Appraisal of Guidelines for Research & Evaluation Instrument
AOR	Adjusted odds ratio
ARSP	Antimicrobial Resistance Surveillance Program
ATS	American Thoracic Society
CAP	Community acquired pneumonia
COPD	Chronic Obstructive Pulmonary Disease
CPG	Clinical Practice Guidelines
CRP	C-reactive Protein
CXR	Chest xray
ED	Emergency Department
ESBL	Extended Spectrum Beta-Lactamase
FDA	Food and Drug Administration
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GS/CS	Gram stain and Culture with Sensitivity
HCAP	Health-care associated pneumonia
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IPD	Invasive Pneumococcal Disease
IQR	Interquartile range
IV	Intravenous
MDRO	Multiple Drug Resistant Organism
MRSA	Methicillin Resistant Staphylococcus aureus
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
OR	Odds ratio
PCP	Philippine College of Physicians
PCV	Pneumococcal conjugate vaccine
PO	Per orem
PPV/PPSV	Pneumococcal polysaccharide vaccine
PSMID	Philippine Society for Microbiology and Infectious Diseases
RCT	Randomized Controlled Trials
RR	Relative Risk
TFAD	Time of the first antimicrobial dose
TWG	Technical Working Group
95% CI	95% Confidence Interval

HOW TO USE THIS DOCUMENT

This guideline can be kept at hand as reference when handling patients with CAP. A summary of the recommendations is in page 5. However, the detailed discussion and justification of each recommendation is available starting at page 16. For an in-depth critical analysis of the evidences, the journals and articles used are available in the references section. All evidence-based summary tables and the proceedings of the CPG Panel session are attached in the appendix.

When using the guidelines and recommendations for lectures, research papers and other material purposes, kindly provide the proper citation. For any queries, clarifications, suggestions, and other issues regarding this CPG, please contact PSMID.

EXECUTIVE SUMMARY

Community acquired pneumonia is a significant cause of morbidity and mortality among adults, still remaining as the leading cause of death from an infectious disease. Since the last publication of Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia in Immunocompetent Adults in 2016, several important changes have emerged, including increasing rates of multi-drug resistant organisms (MDROs) among respiratory pathogens, the development of new antimicrobial agents meant to address these MDROs, the misuse and overuse of antimicrobial agents. It is for these reasons that an update on the management of CAP is needed.

The following are the guideline's objectives:

1. To provide an evidence–based approach to the empiric antimicrobial management and prevention of CAP in adults to help standardize care
2. To update the 2016 Philippine CPG on CAP in Adults with recent and up-to-date medical evidences on new developments at the global level yet localizing it in the Philippine setting, including the increasing rates of MDROs among respiratory pathogens and the development of new antimicrobial agents meant to address these MDROs

This guideline is intended for use of medical specialists in infectious diseases, pulmonology, family medicine, as well as general practitioners, clinical practitioners, nurses and other health care providers as well as administrators, and policy makers. It can be used in the hospital and community setting—from primary to tertiary level in both private and government clinics or hospitals.

The guideline shall cover all adults, including the elderly, presenting with CAP in the outpatient and in-patient setting except:

1. CAP occurring in immunocompromised patient including bone marrow, solid organ or stem cell recipient
2. Patients receiving cancer chemotherapy or immune-modulators
3. Long term high dose corticosteroid >30days (> or = 20mg/day prednisone or its equivalent)
4. Patients with congenital and acquired immunodeficiency (including cystic fibrosis, autoimmune and HIV)
5. Pneumonia in children < 18 years old
6. Pulmonary tuberculosis co-infection

There are 17 priority questions identified and 30 corresponding recommendations developed by a group of experts composed of an Oversight Committee, a Guideline Writing Panel and a Technical Review Committee (*Table 1*). Based on the best available evidences, the quality and strength of evidence was rated using the Grading of Recommendations, Assessment, Development and evaluation (GRADE) approach. Draft recommendations were finalized after these were presented to and voted on by the members of the Consensus Panel.

Table 1. Summary of Clinical Practice Guideline Recommendations

No	Recommendations	Strength of Panel Recommendations	Quality of Evidence
DIAGNOSIS			
1	***GSCS*** **Recommendation 1:** We do not recommend gram stain and culture of respiratory secretions for low risk CAP	*Strong recommendation*	*very low quality of evidence*
	Recommendation 2: We recommend gram stain and culture of respiratory secretions for patients with moderate to high risk CAP, or with risk factors for MDRO infection	*Strong recommendation*	*low quality of evidence*
2	***Blood Culture*** **Recommendation 3:** We recommend blood cultures for patients with moderate and high risk CAP.	*Strong recommendation*	*low quality of evidence*
3	***Influenza Test*** **Recommendation 4:** We recommend testing of respiratory secretions for influenza through rapid molecular testing using rapid nucleic acid amplification tests during periods of high influenza activity (July to January) for patients with high risk CAP preceded by influenza-like illness symptoms (sore throat, rhinorrhea, body malaise, joint pains) and any of the following risk factors: • Aged 60 years and above • Pregnant • Asthmatic • Other co-morbidities: uncontrolled diabetes mellitus, active malignancies, neurologic disease in evolution, congestive heart failure class II-IV, unstable coronary artery disease, renal failure on dialysis, uncompensated COPD, decompensated liver disease	*Conditional recommendation*	*low to moderate quality of evidence*
4	***Legionella Test*** **Recommendation 5:** Legionella urine antigen tests may be considered for patients with high risk CAP.	*Conditional recommendation*	*low quality of evidence*
5	***Multiplex PCR*** **Recommendation 6:** We do not recommend the routine use of multiplex polymerase chain reaction	*Strong recommendation*	*moderate quality of evidence*

	among adult patients with CAP		
TREATMENT			
6	***Empiric Treatment for Low-risk CAP*** **Recommendation 7:** The following antibiotics should be started for empiric treatment of patients with low risk CAP without co-morbidities: Amoxicillin 1 gram, three times daily **OR** Clarithromycin 500mg, twice daily **OR** Azithromycin 500mg once daily	 *Strong recommendation* *Strong Recommendation*	 *low quality of evidence* *low quality of evidence*
	Recommendation 8: The following antibiotics should be started for empiric treatment of patients with low risk CAP with stable co-morbidities: *Beta-lactam* Co-amoxiclav (amoxicillin/clavulanate 500 mg/125 mg three times daily, OR amoxicillin/ clavulanate 875 mg/125 mg twice daily) **OR** Cefuroxime 500mg, twice daily **PLUS OR MINUS (+/-)** *Macrolide* Clarithromycin 500mg, twice daily **OR** Azithromycin 500mg once daily **OR** Doxycycline 100mg, twice daily	 *Strong recommendation* *Strong recommendation* *Conditional recommendation*	 *moderate quality of evidence* *low quality of evidence* *low quality of evidence*
7	***Empiric Treatment for Moderate-risk CAP*** **Recommendation 9:** The following antibiotics should be started for empiric treatment of patients with moderate risk CAP without MDRO infection *Non-pseudomonal Beta-lactam antibiotic* Ampicillin-sulbactam 1.5–3 g every 6 h **OR** Cefotaxime 1–2 g every 8 h **OR** Ceftriaxone 1–2 g daily **PLUS**	 *Strong recommendation*	 *moderate quality of evidence*

	Macrolide Azithromycin 500 mg daily **OR** Clarithromycin 500 mg twice daily		
8	***Empiric Treatment for High-risk CAP without MDRO infection*** **Recommendation 10:** The following antibiotics should be started for empiric treatment of patients with high risk CAP without MDRO infection: **FIRST LINE THERAPY** *Non-pseudomonal Beta-lactam antibiotic* Ampicillin-sulbactam 1.5–3 g IV every 6 h **OR** Cefotaxime 1–2 g IV every 8 h **OR** Ceftriaxone 1–2 g IV daily **PLUS** *Macrolide* Azithromycin 500 mg PO/IV daily **OR** Erythromycin 500 mg PO every 6 hours **OR** Clarithromycin 500 mg PO twice daily **ALTERNATIVE THERAPY** *Non-pseudomonal Beta-lactam antibiotic* **PLUS** *Respiratory fluoroquinolone** Levofloxacin 750 mg PO/IV daily **OR** Moxifloxacin 400 mg PO/IV daily ** given as 1 hour IV infusion*	*Strong recommendation* *Conditional recommendation*	*low quality of evidence* *low quality of evidence*
9	***Atypical coverage for Aspiration pneumonia*** **Recommendation 11:** Routine anaerobic coverage for suspected aspiration pneumonia is NOT	*Conditional recommendation*	*Very low quality of evidence*

<table>
<tr><td></td><td>recommended, unless lung abscess or empyema is suspected</td><td></td><td></td></tr>
<tr><td>10</td><td>Empiric Treatment for MDROs and their risk factors

Recommendation 12: The following antibiotics should be started for empiric treatment of patients with moderate to high risk CAP and with risk factors for MDROs
<table>
<tr><th>Risk Factors and Organisms</th><th>Empiric Antibiotic Recommendations</th></tr>
<tr><td>Risk for Methicillin Resistant Staphylococcus aureus (MRSA)

• Prior colonization or infection with MRSA within 1 year
• Intravenous antibiotic therapy within 90 days</td><td>Non-pseudomonal Beta lactam antibiotic
PLUS
Macrolide OR respiratory fluoroquinolone*

PLUS
Vancomycin 15 mg/kg IV every 12 hours^
OR
Linezolid 600 mg IV every 12 hours ^
OR
Clindamycin 600 mg IV every 8 hours^</td></tr>
<tr><td>Risk for ESBL

• Prior colonization or infection with ESBL-producing organisms within 1 year</td><td>REPLACE Non-pseudomonal Beta lactam antibiotic with:
Ertapenem 1g IV every 24 hours
OR
Meropenem 1 g IV every 8 hours (if Ertapenem is not available)

PLUS
Macrolide OR respiratory fluoroquinolone*</td></tr>
<tr><td>Risk for Pseudomonas aeruginosa</td><td>REPLACE Non-pseudomonal Beta lactam antibiotic</td></tr>
</table></td><td>Strong recommendation</td><td>Low to moderate quality of evidences</td></tr>
</table>

	• Prior colonization or infection with P aeruginosa within 1 year • Severe bronchopulmonary disease (severe COPD, bronchiectasis, prior tracheostomy)	with: Piperacillin-Tazobactam 4.5g IV every 6 hours **OR** Cefepime 2 g IV every 8 hours **OR** Ceftazidime 2 g IV every 8 hours **OR** Aztreonam 2 g IV every 8 hours **OR** Meropenem 1 g IV every 8 hours (especially if with ESBL risk) **PLUS** *Macrolide* **OR** *respiratory fluoroquinolone**		
11	***Antiviral Treatment*** **Recommendation 13:** We recommend antiviral therapy in addition to antibacterial therapy among patients with high risk CAP and any of the following risk factors (aged 60 years and above, pregnant, asthmatic, other co-morbidities: uncontrolled diabetes mellitus, active malignancies, neurologic disease in evolution, congestive heart failure class II-IV, unstable coronary artery disease, renal failure on dialysis, uncompensated COPD, decompensated liver disease) who test positive for influenza virus.		*Strong recommendation*	*low quality of evidence*
	Recommendation 14: If diagnostic tests are not accessible, empiric antiviral therapy may be considered in addition to antibacterial therapy during periods of high influenza activity (July to January) among patients with high risk CAP preceded by influenza-like illness symptoms (sore		*Conditional recommendation*	*very low quality of evidence*

	throat, rhinorrhea, body malaise, joint pains) and any of the following risk factors: • Aged 60 years and above • Pregnant • Asthmatic • Other co-morbidities: uncontrolled diabetes mellitus, active malignancies, neurologic disease in evolution, congestive heart failure class II-IV, unstable coronary artery disease, renal failure on dialysis, uncompensated COPD, decompensated liver disease		
12	***Initiation of Treatment*** **Recommendation 15:** As soon as diagnosis is established, treatment of community acquired pneumonia, regardless of risk, should be initiated within 4 hours.	*Strong recommendation*	*very low quality of evidence*
13	***Duration of Treatment*** **Recommendation 16:** Among patients with low to moderate risk CAP, a treatment duration of 5 days is recommended as long as the patient is clinically stable (afebrile within 48 hours, able to eat, normal blood pressure, normal heart rate, normal respiratory rate, normal oxygen saturation, and return to baseline sensorium).	*Strong recommendation*	*moderate quality of evidence*
	Recommendation 17: Antibiotic therapy may be extended according to clinical consideration such as: (1) pneumonia is not resolving, (2) pneumonia complicated by sepsis, meningitis, endocarditis and other deep-seated infection, (3) infection with less common pathogens (i.e. Burkholderia pseudomallei, Mycobacterium tuberculosis, endemic fungi, etc), (4) infection with a drug resistant pathogens.	*Best practice*	
14	***De-escalation*** **Recommendation 18:** De-escalation of initial empiric broad spectrum or extended spectrum antibiotic with coverage for MRSA, Pseudomonas or ESBL to targeted or oral antibiotics based on culture results is recommended once the patient is clinically	*Strong recommendation*	*moderate quality of evidence*

	improving, hemodynamically stable and able to tolerate oral medications.		
15A	***Monitoring Response with Chest x-ray*** **Recommendation 19:** Among adult patients who are being treated for community-acquired pneumonia and who are clinically improving, follow up chest x-ray should NOT routinely be performed to monitor response to treatment.	*Strong recommendation*	*low quality of evidence*
	Recommendation 20: We recommend post-treatment chest x-rays after a minimum of 6 to 8 weeks among patients with CAP to establish baseline and to exclude other conditions.	*Strong recommendation*	*low quality of evidence*
15B	***Monitoring Response with CRP*** **Recommendation 21:** We do not recommend the use of CRP to monitor treatment response among patients with CAP	*Strong recommendation*	*low quality of evidence*
15C	***Monitoring Response with Procalcitonin*** **Recommendation 22:** We do not recommend the use of procalcitonin to monitor treatment response among patients with moderate or high risk CAP	*Strong recommendation*	*low quality of evidence*
	Recommendation 23: Procalcitonin may be used to guide antibiotic discontinuation among patients with moderate or high risk CAP.	*Conditional recommendation*	*low quality of evidence*
16	**Inadequate response after 72 hours of empiric antibiotic therapy** **Recommendation 24:** The clinical history, physical examination, and the results of all available investigations should be reviewed. The patient should be reassessed for possible resistance to the antibiotics being given or for the presence of other pathogens such as Mycobacterium tuberculosis, viruses, parasites, or fungi. Treatment should then be revised accordingly.		*Moderate quality evidence (Grade B)*
	Recommendation 25: Follow-up chest radiograph is recommended to investigate for other conditions such as pneumothorax, cavitation, and extension to previously uninvolved lobes, pulmonary edema, and acute respiratory distress syndrome.		*Moderate evidence (Grade B)*

	Recommendation 26: Obtaining additional specimens for microbiologic testing should be considered		*Moderate evidence (Grade B)*
PREVENTION			
17	***Pneumococcal and Influenza Vaccine*** **Recommendation 27:** Pneumococcal polysaccharide vaccine (PPSV) or pneumococcal conjugate vaccine (PCV) are recommended for the prevention of invasive pneumococcal disease in adults 50 years old and older.	*Strong recommendation*	*moderate quality of evidence*
	Recommendation 28: Pneumococcal polysaccharide vaccine is recommended for adults to prevent (a) pneumococcal pneumonia, (b) mortality from IPD or pneumonia and (c) pneumonia among high-risk groups and adults 50 years and above.	*Strong recommendation*	*low quality of evidence*
	Recommendation 29: Influenza vaccine is recommended to prevent influenza, influenza-like illness and hospitalization in all adults.	*Strong recommendation*	*low quality of evidence*
	Recommendation 30: Administration of both influenza and pneumococcal vaccine is recommended to prevent pneumonia, hospitalization and mortality in adults 50 years old and above.	*Strong recommendation*	*very low quality of evidence*

I. INTRODUCTION

In the Philippines, the Department of Health recognizes that community acquired pneumonia is a significant cause of morbidity and mortality among adults. The burden of CAP is a public health concern and is evident since it is the top medical claims reimbursed as reported by the country's largest insurance provider, PhilHealth.

In managing pneumonia, the treatment should not only stop the infection but prevent complications as well. Treatment is usually through empiric antibiotics, however, practice variations among different health care providers and health care systems exist. With the goal to optimize patient care, the CPG intends to standardize the treatment based on systematic review of evidences available.

Since the last publication of Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia in Immunocompetent Adults in 2016, several important changes have emerged, including increasing rates of multi-drug resistant organisms among respiratory pathogens, the development of new antimicrobial agents meant to address these MDROs. It is for these reasons that an update on the management of CAP is needed. Given the new guidelines, practice variation will be reduced and the misuse, abuse and overuse of antimicrobial agents will be limited while adequately managing the infection and preventing the complications of CAP.

II. GUIDELINE DEVELOPMENT METHODS

A. Organization of the Process

A group composed of infectious disease specialists, clinicians, epidemiologists and academicians was created, headed by a Steering Committee. An orientation and training workshop on the objectives, context and processes was done. Based on the relevance and need, total of nine questions were chosen, eight of which are for treatment while one is for prevention.

B. Search and retrieval of relevant articles

A systematic literature search was conducted by the technical working group (TWG) committee using electronic databases. Aside from electronic databases, manual searching of bibliographies was done and unpublished studies were obtained through local experts. Relevant search articles were retrieved and appraised for directness, validity and applicability. Existing CPGs on pneumonia worldwide were identified and appraised using the Appraisal of Guidelines for Research & Evaluation (AGREE II) Instrument.

C. Grading of quality of evidence and preparation of evidence summaries

Evidence summaries were constructed for each of the questions and the identified important outcomes. The TWG used GRADE to rate the quality of evidence *(Table 2)* and strength of recommendation. When evidence is minimal or not available, recommendations are based on the Guideline Development Group's experience and opinion which is labelled "Best Practice". The overall quality of evidence for the recommendation was based on the

lowest quality of evidence for the outcomes that were critical to reaching a decision. After reviewing and evaluating the evidence summaries, draft recommendations were done.

Table 2. Basis of Quality of evidence in GRADE

Quality level	Definition
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is *likely* to have impact on the confidence in the estimate of effect
Low	Further research is *very likely* to have an important impact on the confidence in the estimate of effect
Very low	Any estimate of effect is *very uncertain*

Additional categories considered when grading quality of evidence: (1) risk of bias (study limitations); (2) indirectness; (3) inconsistency; (4) imprecision; and (5) publication bias.

D. Consensus development process

The evidence-based draft was circulated to the panelists prior to the en-banc meeting. During the meeting, the members of the TWG presented each recommendation with the supporting evidences. Using nominal group technique, each recommendation was discussed not only on the basis of quality of evidence, but also on other criteria listed in the table below:

Table 3. Criteria for Consideration in Recommendation Development

Domain	Rationale
Quality of evidence	Assessment of the degree of confidence in the estimate of the effect
Benefits and Harms (Risks)	Desirable effects (benefits) need to be weighed against harmful or undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favor of the benefits over the risks, the more likely that a strong recommendation will be made
Values and preferences	Judgment of how much the people affected by the intervention or option value each of the outcomes
Acceptability	How much an intervention or recommendation is accepted by the people who are affected by it or who are implementing it. If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. If there is a great deal of variability or strong reasons that a recommendation is unlikely to be accepted, it is more likely that a weak recommendation will be made
Feasibility (including resources use consideration)	Whether an intervention is achievable and sustainable in a setting where the greatest impact is expected

Using these criteria, the panel gave each recommendation an assessment of "strong recommendation", "conditional recommendation" or "no recommendation". A preliminary vote was obtained for each recommendation and consensus was arrived at when at least 75% of the votes obtained are in agreement.

A second draft incorporated all the comments, feedbacks and discussions from the meeting. It will be circulated to the stakeholders panel for further comments and revisions. The revised draft will be presented in a public forum consisting of other stakeholders. Verbal or written feedback on the recommendations will be encouraged and taken into consideration. A third and final version of the guideline will be produced.

III. RESULTS

A. Appraisal of Existing Guidelines

Existing CPGs on pneumonia worldwide were identified and appraised using the AGREE II. Five CPGs (Metlay et.al, 2019; National Institute for Health and Care Excellence, 2019; Spindler, et.al 2012; Cao,et.al 2016 and Boyles, 2017) were considered for inclusion in the primary CPG. However, by consensus, the TWG team will be looking into the relevant answers per questions primarily in the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines 2019 and National Institute for Health and Care Excellence (NICE) 2014 guidelines with 2019 updates (see Appendix A). If no answers were found in the first two guidelines, the other three guidelines will be utilized. If none of the guidelines will be able to answer the questions, then the team shall proceed to synthesize the evidence de novo. Since both the IDSA and NICE guidelines ended their relevant searches by 2017, a currency update check was performed by each of the teams and additional relevant evidences from 2017 to 2019 were gathered.

B. Research Questions

Sixteen research questions were considered and will be covered in this guideline.

1. Among adult patients diagnosed with CAP, when should Gram stain and Culture with Sensitivity (GS/CS) testing of respiratory secretions be performed?
2. Among adult patients diagnosed with CAP, when should blood cultures be requested?
3. Among adult patients with CAP, should testing of respiratory secretions for Influenza Virus at the time of diagnosis be done to minimize morbidity and mortality?
4. Among patients with CAP, should Legionella urine antigen test be requested?
5. Among adult patient with CAP, what is the clinical utility of multiplex PCR?
6. What antibiotics are recommended for the empiric treatment of low-risk CAP?
7. What antibiotics are recommended for the empiric treatment of moderate risk CAP?
8. What antibiotics are recommended for the empiric treatment of high risk CAP?
9. Among adults with suspected aspiration pneumonia, should additional anaerobic coverage beyond empiric treatment for CAP be given?
10. Among patients with CAP, who are the patients at risk for MRSA, *Pseudomonas aeruginosa*, ESBL producing organisms and should receive empiric antibiotic coverage for these organisms?
11. Among adult patients with CAP who test positive for Influenza virus, should antiviral therapy be started?

12. Among adults with CAP, how soon should empiric treatment be started?
13. Among adult patients with CAP, what is the appropriate duration of treatment?
14. Among patients on empiric antibiotic therapy for CAP, should de-escalation be done?
15. Among patients with clinical improvements while ongoing treatment, should the following tests be performed to monitor response to treatment?
    a. Chest xray
    b. CRP
    c. Procalcitonin
16. Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

One research question was retained from the 2010 CAP guidelines.

1. What should be done for patients who are not improving after 72 hours of empiric antibiotic therapy?

C. The CPG Panel

A total of 13 panelists participated in the en banc meeting last 23 November 2019 for questions on Treatment and Prevention. The panelists included infectious disease specialists (from the PSMID and the National Antibiotic Guidelines Committee), a pulmonologist, a radiologist, a general internist, family medicine and geriatric medicine practitioners, an emergency medicine practitioner, a Municipal Health Officer, a medical technologist, and a representative from Department of Health, as well as a lay individual. There were 6 males and 7 females.

A total of 10 panelists participated in the en banc meeting last 11 January 2020 for questions on Diagnostics. The panelists included infectious disease specialists, a pulmonologist, a radiologist, a general internist, family medicine and geriatric medicine practitioners, an emergency medicine practitioner, and a representative from Department of Health. There were 6 males and 4 females.

An infectious disease specialist had to abstain for the question on prevention due to conflict of interest (since he was associated with a company for a pneumococcal vaccine).

D. Final Recommendations

The panelists weighed the relative importance of the different outcomes by using a scoring system from 1 to 9. Outcomes with a score of 1 to 3 are not considered important, score of 4 to 6 are important while a score of 7 to 9 are considered critical. The panelists voted the outcomes of microbiologic/etiologic diagnosis, detection of outbreaks, and duration of hospital stay as important. The rest of the outcomes of clinical diagnosis, antimicrobial stewardship, accuracy of test, cost effectiveness, morbidity and mortality were considered critical.

For each question, a summary of the evidences were presented and discussed in relation to the critical outcomes. Draft recommendation from the TWG was presented and a nominal group technique was done. Voting was done after and consensus was obtained by majority rule. All issues were resolved during the consensus and no further correspondence or voting outside of the meeting was necessary.

IV. EVIDENCE AND RECOMMENDATIONS

A. Diagnostics

1. GSCS

A 2019 systematic review and meta-analysis on the utility of sputum gram stain (GS) for CAP in the outpatient setting involving a total of 5,619 patients demonstrated that the mean sensitivity of sputum GS is 65.7% and the mean specificity is 84.9%. The study also demonstrated pathogen-associated variability, with sensitivity of 59% and specifity of 87% for *Streptococcus pneumoniae*, sensitivity of 78% and specificity of 96% for *Haemophilus influenzae*, sensitivity of 72% and specificity of 97% for *Staphylococcus aureus*, and sensitivity of 64% and specificity of 99% for Gram negative bacilli.

The study showed that sputum GS is HIGHLY SPECIFIC for identifying *S. pneumoniae*, *H. influenzae*, *S. aureus* and Gram-negative bacilli infection. A positive sputum GS result can confirm the causative pathogen of CAP. The positive likelihood ratios of sputum GS were also high, at >4 for *S. pneumoniae* and >10 for *H. influenzae*, *S. aureus* and Gram-negative bacilli.

False-negative rates were variable, with values ranging from 22% for *H. influenzae* and 44% for *S. pneumoniae*. Negative GS results cannot be used to conclude absence of respiratory pathogen; hence, discontinuation of antimicrobials in GS-negative sputum may be inappropriate. In addition, the negative likelihood ratios for sputum GS were not lower than 0.1. The cut-off value of 0.1 is regarded as strong evidence to reliably exclude diagnoses. Negative sputum GS results produce only minor changes in the probability of the etiologic diagnosis of CAP (Del Rio-Pertuz et al. 2019).

A prospective study on the utility of sputum GS among 533 inpatients with CAP showed similar results. Despite pathogen-associated variability, specificity values were high and ranged from 96.7% to 99.4%. Sensitivity values were lower, ranging from 35.4% to 82.3% (Roson et al. 2000).

Based from these 2 studies, sputum Gram stain test is SENSITIVE AND HIGHLY SPECIFIC for identifying causative pathogens in adult patients with CAP.

The Infectious Diseases Society of America (IDSA) guidelines for the treatment of CAP recommend that sputum GS/CS be obtained for hospitalized patients, especially those at risk for methicillin-resistant *Staphylococcus aureus* (MRSA) and Pseudomonas infectious and those who received intravenous antibiotics within 90 days prior to admission (Metlay JP et al. 2019). Similarly, the National Institute for Health and Care Excellence (NICE) guidelines recommend that sputum cultures be done only for individuals with moderate or high severity CAP (National Clinical Guideline Centre 2014).

Table 4: Sensitivity, specificity, likelihood ratios and predictive values of sputum GS in community acquired pneumonia

	Sensitivity (%)	Specificity (%)	Likelihood ratio (LR)/ Predictive value (PV)
Del Rio-Pertuz et al. 2019			
Streptococcus pneumoniae	59	87	Positive LR: 4.69 Negative LR: 0.39
Haemophilus influenzae	78	96	Positive LR 21.08

			Negative LR 0.23
Staphylococcus aureus	97	72	Positive LR 16.27 Negative LR 0.40
Gram negative bacilli	64	99	Positive LR 37.49 Negative LR 0.45
Roson et al. 2000			
Pneumococcal pneumoniae (definitive and presumptive)	57	97.3	Positive PV: 95.1 Negative PV: 71.3
Pneumococcal pneumoniae (definitive diagnosis)	35.4	96.7	Positive PV 90.6 Negative PV 62.7
Haemophilus influenzae (definitive and presumptive)	82.3	99.2	Positive PV 93.3 Negative PV 97.6
Haemophilus influenzae (definitive diagnosis)	42.8	99.4	Positive PV 75 Negative PV 98.2

Remarks and Consensus Issues

One panelist voted abstain in recommendation 2 due to issues of applicability and implementation, since not all patients with moderate risk CAP are hospitalized. The panel agreed to maintain the risk stratification of CAP regardless of setting of care.

RECOMMENDATION 1

We do NOT recommend gram stain and culture of respiratory secretions for low risk CAP. (*Strong recommendation, very low quality of evidence*)

RECOMMENDATION 2

We recommend gram stain and culture of respiratory secretions for patients with moderate to high risk CAP, or with risk factors for MDRO infection. (*Strong recommendation, low quality of evidence*)

2. Blood CS

A 2004 retrospective cohort study involving 13,043 patients with pneumonia found that predictors of bacteremia include systolic BP <90 mmHg (odds ratio [OR] 1.7, 95% CI 1.3–2.3), temperature <35 or ≥40°C (OR 1.9, 95% CI 1.4–2.6), pulse rate ≥125/min (OR 1.9, 95% CI 1.6–2.3), liver disease (OR 2.3, 95% CI 1.6–3.4), blood urea nitrogen ≥30 mg/dL (OR 2.0, 95% CI 1.8–2.3), serum sodium <130 mmol/L (OR 1.6, 95% CI 1.3–2.1), and WBC <5,000/mm^3 or > 20,000/mm^3 (OR 1.7, 95% CI 1.4–2.0). These predictors of bacteremia are more often found in individuals with severe illness (Metersky ML et al. 2004).

A 2001 prospective cohort study of 209 patients with pneumonia found a statistically significant trend towards bacteremia among patients with higher Pneumonia Severity Index (PSI) grade. The PSI is an early prediction rule that uses a combination of demographic factors, co-morbid illnesses, laboratory and chest x-ray findings to determine prognosis (Fine et al. 1997). In the cohort study, 38 patients had positive blood cultures. Out of the 38 patients, 66% had PSI III or IV which connotes more severe (Waterer et al. 2001).

A 2011 study used a structured systematic chart audit of hospitalized patients with CAP to find predictors of bacteremia. The records of 89 patients with positive blood cultures and 169 patients with negative blood cultures were reviewed. After logistic regression

analysis, 4 variables were significantly associated with positive blood culture results, namely WBC <4.5×10^9/L (likelihood ratio [LR] 7.75, 95% CI 2.31-26), serum creatinine >106 µmol/L (LR 3.15, 95% CI 1.71-5.8), serum glucose <6.1 mmol/L (LR 2.46, 95% CI 1.14-5.32), and temperature >38°C (LR 2.25, 95% CI 1.21-4.2). Similarly, these variables are often associated with more severe disease (Campbell et al. 2011).

In 2009, a scoring system to predict bacteremia was constructed based on epidemiological and clinical variables among patients with CAP. Derivation and internal validation cohorts were acquired through retrospective analysis of database of 3,116 patients. Derivation of predictive factors for bacteremia was done via multivariate logistic regression. Predictive factors such as presence of liver disease, tachycardia, tachypnea, pleuritic pain, systolic hypotension (<90 mmHg) and absence of prior antibiotic treatment were identified and assigned a score of 1 point for each variable. Bacteremia was present in less than 8% of patients who scored $\leq$1, and in 14-63% of patients who scored $\geq$ 2. This study demonstrated that the risk of bacteremia is higher in patients with severe illness (Falguera et al. 2009).

In contrast, in a prospective cohort of patients suspected of CAP, no association was found between the severity of illness as determined by the PSI score and the positivity rate of blood cultures. The investigators also found that patients with a positive blood culture had only a 34.8% chance of having a change in treatment based on blood culture results (Campbell et al. 2003).

An observational study of hospitalized patients with pneumonia admitted through the emergency room also showed a low positivity rate of blood cultures (23 out of 684 blood cultures or 3.4%). This study, however, did not differentiate between patients with CAP and those with hospital-acquired pneumonia (Benenson et al. 2007).

The IDSA guidelines for the treatment of CAP pneumonia recommend that blood cultures be obtained for hospitalized patients. Similarly, the NICE guidelines for the same condition recommend that blood cultures be done only for individuals with moderate- or high-severity CAP.

Remarks and Consensus Issues

The panelists discussed that the benefits of blood CS are for prognostication and antimicrobial surveillance. The downside would be the cost of the test. There may be an implementation issue, since there will be lower yield in the blood CS once the patient is given antibiotics.

One panelist voted abstain in recommendation 4 since in his opinion, blood CS should be recommended for high risk CAP only

RECOMMENDATION 3

We recommend blood cultures for patients with moderate and high risk CAP. (*Strong recommendation, low quality of evidence*)

3. Influenza Testing

Influenza infection is a self-limited disease which causes uncomplicated, acute febrile respiratory symptoms but may also cause significant morbidity and mortality (Uyeki et al. 2019). Influenza virus can result in pneumonia which may be severe or fatal. Individuals infected with influenza are also at risk for co-infection or secondary infection by bacterial pathogens. The defined influenza season in the Philippines is from June to November (Lucero et al. 2016).

Shown in Figure 1 is a guide from the U.S. Centers for Disease Control website for influenza testing when influenza virus is circulating in the community (Centers for Disease Control and Prevention 2009).

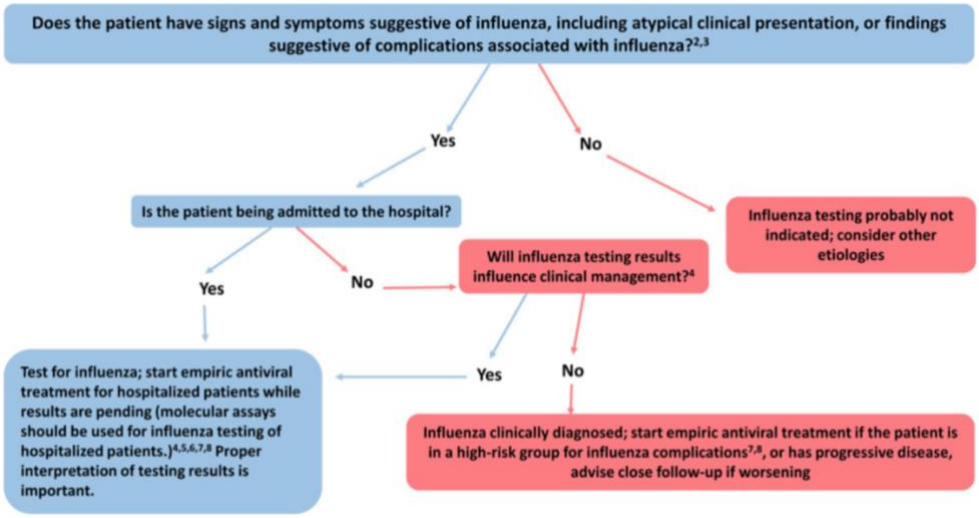

Figure 1. Guide for influenza testing from Centers for Disease Control

The benefits of antiviral therapy support testing of patients during periods of high influenza activity (Metlay et al. 2019). IDSA recommends the use of rapid influenza molecular assays over rapid influenza diagnostic tests (RIDTs) for detection of influenza viruses in respiratory specimens of outpatients, and the use of Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or other molecular assays for hospitalized patients (Uyeki et al. 2019).

A systematic review and meta-analysis done in 2017 evaluated the diagnostic accuracy of commercialized RIDTs, digital immunoassays (DIAs), and rapid nucleic acid amplification tests (NAATs) compared with RT-PCR as the reference standard in detecting influenza A and B infection among children and adults with suspected influenza. The study also evaluated patient, test, and methodological factors associated with test accuracy within each of the 3 classes of rapid tests. A total of 162 studies were included, with 130 studies on RIDTs, 19 studies on DIAs, and 13 studies on NAATs (Merckx et al. 2017).

Results of the meta-analysis showed that the pooled sensitivity of NAATs is higher compared to DIAs and RIDTs. The specific values are shown in Table 5.

Table 5. Pooled sensitivity of diagnostic tests for influenza A and B.

	Sensitivity of NAATs % (95% CI)	Sensitivity of DIAs % (95% CI)	Sensitivity of RIDTs % (95% CI)
Influenza A	91.6 (84.9-95.9)	80 (73.4-85.6)	54.4 (48.9-59.8)
Influenza B	95.4 (87.3-98.7)	76.8 (65.4-85.4)	53.2 (41.7-64.4)

A 2019 systematic review and meta-analysis evaluated the diagnostic accuracy of rapid molecular tests for respiratory viruses such as influenza and respiratory syncitial virus compared to conventional molecular tests. Based on data from 56 studies, rapid molecular tests showed high pooled sensitivity of 90.9% (95% CI 88.7%-93.1%) and high pooled

specificity of 96.1% (95% CI 94.2%-97.9%). Of the 56 studies, 29 were on rapid molecular tests for influenza (Vos et al. 2019).

The same 2019 study also included a systematic review of 15 clinical impact studies of rapid molecular tests for respiratory viruses. The studies were heterogenous, with wide variation in design and quality. Results of the impact of rapid molecular tests on antibiotic prescriptions, duration of antibiotic therapy, oseltamivir prescriptions, length of hospital stay, hospital admissions, safety, costs, and turnaround time were inconclusive (Vos et al. 2019).

RECOMMENDATION 4

We recommend testing of respiratory secretions for influenza through rapid molecular testing using rapid nucleic acid amplification tests during periods of high influenza activity (July to January) for patients with high risk CAP preceded by influenza-like illness symptoms (sore throat, rhinorrhea, body malaise, joint pains) and any of the following risk factors:

- Aged 60 years and above
- Pregnant
- Asthmatic
- Other co-morbidities: uncontrolled diabetes mellitus, active malignancies, neurologic disease in evolution, congestive heart failure class II-IV, unstable coronary artery disease, renal failure on dialysis, uncompensated COPD, decompensated liver disease

(*Conditional recommendation, low to moderate quality of evidence*)

4. Legionella Urine Antigen Test

The 2018 NICE clinical practice guidelines for the diagnosis and management of pneumonia in adults recommends considering the use of *Legionella* urine antigen tests (UATs) in moderate to severe CAP (conditional recommendation, low quality of evidence) (National Clinical Guideline Centre 2014).

The 2019 American Thoracic Society (ATS) and IDSA guidelines suggest not routinely testing urine for *Legionella* antigen in adults with CAP unless indicated by epidemiological factors such as in *Legionella* outbreaks, patients with history of recent travel, or patients with severe CAP (conditional recommendation, low quality of evidence) (Metlay et al. 2019).

A 2009 systematic review and meta-analysis evaluated the use of UATs for diagnosing Legionellosis. The pooled sensitivity for *Legionella* UATs was 74% (95% CI 68%-81%). Pooled specificity was high at 99.1% (95% CI 98.4%-99.7%). However, the studies included in the review did not provide information on the severity of pneumonia or the patients' immune status (Shimada T et al. 2009).

A multicenter, prospective, surveillance study of hospitalized patients with CAP in 2018 evaluated the sensitivity and specificity of the IDSA/ATS indications for performing UATs in identifying *Legionella*. These indications include ICU admission, failure of outpatient antibiotic therapy, active alcohol abuse, recent travel, and pleural effusion. Among 1,941 patients with UAT results, 32 (1.6%) tested positive for *Legionella*. The presence of ≥ 1 IDSA/ATS indication for *Legionella* UAT had 63% sensitivity (95% CI 44%-79%) and 35% specificity (95% CI 33%-37%) for detecting *Legionella pneumophila* (Bellew et al. 2018).

A major issue with the use of UAT is whether positive results will significantly alter therapy, since most guidelines recommend that patients with severe CAP be given empiric

treatment with antibiotics active against this pathogen. A randomized control trial was conducted in 2009 on 177 hospitalized patients with CAP who were given empiric guideline-directed treatment or pathogen-directed treatment based on UAT results. Out of the 88 patients given pathogen-directed treatment, 25 (28%) had positive UAT results, with 22 patients positive for *Streptococcal pneumoniae* and 3 patients positive for *Legionella*. There were no statistical differences in death (relative risk [RR] 1.96, 95% CI 0.08-46.86), clinical relapse (RR 6.08, 95% CI 1.29-28.46), ICU admission (RR 1.96, 95% CI 0.08-46.86), length of hospitalization, and length of antibiotic treatment in the 2 treatment groups (Falguera et al, 2009).

Another randomized study in 2005 evaluated empiric versus pathogen-directed treatment among hospitalized patients with moderate to high risk CAP. Out of 262 patients, only 14 (5.34%) had positive *Legionella* UATs. Patients who received pathogen-directed treatment had similar clinical outcomes compared to those given empiric guideline-directed treatment, including mortality (odds ratio [OR] 1.99, 95% CI 0.95-4.18), rates of clinical failure (OR 1.13, 95% CI 0.66-1.95), and length of hospitalization (van der Eerden, 2005).

In an observational study conducted in 54 countries to describe real-life microbiological testing of adults hospitalized with CAP, it was observed that 30.1% or 1,113 patients out of the total 3,702 patients hospitalized with CAP had *Legionella* UAT done (Carugati et al. 2018).

A multicenter retrospective study evaluated factors that contributed to targeted antibiotic treatment prescription. The study involved 861 adult patients with positive UAT, of which 174 (20.2%) were positive for *Legionella,* Results showed that antibiotic reassessment leading to targeted prescription occurred in only 25.3% of patients with *Legionella* infections (Mothes et al. 2016).

In summary, RCTs do not demonstrate benefit for *Legionella* UAT. This finding is accompanied by concerns that narrowing the spectrum of antibiotic therapy in response to positive UATs could lead to increased risk of clinical relapse. Current empiric treatment recommendations for patients with severe CAP already include the use of antibiotics with activity against *Legionella*.

RECOMMENDATION 5

Legionella urine antigen tests may be considered for patients with high risk CAP.

(*Conditional recommendation, low quality of evidence*)

5. Multiplex PCR

One open-label pragmatic RCT conducted in 2017 evaluated the impact of routine point-of-care testing for respiratory viruses using multiplex polymerase chain reaction (PCR) compared to routine clinical care among adults with acute respiratory illness. Results of the study showed no significant reductions in antibiotic use (OR 0.99, 95% CI 0.57-1.70) and duration of antibiotic use (mean difference [MD] -0.4 days, 95% CI -1.2 to 0.4). The mean length of hospital stay was shorter in the point-of-care testing group (MD -1.1 days, 95% CI -2.2 to -0.3). There was a trend towards benefit for multiplex PCR guided-antiviral use (OR 1.33, 95% CI 0.89-1.99), safety (OR 0.82, 95% CI 0.6-1.2), use of hospital isolation facilities (OR 1.45, 95% CI 0.94-2.27), and mortality within 30 days (OR 0.54, 95% CI 0.3-1.2) (Brendish et al. 2017).

Similar results were found in 2 observational studies that evaluated respiratory virus testing using multiplex PCR. The observational study in 2015 involved 1,136 participants with acute respiratory tract illness (Rogers et al. 2015). The other observational study was conducted in 2017 and involved 800 patients admitted with respiratory symptoms (Semret et al. 2017). These 2 studies demonstrated similar trends toward benefit of multiplex PCR in the reduction in antibiotic use, duration of antibiotic use, length of hospital stay, and use of hospital isolation facilities, and multiplex PCR guided-antiviral use. However, the results were not statistically significant.

RECOMMENDATION 6

We do not recommend the routine use of multiplex polymerase chain reaction among adult patients with CAP. (*Strong recommendation, moderate quality of evidence*)

B. Treatment

6. Empiric Treatment for Low-risk CAP

Comparison of different antibiotic regimen in patients with low risk CAP showed similar outcomes across antibiotic types. A systematic review (Maimon et al. 2008) comparing cephalosporins (oral, cefuroxime [500 mg twice daily for 10 days] or cefditoren [200/400 mg twice daily for 14 days]) and co-amoxiclav (oral, 125/500 mg three times daily for 10 days or 125/875 mg twice daily for 14 days) showed similar clinical success within 10 days following treatment completion between the two groups (2 Randomized Controlled Trials [RCTs], n=551, 90.7% versus 91.8%, Relative Risk (RR) 1.01, 95% CI 0.95-1.08). Likewise, a trial by Llor and colleagues (2017) that compared amoxicillin (oral, 1 g three times daily for 10 days) and phenoxymethylpenicillin (oral, 1,600,000 IU three times daily for 10 days) in adults with community-acquired pneumonia treated as outpatients showed a trend in favor of amoxicillin for clinical cure at day 14 in intention-to-treat analysis (1 RCT, n=39, RR 1.40, 95% CI 1.00-1.96, Number needed to treat (NNT) 4 [2 to 21]. In the intention-to-treat analysis, amoxicillin was not significantly different to phenoxymethylpenicillin for complete clinical resolution (defined as total resolution of acute symptoms and signs related to infection or adverse events) at day 14 (1 RCT, n=39, 48.0% versus 21.4%, RR 2.24, 95% CI 0.76-1.96), but amoxicillin was significantly more effective than phenoxymethylpenicillin at day 30 (1 RCT, n=39, 92.0% versus 57.1%, RR 1.61, 95% CI 1.01-2.57, NNT 3 [2 to 15].

Comparison between the different macrolides (azithromycin vs clarithromycin, clarithromycin vs erythromycin) by Pakhale and colleagues (2014) showed no difference in clinical response at 14 to 21 days and bacteriologic response. The most common adverse events noted were abdominal pain, nausea and vomiting. However, there was no difference in the number of adverse events between azithromycin and clarithromycin (1 RCT, n=499, 26.3% versus 24.6%, RR 1.07, 95% CI 0.79-1.44), while higher adverse events, majority being gastrointestinal symptoms, were present in the erythromycin group as compared to the clarithromycin group (2 RCTs, n=476, 45.7% vs. 21.4%, RR 0.46, 95% CI 0.35-0.61).

Comparison of a beta lactam (cefixime) and a fluoroquinolone (ciprofloxacin) by Ige and colleagues (2015) showed lower rates of people with radiologic consolidation at day 14 (RR 0.27, 95% CI 0.10-0.75) in the cefixime group; there was no difference in the number of people with bacterial isolates at day 3 (RR 0.90, 95% CI 0.72-1.13); and fewer people with bacterial isolates at day 14 among patients on beta lactam (cefixime) (RR 0.20, 95% CI 0.06-0.65). Three RCT comparing fluoroquinolones and macrolides, on the other hand, showed

no difference in clinical success and bacteriologic response among patients with CAP (Fogarty 1999; Gotfried 2002 ; D'Ignazio et al. 2005).

There is only one small study (n=243) with a low quality of evidence showing similar efficacy of doxycycline compared to a macrolide in treatment of patients with acute bronchitis and pneumonia (RR 0.89, 95% CI 0.64-1.22) (Weisner, 1993).

In the choice of treatment regimen among patients with low risk CAP, two randomized controlled trials comparing macrolide versus beta lactam showed similar rates of clinical cure, bacteriologic response and pathogen eradication (Salvazerra et al, 2018; Bonvehi 2003). Similarly, another RCT (n=268) by Paris and colleagues (2008) demonstrated equivalence between a beta lactam (Amoxicillin-Clavulinate) and macrolide (azithromycin) in terms of clinical success (92.6% vs 93.1%; RR 0.99, 95% CI 0.93-1.06) and bacteriological response and (91.4% vs 90.9%, RR 1.01, 95% CI 0.87-1.17) at the end of therapy (day 8 to 12).

Table 6. Summary of Evidence for Low-Risk CAP

OUTCOMES	Measure of Treatment Effect	95% Confidence Interval	Interpretation	Basis
B-lactam vs Fluoroquinolone				
Number of people with radiologic consolidation at day 14	RR 0.27	0.10-0.75	Favors B-lactam	1 RCT
Number of people with bacterial isolates at day 3	RR 0.90	0.72-1.13	Not significant	1 RCT
Number of people with isolates at day 14	RR 0.20	0.06-0.65	Favors B-lactam	1 RCT
Macrolide vs Fluoroquinolone				
Clinical response	RR 0.99	0.96 – 1.03	Not significant	3 RCTs
Bacteriologic response	RR 0.99	0.95 – 1.03	Not significant	3 RCTs
Any adverse events	RR 1.15	0.96 – 1.37	Not significant	3 RCTs
Macrolide vs Doxycycline				
Clinical response	RR 0.89	0.64 – 1.22	Not significant	1 RCT
Macrolide vs B-lactam				
Clinical cure	RR 1.03	0.97 – 1.10	Not significant	2 RCTs
Bacteriologic response	RR 0.97	0.88 – 1.06	Not significant	2 RCTs
Pathogen eradication	RR 0.98	0.91 – 1.05	Not significant	1 RCT
Number of people reporting adverse event	RR 1.50	0.93 – 2.42	Not significant	1 RCT
Clinical success at end of therapy	RR 0.99	0.93-1.06	Not significant	1 RCT
Bacteriologic response at end of therapy	RR 1.01	0.87-1.17	Not significant	1 RCT
Number of people reporting serious adverse events	RR 0,97	0.20-4.72	Not significant	1 RCT

The advantage of using some extended macrolides over amoxicillin on Streptococcus pneumoniae is the once-a-day dosing of azalide. Currently the 2018 Antimicrobial Resistance Surveillance Program (ARSP) report showed a 13% erythromycin resistance for Streptococcus pneumonia. In terms of side effects, however, Paris and colleagues (2008) demonstrated significantly more reports of abdominal pain in patients

given macrolides (azithromycin) compared to a beta lactam (co-amoxiclav) (1 RCT, n=268, 9.6% versus 1.5%, RR 6.31, 95% CI 1.45-27.42).

The 2018 ARSP report also shows consistent level of resistance of Streptococcus pneumoniae to penicillin using meningeal breakpoints at 16%, hence the recommendation to maintain dose of Amoxicillin at 1 g TID.

Studies on the need of atypical coverage among patients with low risk pneumonia are limited; data on the effectiveness of atypical coverage primarily comes from studies among hospitalized patients with moderate to severe pneumonia. A large meta-analysis (Eliakim-Raz, 2012) which included 28 trials with 5,939 patients showed no difference in terms of 30 day mortality, total adverse events, and treatment discontinuation between patients who received atypical antibiotics and those who did not. Other studies among hospitalized patients showed that atypical coverage reduced mortality and economic burden (Ye et al, 2015) and improved clinical stability (Garin et al, 2014). However, the 2019 IDSA recommended a beta lactam or cephalosporin in combination with either a macrolide or doxycycline for low risk pneumonia patients with co-morbidities to ensure adequate coverage. Such patients have risk factors for antibiotic resistance by virtue of previous contact with the healthcare system and/or prior antibiotic exposure and are likely more vulnerable to poor outcomes if the initial empiric antibiotic regimen is inadequate (Metlay et al 2019).

The choice between these antibiotics requires a risk–benefit assessment for each patient. The US Food and Drug Administration (FDA) warned regarding fatal arrhythmia for azithromycin while fluoroquinolones have FDA labels for tendonitis, tendon rupture, central nervous system effects, peripheral neuropathy, myasthenia gravis exacerbation, QT prolongation and Torsades de Pointes, phototoxicity, and hypersensitivity. Hence careful selection regarding choice of antibiotic regimen should be considered.

Remarks and Consensus Issues

The consensus panel voted against monotherapy of Doxycyline and Levofloxacin for treatment of low risk CAP due to inferiority in coverage for Streptococcus pneumonia and prevalence of tuberculosis in the country, respectively.

RECOMMENDATIONS 7 and 8

For empiric treatment of low-risk CAP, we recommend the use of the following:

Patients with low risk CAP without co-morbidities:	Amoxicillin 1 gram, three times daily *(Strong recommendation, low quality of evidence)* **OR** Clarithromycin 500mg, twice daily **OR** Azithromycin 500mg once daily *(Strong Recommendation, low quality of evidence)*
Patients with low risk CAP with stable co-morbidities	*Beta-lactam* Co-amoxiclav (amoxicillin/clavulanate 500 mg/125 mg three times daily, OR amoxicillin/ clavulanate 875 mg/125 mg twice daily) **OR** Cefuroxime 500mg, twice daily *(Strong recommendation, moderate quality of evidence)*

	PLUS OR MINUS (+/-) *Macrolide* Clarithromycin 500mg, twice daily **OR** Azithromycin 500mg once daily *(Strong recommendation, low quality of evidence)* **OR** Doxycycline 100mg, twice daily *(Conditional recommendation, low quality of evidence)*

7. *Empiric Treatment for Moderate-risk CAP*

Based on moderate quality of evidence, combination beta-lactam plus macrolide therapy have similar clinical outcomes compared to fluoroquinolone monotherapy in patients with moderate risk CAP.

Eight randomized controlled trials of hospitalized patients with community acquired pneumonia comparing beta lactam plus macrolide therapy versus fluoroquinolone monotherapy showed a trend towards increased clinical response in the beta-lactam + macrolide group (7 RCTs, n=1167, RR 1.05, 95% CI 1.00-1.11); rates of 90-day mortality, bacteriologic response and adverse events were comparable between two groups. [IDSA/ATS 2019 (Lee 2002; Ling 2007; Frank et al 2002; Fogatry et al 2004, Portier 2005; Postma 2015; Xu 2006; and Zervos 2004)].

A meta-analysis comparing fluoroquinolones (Levofloxacin or moxifloxacin) versus combination therapy with macrolides (azithromycin, erythromycin, clarithromycin, roxithromycin) plus beta-lactam (ceftriaxone, co-amoxiclav, amoxicillin, penicillin and cefoperazone) was done by Raz-Pasteur and colleagues (2015), in hospitalized adult patients with CAP. The study included all the studies used in the IDSA/ATS 2019 evidence profile and one other study by Ramirez et al, 2003. The meta-analysis became the basis of the NICE evidence profile. The meta-analysis showed that fluoroquinolones as monotherapy were not significantly different to macrolides plus beta-lactams as combination therapy in adults with community-acquired pneumonia for 30 days mortality (5 RCTs, n=2,683, RR 0.99, 95% CI 0.70 to 1.40) and microbiologic failure (7RCTs, n = 35, RR 0.93, 95% CI 0.63 to 1.38). Fluoroquinolones as monotherapy showed significantly lower clinical failure (9 RCT, n=2241, RR 0.72, 95% CI 0.57-0.91), and treatment discontinuation (6 RCTs, n=2,179, RR 0.65, 95% CI 0.54-0.78), Although not statistically significant , in the subgroup of patients with pneumococcal pneumonia, higher clinical failure rate was seen in the quinolone monotherapy arm (7 RCT, n=145, RR 2.03, 95% CI 0.94–4.38). Rates of adverse events were similar between the two groups (RR 0.90, 95% CI 0.81-1.00). Fewer people reported diarrhea (3 RCTs, n=617, RR 0.13, 95% CI 0.05-0.34) in the fluoroquinolone monotherapy arm compared to the combination arm.

However, potential serious adverse effects should be considered in the use of fluoroquinolones. The US FDA, currently has warnings about fluoroquinolone's risks for tendonitis, tendon rupture, central nervous system effects, peripheral neuropathy, myasthenia gravis exacerbation, QT prolongation and Torsades de Pointes, phototoxicity,

and hypersensitivity. A meta-analysis by Liu, X and colleagues (2017) showed increased risk of serious arrhythmias (RR 2.29, 95% CI: 1.20–4.36) and increased risk of cardiovascular death (RR 1.60, 95% CI: 1.17–2.20) in both current and former users of fluoroquinolones. In the subgroup analysis of fluoroquinolone type, gatifloxacin (RR 6.27, 95% CI 3.11–12.66), moxifloxacin (RR 4.20, 95% CI 1.91–9.27), and levofloxacin (RR 1.41, 95% CI 1.16–1.70) showed increased risk of serious arrhythmia. Overall treatment with fluoroquinolones, on the other hand, was not associated with an increased risk of all-cause death (RR 1.02, 95% CI 0.76–1.37, P=.92). Hence, fluroquinolones should be used with caution, especially among patients with cardiac risks. Likewise, we do not recommended fluoroquinolone as first line treatment option for moderate risk CAP due to issue of mycobacteria tuberculosis resistance. It is recommended that fluoroquinolones be reserved for the treatment of pulmonary tuberculosis, particularly for multi-drug resistant tuberculosis.

Two randomized trials by Garin (2014) and Postma and colleagues (2015) comparing beta-lactam monotherapy versus beta-lactam plus macrolide in treatment of hospitalized community acquired pneumonia showed that the treatment regimens were comparable with regards to 30 day mortality (RR 1.39, 95% CI 0.63-3.08) presence of any adverse events (RR 0.99, 95% CI 0.20-0.48), and in-hospital length of stay (median length of stay comparable in both groups). However, although most secondary outcomes (ICU admission, new pneumonia, complicated pleural effusion, in-hospital mortality) did not differ between the 2 treatment groups, patients in the beta-lactam monotherapy had more re-admissions within 30 days (RR 2.54, 95% CI 1.19-5.39) compared to the beta-lactam plus macrolide treatment .

Table 7. Summary of Evidence for Moderate Risk CAP

OUTCOMES	Measure of Treatment Effect	95% Confidence Interval	Interpretation	Basis
Fluoroquinolone vs B-lactam + macrolide				
Clinical response	RR 1.05	1.00 – 1.10	Trend towards increase in fluoroquinolones	7 RCTs
Bacteriologic response	RR 1.02	0.90 – 1.16	Not significant	6 RCTs
Any adverse events	RR 0.98	0.88 – 1.09	Not significant	7 RCTs
90-day mortality	AOR 1.37	0.96-1.97	Not significant	1 RCT
30 days mortality	RR 0.99	0.70-1.40	Not Significant	5 RCT
Microbiologic failure	RR 0.93	0.63 – 1.38	Not significant	7 RCTs
Clinical failure	RR 0.72	0.57-0.91	Decreased in fluoroquinolones	9 RCTs
Treatment discontinuation	RR 0.65	0.54-0.78	Decreased in fluoroquinolones	6 RCTs
Clinical failure in pneumococcal pneumonia	RR 2.03	0.94-4.38	Not significant	7 RCTs
Number of people reporting diarrhea	RR 0.13	0.05-0.34	Decreased in fluoroquinolones	3 RCTs
Any adverse events	RR 0.90	0.81-1.00	Trend towards	7 RCTs

			decrease in fluoroquinolones	
B-lactam vs B-lactam + macrolide				
30-day Mortality	RR 1.39	0.63-3.08	Not significant	1 RCT
In hospital mortality	RR 1.14	0.42-3.09	Not significant	1 RCT
ICU admission	RR 0.85	0.40-1.81	Not significant	1 RCT
New pneumonia	RR 1.66	0.61-4.49	Not significant	1 RCT
Complicated pleural effusion	RR 0.57	0.24-1.33	Not significant	1 RCT
In-hospital mortality	Median and IQR provided for both studies. Garin: BL=8 (6-13) days and for BL/M=8 (6-12) days. Postma: BL=6 (4- 8) days and BL/M=6 (4-10) days.			2 RCTs
Re-admission within 30 days	RR 2.54	1.19-5.39	Increased in beta-lactam group	1 RCT

AOR: Adjusted Odds Ratio; IQR: Interquartile range

A search was done beyond the end of search date of the 2019 IDSA/ATS and NICE guidelines for additional studies. A study by Liu (2019) comparing respiratory fluoroquinolone monotherapy and beta-lactams with or without macrolides for patients hospitalized for CAP showed non-significant advantage of respiratory fluroquinolone over beta lactam with or without macrolide with similar clinical and microbiologic success but with low quality of evidence.

Remarks and Consensus Issues

Since Ceftaroline has a broader coverage including against MRSA, the consensus panel voted against its use for moderate risk CAP due to antimicrobial stewardship. The alternative therapy of using monotherapy of respiratory fluoroquinolone was not accepted by the consensus panel due to prevalence of tuberculosis in the country.

RECOMMENDATION 9

For empiric treatment of moderate-risk CAP without MDRO infection, we recommend a combination therapy using the following:

Patients with moderate risk CAP without MDRO infection	*Non-pseudomonal Beta-lactam antibiotic* Ampicillin-sulbactam 1.5–3 g every 6 h **OR** Cefotaxime 1–2 g every 8 h **OR** Ceftriaxone 1–2 g daily **PLUS** *Macrolide* Azithromycin 500 mg daily **OR** Clarithromycin 500 mg twice daily) *(Strong recommendation, moderate quality of*

	evidence)

8. *Empiric Treatment for High-risk CAP*

Based on low to moderate level of evidence, macrolide-containing regimens for high-risk CAP were associated with a significant mortality reduction compared to non macrolide-containing therapies.

In a systematic review which included 17 studies involving 16,684 hospitalized patients with CAP, Vardakas and colleagues (2017) showed that the combination of beta-lactam/fluoroquinolone therapy was associated with higher mortality than beta-lactam/macrolide combination therapy (RR 1.33, 95% CI 1.15-1.54).

A search was done for additional studies beyond the end of search date (2017) of the 2019 IDSA/ATS and NICE CAP guidelines. A meta-analysis by Liu (2019) included 22 studies with 6,235 patients compared respiratory fluoroquinolone monotherapy vs beta-lactams with or without macrolides for hospitalized CAP showed similar mortality (RR 0.82, 95% CI 0.65-1.02), clinical success (RR 1.03, 95% CI 0.99-1.08), and adverse event rates (RR 0.99, 95% CI 0.74-1.34) in both groups.

Regarding the choice of macrolide to be used in combination with a beta-lactam, a non-inferiority trial by Tamm and colleagues (2007), (n=278) compared ceftriaxone plus azithromycin versus ceftriaxone plus clarithromycin/erythromycin in hospitalized patients for CAP. Results of the study showed no significant difference between treatment groups for bacterial eradication (RR 1.09, 95% CI 0.83 – 1.43), clinical success (RR 1.13, 95% CI 0.64 – 1.99), and incidence for adverse events (RR 0.80, 95% CI 0.59-1.10).

Other considerations:

A separate, retrospective study (Zervos 2003) that examined the relationship of fluoroquinolone use and the development of fluroquinolone resistance over a 10 year period, across 10 institutions in the United States, showed that increasing institutional use of fluoroquinolones was associated with decreased percentage of fluoroquinolone susceptibility of *E.coli, P.aeruginosa, E.cloacae ,* and *S.aureus*.

Remarks and Consensus Issues

Similar to moderate risk CAP recommendation, the consensus panel voted against the use Ceftaroline for high risk CAP due to antimicrobial stewardship.

RECOMMENDATION 10

For empiric treatment of high-risk CAP without risk for MDRO infection, we recommend the use of the following:

Patients with high risk CAP without MDRO infection	**FIRST LINE THERAPY** *Non-pseudomonal Beta-lactam antibiotic* Ampicillin-sulbactam 1.5–3 g IV every 6 h **OR** Cefotaxime 1–2 g IV every 8 h **OR**

	Ceftriaxone 1–2 g IV daily **PLUS** *Macrolide* Azithromycin 500 mg PO/IV daily **OR** Erythromycin 500 mg PO every 6 hours **OR** Clarithromycin 500 mg PO twice daily *(Strong recommendation, low quality of evidence)*
	ALTERNATIVE THERAPY *Non-pseudomonal Beta-lactam antibiotic* **PLUS** *Respiratory fluoroquinolone** Levofloxacin 750 mg PO/IV daily **OR** Moxifloxacin 400 mg PO/IV daily (*Conditional recommendation, low quality of evidence)* ** given as 1 hour IV infusion*

IV: Intravenous; PO: per orem

9. *Atypical coverage for Aspiration pneumonia*

The contribution of anaerobic bacteria to the pathogenesis of aspiration pneumonia continues to be the subject of debate because of the tedious and delicate techniques required for the transport media and culture of these organisms. Limited studies have shown isolation of anaerobes among hospitalized patients with suspected aspiration. In a descriptive study of institutionalized elderly with severe aspiration by El Sohl and colleagues (2003) and Bowerman and colleagues (2018), results showed that both gram-negative and gram-positive bacteria isolates predominates among patients with suspected aspiration, while anaerobes were infrequently identified.

To this date there are no clinical trials available comparing treatment regimens with and without anaerobic coverage for patients hospitalized with suspected aspiration. However, in the background of increasing prevalence of antibiotic resistant pathogens and antibiotic complications, judicious use of antibiotics is encouraged, such that IDSA 2019 CAP guideline does not recommend routinely adding anaerobic coverage for suspected aspiration pneumonia unless lung abscess or empyema is suspected (Conditional recommendation, very low quality of evidence).

RECOMMENDATION 11

Routine anaerobic coverage for suspected aspiration pneumonia is NOT recommended, unless lung abscess or empyema is suspected *(Conditional recommendation, Very low quality of evidence)*

10. *Empiric Treatment for MDROs and their risk factors*

The IDSA 2019 CAP guidelines abandoned the use of the categorization of Healthcare-associated pneumonia (HCAP). Many studies showed that the risk factors that defined HCAP did not predict higher prevalence of pathogens resistant to standard first-line antibiotic therapy. More importantly, the use of HCAP only resulted in a significant increased use of broad-spectrum antibiotics (especially vancomycin and antipseudomonal beta-lactams) without improvement in patient outcomes. As a replacement, the IDSA 2019 CAP guidelines proposed obtaining local data on the prevalence of multi-drug resistant organisms (MDRO) in patients with CAP, along with identification of risk factors for these infections at a local level.

A recent multicenter, prevalence study involving 3,193 adult hospitalized CAP patients from 54 countries (excluding the Philippines) with microbiologic test done reported that 3% of infections are due to MRSA (Aliberti 2016). Subanalyses of the same cohort reported a prevalence of 4.2% for CAP due to *Pseudomonas aeruginosa* (Restrepo 2018) and 6% for drug-resistant Enterobacteriaceae (Villafuerte 2019). However, there are no systematic reviews on the risk factors associated with CAP due to MDROs, and no validated scoring systems exist to identify patients who are at risk for CAP due to MRSA and *P. aeruginosa.* Observational cohort studies have identified the risk factors distinct for MRSA, *P. aeruginosa*, and MDR Enterobacteriaceae**.**

MRSA

The most strongly and consistently associated risk factors for CAP due to MRSA were previous MRSA colonization or infection, especially of the respiratory tract, within 1 year [(OR 6.21, 95% CI 3.25-11.85), Aliberti 2016; (OR 6.05, 95% CI 2.99-12.22), Jung 2013], and intravenous antibiotic therapy within 90 days (OR 4.87, 95% CI 2.35-10.1), Wooten 2012).

P. aeruginosa

Previous *P. aeruginosa* colonization or infection of the respiratory tract (OR 16.10, 95%CI 9.48-27.35) and severe bronchopulmonary disease [very severe chronic obstructive pulmonary disease {COPD} (OR 2.76, 95% CI 1.25-6.06)], bronchiectasis (OR 2.88, 95% CI 1.65-5.05), prior tracheostomy (OR 6.5, 95% CI 2.61-16.19) were independent risk factors for CAP due to *P. aeruginosa* (Restrepo 2018). A single-center, observational study in the Spain involving 2,023 adult hospitalized patients also cited chronic respiratory illness as an independent risk factor for *P. aeruginosa* CAP (OR 2.26, 95% CI, 1.25-4.10), (Cilloniz 2016). Intravenous antibiotic therapy within 90 days, meanwhile was an independent risk factor for drug-resistant *P. aeruginosa* CAP (Cilloniz 2016).

Enterobacteriaceae

Prior colonization or infection with extended-spectrum beta-lactamase (ESBL) producing organisms were associated with CAP due to MDR EB (OR 8.50, 95% CI 3.12-23.16) (Villafuerte 2019).

As emphasized in the IDSA 2019 CAP guideline, obtaining local data on the prevalence of MDRO in patients with CAP is important along with identification of risk

factors for these infections at a local level. Strong independent risk factors for respiratory infection with MDRO have been identified in several studies and include prior isolation or colonization of these organisms, recent hospitalization, and exposure to parenteral antibiotics.

There are no randomized trials comparing empiric antibiotic treatment for CAP caused by MRSA, Pseudomonas, or ESBL. The choice of antibiotics should still be based on antibiotic susceptibility test results.

The IDSA 2019 CAP guideline recommended the addition of either vancomycin or linezolid in the empiric treatment of CAP with risk for MRSA. This was based on the recommendation of the 2016 IDSA/ATS CPG for the management of adults with HAP and VAP. In hospitalized adult patients with hospital-acquired pneumonia, treatment with linezolid versus vancomycin had similar clinical success and mortality rates, however, nephrotoxicity was associated more frequently with vancomycin use (IDSA 2016).

The use of clindamycin for empiric coverage of MRSA is not recommended in the US setting due to increased resistance rate of isolates to the drug (Moran *et al.* 2012). However, based on the 2018 ARSP Annual Report, percent resistance for MRSA is only 11.6% in our setting.

As summarized in the 2016 IDSA analysis of randomized controlled studies evaluating empiric antibiotic treatments for HAP and VAP with Pseudomonas cohort, there was no difference in all-patient mortality with the use of the antimicrobial agents with *Pseudomonas* activity (IDSA 2016).

There are no studies on the use of ceftazidime-avibactam, tigecycline, ceftolozane-tazobactam, or ceftriaxone-sulbactam among patients with CAP with risk for MDRO.

RECOMMENDATION 12

For moderate to high risk CAP with risk factors for MDROs, empiric antibiotics should be started for the following risk categories as tabulated below: *(Strong recommendation, Low to moderate quality of evidences)*

Risk Factors and Organisms	**Empiric Antibiotic Recommendations**
Risk for Methicillin Resistant Staphylococcus aureus (*MRSA*) • Prior colonization or infection with MRSA within 1 year • Intravenous antibiotic therapy within 90 days	*Non-pseudomonal Beta lactam antibiotic* **PLUS** *Macrolide* **OR** *respiratory fluoroquinolone** **PLUS** Vancomycin 15 mg/kg IV every 12 hours^ **OR** Linezolid 600 mg IV every 12 hours ^ **OR** Clindamycin 600 mg IV every 8 hours^
Risk for *ESBL* • Prior colonization or infection with ESBL-producing organisms within 1 year	**REPLACE** *Non-pseudomonal Beta lactam antibiotic* with: Ertapenem 1g IV every 24 hours **OR** Meropenem 1 g IV every 8 hours (if Ertapenem is not available)

	PLUS *Macrolide* **OR** *respiratory fluoroquinolone**
Risk for *Pseudomonas aeruginosa* • Prior colonization or infection with P aeruginosa within 1 year • Severe bronchopulmonary disease (severe COPD, bronchiectasis, prior tracheostomy)	**REPLACE** *Non-pseudomonal Beta lactam antibiotic* with: Piperacillin-Tazobactam 4.5g IV every 6 hours **OR** Cefepime 2 g IV every 8 hours **OR** Ceftazidime 2 g IV every 8 hours **OR** Aztreonam 2 g IV every 8 hours **OR** Meropenem 1 g IV every 8 hours (especially if with ESBL risk) **PLUS** *Macrolide* **OR** *respiratory fluoroquinolone**

^ dose based on 2011 IDSA guideline for treatment of MRSA pneumonia
*given as 1 hour IV infusion
Certain agents require higher doses than normally used for non MDR infections based on PK/PD data. All doses listed are for patients with normal renal function.

11. Antiviral Treatment

The CAP guideline of the ATS/IDSA favors the use of antiviral therapy for adults with CAP who test positive for influenza virus. For inpatients, use of antiviral therapy is a strong recommendation based on moderate quality of evidence. For outpatients, use of antiviral therapy is a conditional recommendation based on low quality of evidence (Metlay et al. 2019).

The IDSA influenza guideline recommends giving antibiotic and antiviral treatment for patients with suspected or laboratory-confirmed influenza with bacterial coinfection who present with severe disease such as extensive pneumonia, respiratory failure, hypotension, and fever (Uyeki et al. 2019).

A randomized, open label, trial evaluated the effect of providing oseltamivir compared to standard of care on clinical failure. Clinical failure was defined as failure to reach clinical improvement within 7 days, transfer to the intensive care unit after 24 hours in a ward, or need for re-hospitalization within 30 days. The study involved 1,107 adult patients hospitalized with influenza-associated lower respiratory tract infections. Results of the study showed no significant difference in clinical failure (RR = 0.56, 95% CI 0.20-1.60) (Ramirez et al. 2018).

RECOMMENDATION 13

We recommend antiviral therapy in addition to antibacterial therapy among patients with high risk CAP and any of the following risk factors (aged 60 years and above, pregnant, asthmatic, other co-morbidities: copy comorbids as with the stratification) who test positive for influenza virus. (*Strong recommendation, low quality of evidence*)

RECOMMENDATION 14

If diagnostic tests are not accessible, empiric antiviral therapy may be considered in addition to antibacterial therapy during periods of high influenza activity (July to January) among patients with high risk CAP preceded by influenza-like illness symptoms (sore throat, rhinorrhea, body malaise, joint pains) and any of the following risk factors:

- Aged 60 years and above
- Pregnant
- Asthmatic
- Other co-morbidities: uncontrolled diabetes mellitus, active malignancies, neurologic disease in evolution, congestive heart failure class II-IV, unstable coronary artery disease, renal failure on dialysis, uncompensated COPD, decompensated liver disease

(*Conditional recommendation, very low quality of evidence*)

12. *Initiation of Treatment*

Antibiotics, the mainstay for the treatment of pneumonia, should be initiated as soon as a diagnosis of CAP is made. Time of the first antimicrobial dose (TFAD) is defined as the time in hours from arrival at the emergency department (ED) to the intravenous infusion of the antimicrobial. (Bordon 2013) NICE CPG 2019 recommends that antibiotic therapy be started as soon as possible after diagnosis, and within 4 hours of admission (Strong Recommendation, Low Quality of Evidence).

The NICE CAP Guideline Development Group (GDG) acknowledged that making an early confident diagnosis of CAP is not always straightforward. They concluded that when a diagnosis of CAP is made with reasonable confidence, it is desirable to administer antibiotic therapy as soon as possible. However, this has to be balanced with avoiding inappropriate antibiotic prescribing for patients who do not have CAP, but in whom this is considered a potential differential diagnosis. Earlier antibiotic prescribing could be associated with higher rates of misdiagnosis and inappropriate prescribing, which could result in harm to patients (such as adverse events due to antibiotic therapy) and to the wider population (such as increased antibiotic resistance) as well as being wasteful from an economic standpoint. However, it was considered that the cost of adverse events and inappropriate prescribing were likely to be outweighed by the additional risk of mortality associated with inappropriately delayed antibiotic therapy.

Swift diagnostic procedures should be encouraged as part of the timing recommendation wherever possible, without discouraging clinical judgment. In patients with suspected CAP who are severely ill, antibiotic therapy should not be withheld until investigations such as chest X-ray are performed. (NICE CPG CAP, 2019)

The NICE CAP CPG included thirteen cohort studies with majority of the patients having moderate- to high-severity CAP. The studies used a variety of average time to antibiotic administration (timing cut-off), antibiotic therapy and outcomes that made direct comparisons difficult, as well as adjusting for different variables. Inconsistency and imprecision were seen in many results, and some studies did not adequately adjust for

confounding factors hence were considered of low to very low quality by the modified GRADE criteria.

The NICE GDG's review of evidence looked at the effectiveness of early timing of empiric antibiotic treatment in terms of the following outcomes: mortality, clinical cure, length of hospital stay, and adverse events:

Antibiotic therapy ≥ 4 hours vs ≤4 hours

For the key outcome of mortality, the majority of the studies (mainly retrospective chart reviews) suggested that administering antibiotic therapy within the first 4 hours of admission was beneficial in reducing mortality. Data from retrospective studies showed inconsistent results in terms of length of stay and re-admission. Pooled estimates of effect were not provided by the NICE GDG, likely due to the fact that most of the included studies were unable to adjust for all key confounders.

Subgroup data from one retrospective study by Houck et al (2004) including almost 19,000 patients suggested that the benefit of antibiotic administration within the first 4 hours of admission was slightly greater for patients with low-to moderate-severity CAP compared with the high-severity group for the outcomes of (1) 30-day mortality- AOR: 0.62 (95% CI 0.42-0.92) for low-to-mod-severity vs 0.87 (95% CI 0.78-0.97) for high-severity), (2) length of hospital stay AOR 0.86 (95% CI 0.75 - 0.99) for low-to-mod-severity vs 0.92 (95% CI 0.84 - 1.01) for high-severity and (3) re-admission after discharge AOR 0.87 (95% CI 0.70-1.08) for low-to-mod-severity vs 0.99 (95% CI 0.88-1.11) for high-severity.

Antibiotic therapy ≥ 8 hours vs ≤8 hours

For the outcome of mortality, NICE reviewed evidence from six observational studies (four looked at 30-day mortality, two looked at in-hospital mortality). Results were heterogenous across studies, with two of the larger studies (Meehan 1997 and Houck 2004) suggesting benefit in 30-day mortality among those who received antibiotics early.

The clinical events in CAP go from establishment of infection, to onset of symptoms and arrival in the ED to TFAD. The priority of the management of patients with presumptive pneumonia should be to increase the accuracy of the diagnosis of CAP for appropriate and timely antimicrobial therapy. (Bordon 2013) Rather than designating a specific window in which to initiate treatment, the 2007 IDSA guidelines committee felt that hospitalized patients with CAP should receive the first antibiotic dose in the ED. The committee does feel that therapy should be administered as soon as possible after the diagnosis is considered likely.

RECOMMENDATION 15

As soon as diagnosis is established, treatment of community acquired pneumonia, regardless of risk, should be initiated within 4 hours. *(Strong recommendation, very low quality of evidence)*

13. *Duration of Treatment*

Most of the studies regarding the duration of treatment are done among in-patients and a systematic review by Lopez-Alcalde (2018) found that there is lack of evidence on the optimal duration of antibiotic treatment among outpatients with CAP.

The recommendations for the duration of antibiotic therapy for CAP vary across different studies. However, based on moderate level of evidence, there is no significant difference of clinical cure in patients receiving short course versus long course antibiotic treatment among admitted CAP patients. Short course antibiotic treatment is associated with lower mortality rate and fewer adverse events.

In a meta-analysis by Tansaril and colleagues (2018) of 4,816 patients in 21 clinical trials that evaluated the efficacy of short-course antibiotic treatments in adult patients with CAP showed that short course antibiotic treatments are as effective as long course antibiotic therapy. This study showed no significant difference between patients receiving short course treatment ($\leq$ 6 days) versus long course treatment ($\geq$ 7 days) in terms of clinical cure (RR 0.99, 95% CI 0.97-1.01); whether patients were at the outpatient setting (RR 0.98, 95% CI 0.96-1.00) or inpatient setting (RR 1.00, 95% CI 0.92-1.09); or for patients having mild to moderate pneumonia (RR 0.99, 95% CI 0.96- 1.01) or severe pneumonia (RR 1.05, 95% CI 0.96-1.14).

Patients who received short course antibiotic therapy showed lower mortality rate compared to those receiving long course therapy (RR 0.52, 95% CI 0.33-0.82).There is no difference in the antibiotic related adverse events between short and long course treatment groups (RR 1.11, 95%CI 0.94-1.31) which usually includes gastrointestinal symptoms, rash, headache and elevation in transaminase. However, there are fewer serious adverse events including death, life threatening events and prolongation or need for hospitalization in the short course treatment group. (RR 0.73, 95% CI 0.55-0.97).

The IDSA/ATS recommend to treat patients with CAP guided by validated measure of clinical stability (resolution of vital sign abnormalities, ability to eat and normal mentation) for a minimum of 5 days (strong recommendation, moderate quality of evidence). The society recommends a longer duration of therapy in (1) pneumonia complicated by meningitis, endocarditis and other deep-seated infection; or (2) infection with other, less common pathogens (e.g. Burkholderia pseudomallei, Mycobacterium tuberculosis or endemic fungi).

The NICE clinical guidelines for pneumonia in adults, updated in 2019, recommend to determine the duration of antibiotic therapy according to the severity of CAP. The guideline recommends a 5-day course of antibiotic therapy to patients with community-acquired pneumonia unless microbiology results suggest infection with a pathogen that may require longer course length or the person is not clinically stable (if there is presence of fever within 48 hours or more than one sign of clinical instability based on blood pressure, heart rate, respiratory rate and oxygen saturations). (Strong recommendation, low to moderate quality of evidence).

RECOMMENDATION 16:

Among patients with low to moderate risk CAP, a treatment duration of 5 days is recommended as long as the patient is clinically stable (afebrile within 48 hours, able to eat, normal blood pressure, normal heart rate, normal respiratory rate, normal oxygen saturation, and return to baseline sensorium) *(Strong recommendation, moderate quality of evidence)*

RECOMMENDATION 17:

Antibiotic therapy may be extended according to clinical consideration such as:

(1) pneumonia is not resolving, (2) pneumonia complicated by sepsis, meningitis, endocarditis and other deep-seated infection, (3) infection with less common pathogens (i.e. Burkholderia pseudomallei, Mycobacterium tuberculosis, endemic fungi, etc), (4) infection with a drug resistant pathogens. *(Best practice)*

14. *De-escalation*

Treatment is usually started empirically for a patient before the full clinical picture is known. After 48 hours, microbiology, radiographic and clinical information are generally available; the clinician needs to re-evaluate the management given and whether there should be changes in the therapy (Public Health England, 2015). In addition, clinical stability may also be seen by this time (Halm, 1998). Hence, clinical response to antibiotic therapy should be assessed within 48-72 hours after initiation of antibiotics.

A systematic review (Athanassa et al. 2008) of 6 RCTs compared early switch (2-4 days) of IV to oral antibiotic (coamoxiclav, ceftriaxone, levofloxacin or cefuroxime to co-amoxiclav, cefpodoxime plus clarithromycin, erythromycin, levofloxacin or cefuroxime) to continuous IV antibiotics (cefuroxime, ceftriaxone and co-amoxiclav) among adult patients with moderate to severe CAP. Early IV to oral switch compared to the continuous IV antibiotics resulted in significantly less hospitals days (weighted mean difference -3.34, 95% CI -4.42 to -2.25) and less drug-related adverse events (OR 0.73, 95% CI 0.59 to 0.92). No significant difference in mortality (OR 0.81, 95% CI 0.49-1.33), treatment success (OR 0.92, 95% CI 0.61-1.39) or incidence of recurrent infections (OR 1.81, 95% CI 0.70-4.72)

A retrospective observational study of 796 patients done in Hawaii (You 2018) showed that among CAP patients receiving empiric MRSA coverage, only 2.6% was actually MRSA positive and that 35.7% had no evidence of MRSA infection or colonization. Propensity matched subjects (96 subject/arm) in the study showed that continuous vancomycin use among patients with CAP suspected of having MRSA was associated with a longer duration of hospital stay (OR 1.23 95% CI 1.15-1.30) but no difference in mortality compared was observed (You et al, 2018).

In an observational study among 978 adult in patients with CAP whose cultures do not yield any drug resistant organisms, there was also no significant difference between propensity score matched de-escalation and continuous antibiotic treatment groups in 15 day mortality (5% vs 5%, 95% CI -3.6 to 3.6) or in patient mortality (14.4% vs 13.3%, mortality rate diff of 1.1% 95% CI -4.7-6.8). However, mortality rate was significantly higher among patients in the de-escalation group classified as having extremely severe CAP (17.9% vs 2.9%, mortality difference 15% 95% CI 0.4-29.6). (Yamana et al, 2016).

Among 1,536 admitted non-ICU patients suspected of CAP, median time to de-escalation was 3.0 days (IQR 2.0–4.0 days). Crude 30-day mortality was 3.5% (9/257) and 10.9% (107/986) in the de-escalation and continuation groups, respectively. The crude and adjusted hazard ratios for de-escalation compared to continuation were 0.40 (95% CI: 0.20–0.80) and 0.39 (95% CI: 0.19–0.79) for day-30 mortality (van Heijl et al, 2019).

There are no studies evaluating the individual criteria to determine clinical improvement. A meta analysis of observational studies by Rhew in 2001 among adult patients with community acquired pneumonia summarized the criteria for early switch from parenteral to oral therapy. The following parameters maybe used as criteria for de-escalation: resolution of fever for more than 24 hours, improvement of cough and WBC counts, with no respiratory distress, no bacteremia, no signs of unstable comorbid

condition or any life threatening complication, no signs of organ dysfunction; patient is able to take oral fluids and oral medication with no malabsorption and etiologic agent is not a high risk pathogen.

The choice of antibiotics depends on available culture results, antimicrobial spectrum, efficacy, safety and cost. In general, when switching to oral antibiotics either the same agent as the parenteral antibiotic or an antibiotic from the same drug class should be used.

While de-escalation provides no advantage in survival compared to continuous IV therapy, the reduction in the length of hospital stay provides pharmacoeconomic advantages in reducing the cost of healthcare.

Remarks and Consensus Issues

In de-escalating, the duration of antimicrobial treatment is inclusive of the IV treatment.

RECOMMENDATION 18

De-escalation of initial empiric broad spectrum or extended spectrum antibiotic with coverage for MRSA, Pseudomonas or ESBL to targeted or oral antibiotics based on culture results is recommended once the patient is clinically improving, hemodynamically stable and able to tolerate oral medications. *(Strong recommendation, moderate quality of evidence)*

15A. *Monitoring Response with Chest x-ray*

There are limited data follow-up chest x-ray to monitor treatment response in CAP. The latest IDSA/ATS guidelines in 2019 recommend against repeat chest imaging in patients with CAP who are clinically improving. However, studies reviewed to support this recommendation revealed that these are studies wherein a repeat chest xray is done in order to detect a lung malignancy, rather than to monitor for treatment response. Our own search yielded very few studies investigating the role of chest imaging (particularly chest xray) in monitoring response to treatment within a few days of CAP diagnosis. In 2014, Little et al reviewed 618 cases in which the radiologist recommended follow-up imaging for presumed CAP. Compliance with follow-up imaging was 76.7%, complete resolution was seen in 69.1% using chest x-ray. Further chest CT performed for those with persistence or worsening abnormality showed 8% cancer matching abnormality and 23.8% benign diagnosis including TB, eosinophilic pneumonia, fungal infections (Figure 15A.1).

To determine the time to resolution of chest radiograph abnormalities, a prospective study by Bruns (2007) obtained follow up chest x-rays at Day 7 and 28 in patients with pneumonia. At day 7, 25% of the patients had resolution of chest radiograph abnormalities, whereas 56% had clinical improvement (mean difference, 31%; 95% confidence interval, 25%–37%). At day 28, 53% of the patients had resolution of chest radiograph abnormalities, and 78% had clinical cure (mean difference, 25%; 95% confidence interval, 19%–31%).

Another prospective cohort by Bruns (2009) compared radiographic and clinical cure of CAP at day 10 and 28. Radiographic resolution, clinical cure and normalization of

the CAP score were observed in 30.8%, 93% and 32% of patients at day 10, and in 68.4%, 88.9% and 41.7% at day 28, respectively. In mild to moderately severe CAP, resolution of radiographic abnormalities and resolution of symptoms scored by the patient lag behind clinical cure assessed by physicians.

The British Thoracic Society guidelines in 2009 recommends a repeat chest x-ray around 6 weeks for patients with persistent signs and symptoms of signs of pneumonia. They also recommend a repeat chest x-ray after 6 weeks for those patients with an increased chance of having an underlying malignancy, particularly in smokers or in those more than 50 years old. In the study by Little, et al. in 2014 noted that around 1.5% of their subjects were found to have underlying malignancy in follow up imaging.

Remarks and Consensus Issues

This recommendation excludes other conditions that may warrant repeat CXR.

RECOMMENDATION 19:

Among adult patients who are being treated for community-acquired pneumonia and who are clinically improving, follow up chest x-ray should NOT routinely be performed to monitor response to treatment. (*Strong recommendation, low quality of evidence*)

RECOMMENDATION 20:

We recommend post-treatment chest x-rays after a minimum of 6 to 8 weeks among patients with CAP to establish baseline and to exclude other conditions. (*Strong recommendation, low quality of evidence*)

15B. *Monitoring Response with CRP*

C-reactive protein (CRP) has been studied as a screening test for inflammation, a marker for disease severity, and a diagnostic adjunct. Four prospective cohort studies analyzed the diagnostic accuracy of CRP in treatment failure, mortality, and pneumonia complications.

A 2008 study involving 570 patients with CAP showed that CRP levels ≥10 mg/dL is sensitive but nonspecific, with low positive predictive value and high negative predictive value, in predicting 30-day hospital mortality, use of mechanical ventilator or inotropic support, and complicated pneumonia. Sensitivity values ranged from 94.8% to 97.6%, while specificity values ranged from 33.9% to 35.7% (Chalmers et al. 2008).

A 2009 study with 394 participants demonstrated that CRP levels <3 mg/dL on day 3 on treatment has low sensitivity (35%) but high specificity (89%) in predicting absence of severe complications. There was high positive predictive value (97%), and low negative predictive value (11%) (Menendez et al. 2009).

In a 2012 study involving 191 patients with severe CAP, serial CRP measurements were performed and the CRP-ratio, which was calculated in relation to the CRP level at day

1, was calculated. Results showed that higher CRP ratios of >0.5 on day 5 is a marker of poor outcome (sensitivity 81%, specificity 58%). In addition, day 5 CRP ratios of >0.5 was independently associated with ICU mortality (adjusted OR 4.47, 95% CI 1.64-12.20) (Coelho et al. 2012).

A 2009 study with 384 participants showed that an increment of 5 mg/dL of CRP levels on admission increases the risk of the patient to be unstable by 6% (hazard ratio [HR] 1.06, 95% CI 1.02-1.11) (Hohenthal et al. 2009).

The IDSA CAP guideline has no recommendation regarding the use of CRP. In the Korean CAP guideline, there is a weak recommendation based on low level of evidence for the use of repeated CRP measurements to assess the risk of treatment failure and complications in patients who do not clinically show clear symptom improvements (Lee et al. 2018).

RECOMMENDATION 21:

We do not recommend the use of CRP to monitor treatment response among patients with CAP (*Strong recommendation, low quality of evidence*)

15C. *Monitoring Response with Procalcitonin*

In a randomized controlled trial (n=1359) examining the procalcitonin for respiratory infections, the Procalcitonin Guided Antibiotic Therapy and Hospitalization in Patients with Lower Respiratory Tract Infections (ProHOSP) study, concluded that procalcitonin guidance for respiratory patients in a variety of settings resulted in a significant reduction in total antibiotic exposure (median 4 days vs 8 days) with no difference in mortality rates or rates of treatment failure (Schuetz et al. 2009) Furthermore, the largest trial to date was the Stop Antibiotics on Procalcitonin Guidance study (SAPS) also recommends clinician to stop antibiotics if procalcitonin was </=0.5µg/L or if it decreased by >/= 80% of peak value but discourages procalcitonin as a guide for initiation of antibiotics at the time of suspected infection (Assink-de Jong et al. 2013)

RECOMMENDATION 22:

We do not recommend the use of Procalcitonin to monitor treatment response among patients with CAP (*Strong recommendation, low quality of evidence*)

RECOMMENDATION 23:

Procalcitonin may be used to guide antibiotic discontinuation among patients with moderate or high risk CAP. (*Conditional recommendation, low quality of evidence*)

16. What should be done for patients who are not improving after 72 hours of empiric antibiotic therapy?

Nonresponding pneumonia or failure to improve may be due to:

1. Incorrect diagnosis or presence of a complicating noninfectious condition e.g., pulmonary embolism, congestive heart failure, vasculitis, myocardial infarction
2. A resistant microorganism or an unexpected pathogen that is not covered by the antibiotic choice
3. Antibiotic is ineffective or causing an allergic reaction i.e., poor absorption of the oral antibiotic, certain drug interactions, inadequate dose, patient not taking or receiving the prescribed antibiotic
4. Impaired local or systemic host defenses e.g., aspiration, endobronchial obstruction, bronchiectasis, systemic immune deficiency
5. Local or distant complications of pneumonia e.g., parapneumonic effusion, empyema, lung abscess, ARDS, metastatic infection, endocarditis
6. Overwhelming infection
7. Slow response in the elderly patient; S. pneumoniae and L. pneumophila may cause slow resolution of pneumonia in the elderly
8. Exacerbation of comorbid illnesses
9. Nosocomial superinfection

In patients who are seen after the antibiotic therapy has already been initiated, if the choice is among the recommended options and the dose is correct but the patient has not improved after 72 hours, then the antibiotic should be changed. If the dose is inadequate, the dose should be corrected and the drug continued.

RECOMMENDATION 24:

The clinical history, physical examination, and the results of all available investigations should be reviewed. The patient should be reassessed for possible resistance to the antibiotics being given or for the presence of other pathogens such as Mycobacterium tuberculosis, viruses, parasites, or fungi. Treatment should then be revised accordingly. *(Moderate quality of evidence*)

RECOMMENDATION 25:

Follow-up chest radiograph is recommended to investigate for other conditions such as pneumothorax, cavitation, and extension to previously uninvolved lobes, pulmonary edema, and acute respiratory distress syndrome. (*Moderate quality of evidence*)

RECOMMENDATION 26:

Obtaining additional specimens for microbiologic testing should be considered. (*Moderate quality of evidence)*

C. Prevention

16. *Prevention with Pneumococcal and Influenza Vaccine*

Pneumococcal vaccine

There is no head-to-head comparison of Pneumococcal polysaccharide vaccine (PPSV) and Pneumococcal conjugate vaccine (PCV) for pneumonia, invasive pneumococcal disease, and mortality. Thus, individual studies were assessed as to their efficacy.

PPSV23 is effective in preventing CAP among the elderly, invasive pneumococcal disease (IPD) and mortality due to CAP and pneumococcal disease. A meta-analysis by Apolinario et. al pooled results of 9 randomized trials, with a total of 156,194 participants aged 18 years old and above. The study showed RR 0.89 (95% CI 0.79-1.01, I^2 = 28%) of acquiring pneumonia from any cause after administration of PPSV23 versus not receiving the vaccine. A subgroup analysis (7 RCTs, n=3,026) was done among targeted adults that included those ≥ 65 years old and adults 19-64 years old at high risk of acquiring pneumonia, and the study showed a risk ratio of 0.78 (95% CI 0.65-0.94, I^2= 6%).

In a meta-analysis by Moberley, the vaccine was shown to be effective in preventing pneumococcal pneumonia (10 RCTs, n=35,483) with an odds ratio of 0.26 (95% CI 0.15-0.46). The vaccine can also be used for invasive pneumococcal disease from all pneumococcal strains (11 RCTs, n = 36,489) with an odds ratio of 0.26 (95% CI 0.14-0.45). The effect on mortality was also assessed (14 RCTs, n= 47,560) and the vaccine was not associated with preventing all-cause mortality (OR 0.90, 95% CI 0.74-1.09), however it was with a high level of statistically heterogeneity with I^2 of 69%, $p<0.0001$. A sub-group analysis of prevention of mortality due to pneumonia or pneumococcal disease by PPSV (9 RCTs, n=30,723) showed a relative risk of 0.62 (95% CI 0.50-0.76) with significant heterogeneity (I^2=74%). The heterogeneity of studies in the analysis for PPSV23 may be due to the presence of selection bias and detection bias of some of the studies, with inadequate concealment of allocation and inadequate blinding. This is especially true for the older studies, probably due to inadequate reporting, and varied vaccine formulations.

In a large randomized trial by Bonten with 84,492 adult aged 65 years old and older, there was no evidence that PCV13 can prevent pneumococcal community acquired pneumonia (RR 0.95, 95% CI 0.86-1.05) compared to placebo. However, PCV13 was shown to be effective in reducing invasive pneumococcal disease from any pneumococcal strain, which showed a risk ratio of 0.52 (95% CI 0.34-0.78). A risk ratio of 1.00 (95% CI 0.95-1.05) among those who received PCV13 in preventing all-cause mortality was also shown in the same study. Mortality from pneumonia or pneumococcal disease with PCV 13 showed a risk ratio of 0.86 (95% CI 0.29-2.55). However, a meaningful analysis of this data could not be done because of the small number of events.

The most common side effects after vaccination include redness, swelling and soreness at injection site. Fever, malaise and muscle pain can also occur, although this is infrequent. Allergic reactions may also occur due to the vaccine or vaccine components.

Influenza vaccine

A systematic review of by Demicheli, et. al. examined the effect of parenteral influenza vaccine compared to placebo or no vaccination among healthy adults of age16 to 64 years old. A significant reduction on the incidence of influenza was illustrated (25 RCTs, n= 71,221) with influenza vaccine compared to placebo or do nothing with a relative risk of 0.41 (95% CI 0.36-0.47). The study likewise showed (16 RCTs, n=25,795) reduction in influenza-like illnesses (RR 0.84, 95% CI 0.75-0.95) however, both had low quality of evidences. The vaccine showed no difference in the incidence of hospitalizations based on three RCTs (n=11,924) with low quality of evidence (RR 0.96, 95% CI 0.85-1.08). Those who received the influenza vaccine had significantly higher rates of local adverse reaction (RR 2.44, 95% CI 1.82-3.28) but not systemic adverse reactions (RR 1.16, 95% CI 0.87-1.53).

There were no studies that examined the benefit of influenza vaccine in preventing pneumonia among healthy adults. There was, however, a systematic review of influenza vaccine for the elderly that considered influenza, pneumonia and other complications in the outcome by Demicheli. A meta-analysis of three RCTs showed significant reduction in the incidence of influenza (RR 0.42, 95% CI 0.27-0.66) and in influenza-like illness (RR 0.59, 95% CI 0.47-0.73) among those who received the vaccine. Limited information was obtained from one RCT (n=699), a placebo-controlled trial on the effectiveness of influenza vaccination in preventing pneumonia. None of the study participants developed pneumonia over a one-year follow-up period (imputed RR: 0.34, 95%CI: 0.02 to 5.43). There was no significant difference in the two groups in all-cause mortality (RR 1.02, 95% CI 0.11-9.02) and adverse event outcomes such as general malaise and fever, however there were more participants who reported local tenderness and sore arm in the intervention group (RR 3.56, 95% 2.61-4.87).

In the same study for elderly, an analysis of nine cohort studies showed significantly fewer hospitalizations for flu or pneumonia (RR 0.73, 95% CI 0.62-0.85) if the elderly received influenza vaccine compared to without vaccination. Pooled data of two cohort studies that included 18,090 elderly patients also did not show significant difference on the incidence of pneumonia whether the subject received the vaccine or not (RR 0.88, 95% CI 0.64-1.20). There was no difference (RR 0.87, 95% CI 0.70-1.09) on the death rates from influenza or pneumonia among elderly population based on one cohort study. Five cohort studies showed no significant difference for hospitalization for any respiratory disease (RR 0.88 95% CI 0.54-1.43). There was also no significant difference in incidence of influenza and influenza-like illness in the two groups.

The systematic review conducted a subgroup analysis of observational studies in elderly patients with and without risks. Patients without risks experienced fewer incidence of pneumonia (RR 0.59, 95% CI 0.37- 0.92), hospitalization for influenza or pneumonia (RR 0.50, 95% CI 0.40, 0.63), and combined all deaths or severe respiratory disease (RR 0.62, 95% CI 0.54-0.70). The risks identified were lung disease, heart disease, renal disease, diabetes and other endocrine disorders, immunodeficiency or immunosuppressive diseases, cancer, dementia or stroke, vasculitis or rheumatic disease. There was no significant difference in the incidence of influenza, however there was an increase in deaths from respiratory disease among those who received the vaccine (RR 1.41, 95% CI 1.31, 1.53). Among elderly patients with risks, there was no sufficient evidence that influenza vaccine had an effect on the incidence of pneumonia (RR 1.22 95% CI 0.76, 1.94) and influenza (RR 0.40 95% CI 0.14-1.17). There was a significant reduction in hospitalization for influenza or

pneumonia (RR 0.74, 95% CI 0.63-0.86), death from any respiratory disease (RR 0.92, 95% CI 0.86-0.98) and combined all deaths or severe respiratory disease (RR 0.60 95% CI 0.49-0.74).

Table 8. Summary of Evidence for Prevention of CAP

OUTCOMES	Measure of Treatment Effect	95% Confidence Interval	Interpretation	Basis
PNEUMOCOCCAL VACCINES				
Community Acquired Pneumonia				
PPSV23 for all adults vs. placebo	RR 0.89	0.79-1.01	Not significant	9 RCTs
PPSV23 for high risk population including adults 65 years old and above vs. placebo	RR 0.78	0.65-0.94	Favors PPSV23	7 RCTs
PCV 13 vs. placebo	RR 0.95	0.86-1.05	Not significant	1 RCT
Invasive Pneumococcal Disease				
PPSV23 vs. placebo	OR 0.26	0.14-0.45	Favors PPSV23	11 RCTs
PCV 13 vs. placebo	RR 0.52	0.34-0.78	Favors PCV 13	1 RCT
All cause mortality				
PPSV23 vs. placebo	OR 0.90	0.74-1.09	Not significant	14 RCTs
PCV 13 vs. placebo	RR 1.00	0.95-1.05	Not significant	1 RCT
Mortality due to Pneumonia or IPD				
PPSV23 vs. placebo	RR 0.62	0.50-0.76	Favors PPSV23	9 RCTs
PCV 13 vs. placebo	RR 0.86	0.29-2.55	Not significant	1 RCT
INFLUENZA VACCINE				
Community Acquired Pneumonia				
Influenza vaccine among elderly vs. placebo	Imputed RR 0.34	0.02-5.43	Not significant	1 RCT
Influenza				
Influenza vaccine vs. placebo or do nothing	RR 0.41	0.36-0.47	Favors influenza vaccine	25 RCTs
Influenza vaccine among elderly vs. placebo	RR 0.42	0.27-0.66	Favors influenza vaccine	3 RCTs
Influenza-like illness				
Influenza vaccine vs. placebo or do nothing	RR 0.84	0.75-0.95	Favors influenza vaccine	16 RCTs
Influenza vaccine among elderly vs. placebo	RR 0.59	0.47-0.73	Favors influenza vaccine	3 RCTs
Hospitalization for flu or pneumonia				
Influenza vaccine among adults vs. placebo	RR 0.96	0.85-1.08	Not significant	3 RCTs
Influenza vaccine among elderly vs. placebo	RR 0.73	0.62-0.85	Favors influenza vaccine	9 cohort studies
All cause mortality				
Influenza vaccine among elderly vs.	RR 1.02	0.11-9.02	Not significant	1 RCT

placebo				

Combined administration of Pneumococcal and Influenza Vaccines

A meta-analysis of 3 cohort studies on combination of pneumococcal vaccine and influenza vaccine showed significant reduction of hospitalization from influenza or pneumonia or respiratory diseases (RR 0.67, 95% CI 0.64-0.70) and all deaths (RR 0.44 95% CI 0.41-0.46) in the intervention arm compared to those who did not receive the vaccine). Another cohort study also showed significant reduction of deaths from influenza or pneumonia among patients who received a combination of pneumococcal and flu vaccine (RR 0.43, 95% CI 0.33, 0.57).

In a separate systematic review among the elderly by Zhang, pooled results (4 observational studies, n=128,340) showed significant reduction in pneumonia (RR 0.74, 95% CI 0.62-0.88) and all-cause mortality (RR 0.84, 95% CI 0.62-0.88) when both pneumococcal vaccine and influenza vaccine were given to elderly patients compared to those who received influenza vaccine alone. (The studies administered the vaccines either simultaneously or one month apart. The meta-analysis has very low quality of evidence as it combined both elderly patients from the community and from nursing homes. The study did not report any adverse event in concomitant administration of the vaccines.

RECOMMENDATION 27:

Pneumococcal polysaccharide vaccine (PPSV) or pneumococcal conjugate vaccine (PCV) are recommended for the prevention of invasive pneumococcal disease in adults 50 years old and older. *(Strong recommendation, moderate quality of evidence)*

RECOMMENDATION 28:

Pneumococcal polysaccharide vaccine is recommended for adults to prevent (a) pneumococcal pneumonia, (b) mortality from IPD or pneumonia and (c) pneumonia among high-risk groups and adults 50 years and above. (*Strong recommendation, low quality of evidence)*

RECOMMENDATION 29:

Influenza vaccine is recommended to prevent influenza, influenza-like illness and hospitalization in all adults. (*Strong recommendation, low quality of evidence*

RECOMMENDATION 30:

Administration of both influenza and pneumococcal vaccine is recommended to prevent pneumonia, hospitalization and mortality in adults 50 years old and above (*Strong recommendation, very low quality of evidence)*

V. DISSEMINATION AND IMPLEMENTATION

The final version of the guideline will be published as a separated document and to facilitate implementation, the full text will be distributed during the Annual Convention of Philippine College of Physicians (PCP) and Philippine Society for Microbiology and Infectious Diseases (PSMID). The CPG will likewise be accessible online at the PCP and PSMID websites for downloading.

VI. APPLICABILITY ISSUE

The recommendation as to the drug, dosage and frequency are limited to adults with normal kidney and liver functions with no known allergies to the drugs. History and physical examination prior to administration should be done to identify those at risk and adjust accordingly.

In giving empiric treatment, options are provided for the health care provider such that in the case that one drug or one class of drug is contraindicated or is not available, alternatives can be used. This is especially true in community or remote areas where some drugs are sparse and may not be readily available. Although financial capacity may limit access to some drugs (including the vaccines), this should not hinder the patient from getting adequate treatment for CAP.

VII. UPDATING OF THE GUIDELINES

An update of the the guideline shall be planned for after 3 years. Interim updates may be developed if important new evidence becomes available.

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Inadequate response after 72 hours of empiric antibiotic therapy

1**.** Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP) in Immunocompetent Adults 2010 Update. Joint Statement of the Philippine Society for Microbiology and Infectious Diseases, Philippine College of Chest Physicians, Philippine Academy of Family Physicians, Philippine College of Radiology. Retrieved July 16, 2020 from https://www.pcp.org.ph/documents/CPGs/PSMID/CAP%20GUIDELINES%20BOOKLET%202010%20UPDATE.pdf

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IX. APPENDIX A: SUMMARY OF AGREE II SCORES FOR DIFFERENT CPGS ON CAP
APPENDIX B: SUMMARY OF EVIDENCE TABLES WITH GRADE ASSESSMENT FOR OVER-ALL QUALITY
APPENDIX C: FOREST PLOTS AND SUMMARY OF FINDING TABLES

APPENDIX A: SUMMARY OF AGREE II SCORES FOR DIFFERENT CPGS ON CAP

	IDSA	**NICE**	**Swedish**	**China**	**Africa**
TOTAL	89%	89%	75%	67%	67%
Overall quality assessment	Yes (2) Yes with modifications (1)	Yes (2) Yes with modifications (1)	Yes (1) Yes with modifications (1)	Yes with modifications (2)	Yes with modifications (2)
Domain 1. Scope and Purpose	94%	89%	61%	78%	81%
Domain 2. Stakeholder Involvement	78%	87%	14%	67%	94%
Domain 3. Rigour of Development	90%	94%	46%	63%	56%
Domain 4. Clarity of Presentation	96%	94%	86%	89%	86%
Domain 5. Applicability	58%	76%	40%	92%	81%
Domain 6.	94%	75%	67%	58%	46%

Editorial Independence					

APPENDIX B. SUMMARY OF EVIDENCE TABLES WITH GRADE ASSESSMENT FOR OVER-ALL QUALITY

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.1 Cephalosporin vs Co-amoxiclav
NICE, Page 117, Table 37
Maimon 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporins[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Clinical success (including antibiotics unavailable in UK)												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	323/356 (90.7%)	179/195 (91.8%)	RR 1.01 (0.95 to 1.08)	9 more per 1000 (from 46 fewer to 73 more)	⊕⊕OO LOW	CRITICAL
Clinical success (not including antibiotics unavailable in UK)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	55/55 (100%)	49/51 (96.1%)	RR 1.04 (0.97 to 1.11)	38 more per 1000 (from 29 fewer to 106 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable

[1] Cefuroxime, 500mg twice daily for 10 days or cefditoren, 200/400mg twice daily for 14 days
[2] 125/500mg three times daily for 10 days or 125/875mg twice daily for 14 days
[3] Maimon et al. 2008
[4] Downgraded 1 level - systematic review authors judge studies to be at high or unclear risk of bias in multiple domains, as unclear if the populations in each arm are comparable, and either unclear or important differences in the care received by each arm; also unclear if randomisation adequate in 1 trial
[5] Downgraded 1 level - cefditoren is not currently licenced for any indication in the UK

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.2 Amoxicillin vs Phenoxymethylpenicillin

NICE, page 111, Table 31

Llor 2017

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Phenoxy-methylpenicillin[2]	Relative (95% CI)	Absolute		
Clinical cure (per protocol analysis; day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	25/25 (100%)	10/11 (90.9%)	NICE analysis: RR 1.12 (0.90 to 1.40)	109 more per 1000 (from 91 fewer to 364 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (intention to treat analysis; day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	25/25 (100%)	10/14 (71.4%)	NICE analysis: RR 1.40 (1.00 to 1.96)	286 more per 1000 (from 0 more to 686 more)	⊕⊕⊕O MODERATE	CRITICAL
Complete clinical resolution (intention to treat analysis; day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	12/25 (48.0%)	3/14 (21.4%)	NICE analysis: RR 2.24 (0.76 to 6.61)	266 more per 1000 (from 51 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical cure (intention to treat analysis; day 30)												
1[3]	randomised	no serious risk	NA	no serious	serious[4]	none	25/25	10/14	NICE	286 more per 1000	⊕⊕⊕O	CRITICAL
									(1.00 to 1.96)			
Complete clinical resolution (intention to treat analysis; day 30)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	23/25 (92.0%)	8/14 (57.1%)	NICE analysis: RR 1.61 (1.01 to 2.57)	349 more per 1000 (from 6 more to 897 more)	⊕⊕⊕O MODERATE	CRITICAL
Radiological resolution (intention to treat analysis; day 30)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	20/24 (83.3%)	6/11 (54.5%)	NICE analysis: RR 1.53 (0.87 to 2.70)	289 more per 1000 (from 71 fewer to 927 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk

[1] Oral, 1g, three times a day for 10 days

[2] Oral, 1,600,000 IU three times a day for 10 days

[3] Llor et al. 2017

[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with amoxicillin

[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with amoxicillin; wide confidence intervals

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.3. Azithromycin vs Clarithromycin

NICE, Page 114, Table 35

Pakhale 2014

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin microspheres[1]	Clarithromycin[2]	Relative (95% CI)	Absolute		
Clinical response (day 14 to 21; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	187/202 (92.6%)	198/209 (94.7%)	OR 0.69 (0.31 to 1.55)	19 fewer per 1000 (from	⊕⊕⊕⊕	CRITICAL
									NICE analysis: RR 0.98 (0.93 to 1.03)	66 fewer to 28 more)	HIGH	
Bacteriological cure												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	123/134 (91.8%)	153/169 (90.5%)	OR 1.17 (0.52 to 2.61)	9 more per 1000 (from 45 fewer to 81 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
									NICE analysis: RR 1.01 (0.95 to 1.09)			
Adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	65/247 (26.3%)	62/252 (24.6%)	OR 1.09 (0.73 to 1.64)	17 more per 1000 (from 52 fewer to 108 more)	⊕⊕⊕O MODERATE	CRITICAL
									NICE analysis: RR 1.07 (0.79 to 1.44)			

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Single 2g dose of azithromycin, administered as an oral suspension

[2] Extended-release clarithromycin administered orally as 2 500mg capsules once daily for 7 days

[3] Pakhale et al. 2014

[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.4. Clarithromycin vs Erythromycin

NICE, Page 113, Table 33

Pakhale 2014

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
Clinical response (cure and improvement; at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/156 (97.4%)	117/124 (94.4%)	OR 2.27 (0.66 to 7.80) NICE analysis: RR 1.03 (0.98 to 1.09)	28 more per 1000 (from 19 fewer to 85 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological cure (at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/35 (88.6%)	22/22 (100%)	OR 0.28 (0.03 to 2.57) NICE analysis: RR 0.90 (0.78 to 1.05)	100 fewer per 1000 (from 220 fewer to 50 more)	⊕⊕⊕O MODERATE	IMPORTANT
Radiological cure (at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/153 (93.5%)	116/123 (94.3%)	OR 0.91 (0.33 to 2.49) NICE analysis: RR 0.99 (0.94 to 1.06)	9 fewer per 1000 (from 57 fewer to 57 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events (at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	49/229 (21.4%)	113/247 (45.7%)	OR 0.30 (0.20 to 0.46) NICE analysis: RR 0.46 (0.35 to 0.61)	247 fewer per 1000 (from 178 fewer to 297 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; OR – odds ratio; RR – relative risk

[1] 250mg twice daily for 14 days, given at least 1 hour before or 2 hours after meals, mean treatment duration 13 days

[2] 500mg four times daily for 14 days, given at least 1 hour before or 2 hours after meals, mean treatment duration 10 days

[3] Pakhale et al. 2014

[4] Downgraded 1 level - systematic review authors judged studies to be at unclear risk of bias in either 2 or 3 domains: random sequence generation, allocation concealment and source of funding (pharmaceutical sponsor probable)

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.5. Should a beta-lactam versus respiratory fluoroquinolone be used for treatment of CAP in adults in the outpatient setting?

NICE, Page 118, Table 38

Ige 2015

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefixime[1]	Ciprofloxacin[2]	Relative (95% CI)	Absolute		
Temperature (day 3)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	Mean 37.2, SD 0.9 N= 39	Mean 37.5, SD 0.5 N= 34	-	MD 0.3 lower (0.63 lower to 0.03 higher)	⊕OOO VERY LOW	IMPORTANT
Temperature (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[6]	none	Mean 36.8, SD 0.4 N= 39	Mean 37.0, SD 0.5 N= 34	-	MD 0.2 lower (0.41 lower to 0.01 higher)	⊕⊕OO LOW	IMPORTANT
Respiratory rate (day 3)												
1	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	Mean 21.5, SD 11.2 N= 39	Mean 20.7, SD 2.6 N= 34	-	MD 0.8 higher (2.82 lower to 4.42 higher)	⊕OOO VERY LOW	IMPORTANT
Respiratory rate (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[7]	none	Mean 16.5, SD 1.1 N= 39	Mean 17.7, SD 2.5 N= 34	-	MD 1.2 higher (0.29 to 2.11 higher)	⊕⊕OO LOW	IMPORTANT
Pulse rate (day 3)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	Mean 103.9, SD 147.6	Mean 81.1, SD 18.6 N= 34	-	MD 22.8 higher (23.94 lower to 69.54 higher)	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefixime[1]	Ciprofloxacin[2]	Relative (95% CI)	Absolute		
							N= 39					
Pulse rate (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[6]	none	Mean 75.1, SD 6.6 N= 39	Mean 77.7, SD 8.0 N= 34	-	MD 2.6 higher (0.79 lower to 5.99 higher)	⊕⊕OO LOW	IMPORTANT
Number of people with radiological consolidations (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	4/39 (10.3%)	13/34 (38.2%)	RR 0.27 (0.10 to 0.75)	279 fewer per 1000 (from 96 fewer to 344 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Number of people with bacterial isolates (day 3)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[8]	none	30/39 (76.9%)	29/34 (85.3%)	RR 0.9 (0.72 to 1.13)	85 fewer per 1000 (from 239 fewer to 111 more)	⊕⊕OO LOW	IMPORTANT
Number of people with bacterial isolates (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	3/39 (7.7%)	13/34 (38.2%)	RR 0.20 (0.06 to 0.65)	306 fewer per 1000 (from 134 fewer to 359 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Abbreviations: CI – confidence interval; NA – not applicable; SD – standard deviation; MD – mean difference; RR – relative risk												

[1] 400mg twice daily for 14 days
[2] 500mg twice daily for 14 days
[3] Ige et al. 2015
[4] Downgraded 1 level – may not be applicable to UK practice as study conducted in Nigeria; however, antibiotics used are available in UK
[5] Downgraded 2 levels - at a minimal important difference of 0.5x standard deviation of ciprofloxacin, the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a minimal important difference of 0.5x standard deviation of cefixime, the effect estimate is consistent with no meaningful difference or appreciable harm with ciprofloxacin
[7] Downgraded 1 level - at a minimal important difference of 0.5x standard deviation of cefixime, the effect estimate is consistent with no meaningful difference or appreciable harm with cefixime
[8] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with ciprofloxacin

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.6. Should a macrolide versus respiratory fluoroquinolone be used for treatment of CAP in adults in the outpatient setting?

ATS / IDSA, Page E39-40

Fogarty 1999, Gotfried 2002, D'Ignazio 2005

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a macrolide	a respiratory fluoroquinolones	Relative (95% CI)	Absolute (95% CI)		
Clinical response												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	471/529 (89.0%)	480/532 (90.2%)	**RR 0.99** (0.96 to 1.03)	**9 fewer per 1,000** (from 27 more to 36 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effects												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	243/603 (40.3%)	211/593 (35.6%)	**RR 1.15** (0.96 to 1.37)	**53 more per 1,000** (from 14 fewer to 132 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
2	randomised trials	not serious	not serious	not serious	serious [a,b]	none	13/367 (3.5%)	9/355 (2.5%)	**RR 1.40** (0.61 to 3.24)	**10 more per 1,000** (from 10 fewer to 57 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	277/304 (91.1%)	311/337 (92.3%)	**RR 0.99** (0.95 to 1.03)	**9 fewer per 1,000** (from 28 more to 46 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pathogen eradication												
1	randomised trials	not serious	not serious	not serious [c]	serious [a]	none	134/154 (87.0%)	136/155 (87.7%)	**RR 0.99** (0.91 to 1.08)	**9 fewer per 1,000** (from 70 more to 79 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
1	randomised trials	not serious	not serious	serious [c,d]	not serious	none	117/123 (95.1%)	104/118 (88.1%)	**RR 1.08** (1.00 to 1.17)	**71 more per 1,000** (from 0 fewer to 150 more)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. CI does not exclude an appreciable increase or reduction in the absolute risk
b. Few events
c. Not a pre-specified outcome for this group of PICOs
d. Very indirect outcome

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.7. Should a macrolide versus doxycycline be used for treatment of CAP in adults in the outpatient setting?

ATS / IDSA, Page E 38

Wesner 1993

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a macrolide**	**doxycycline**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
1	randomised trials	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	9/11 (81.8%)	12/13 (92.3%)	**RR 0.89** (0.64 to 1.22)	**102 fewer per 1,000** (from 203 more to 332 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

a. Only 21 events among 24 patients
b. Only one small trial, suspect publication bias

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.8. Should a macrolide versus beta-lactam be used for treatment of CAP in adults in the outpatient setting?

ATS/ IDSA, Page E37

Salvazerra 1998, Bonvehi 2003

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a macrolide**	**a B-lactam**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
2	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	144/154 (93.5%)	145/159 (91.2%)	**RR 1.03** (0.97 to 1.10)	**27 more per 1,000** (from 27 fewer to 91 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
2	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	84/104 (80.8%)	96/115 (83.5%)	**RR 0.97** (0.88 to 1.06)	**25 fewer per 1,000** (from 50 more to 100 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pathogen eradication												
1	randomised trials	not serious	not serious	not serious [c]	serious [b]	none	103/113 (91.2%)	126/135 (93.3%)	**RR 0.98** (0.91 to 1.05)	**19 fewer per 1,000** (from 47 more to 84 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Radiographic response												
1	randomised trials	not serious	not serious	serious [c,d]	serious [b]	none	112/118 (94.9%)	113/126 (89.7%)	**RR 1.06** (0.98 to 1.14)	**54 more per 1,000** (from 18 fewer to 126 more)	⊕⊕◯◯ LOW	NOTIMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Salvarezza 1998 was open label. Not expected to be a risk for study outcomes.
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. Not a pre-specified outcome for this group of PICOs
d. Very indirect

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Table Q6.9. Should a macrolide versus beta-lactam be used for treatment of CAP in adults in the outpatient setting?

NICE, Page 115, Table 36

Paris 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Clinical success (end of treatment, day 8-12)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	126/136 (92.6%)	122/131 (93.1%)	NICE analysis: RR 0.99 (0.93 to 1.06)	9 fewer per 1000 (from 65 fewer to 56 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Bacteriological response (end of treatment, day 8-12)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	32/35 (91.4%)	30/33 (90.9%)	NICE analysis: RR 1.01 (0.87 to 1.17)[4]	9 more per 1000 (from 118 fewer to 155 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Clinical success (follow up visit, day 22-26)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	125/135 (92.6%)	120/129 (93%)	NICE analysis: RR 1 (0.93 to 1.06)[4]	0 fewer per 1000 (from 65 fewer to 56 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Bacteriological response (day 22-26)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	21/22 (95.5%)	15/16 (93.8%)	NICE analysis: RR 1.02 (0.87 to 1.19)[4]	19 more per 1000 (from 122 fewer to 178 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Radiological response (day 22-26)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	125/126 (99.2%)	121/121 (100%)	NICE analysis: RR 0.99 (0.97 to 1.01)[4]	10 fewer per 1000 (from 30 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Number of people reporting at least 1 adverse event												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	34/136 (25.0%)	22/132 (16.7%)	NICE analysis: RR 1.50 (0.93 to 2.42)	83 more per 1000 (from 12 fewer to 237 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people reporting drug related adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	23/136 (16.9%)	12/132 (9.1%)	NICE analysis: RR 1.86 (0.97 to 3.58)	78 more per 1000 (from 3 fewer to 235 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people reporting serious adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	3/136 (2.2%)	3/132 (2.3%)	NICE analysis: RR 0.97 (0.20 to 4.72)	1 fewer per 1000 (from 18 fewer to 85 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting abdominal pain												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[7]	none	13/136 (9.6%)	2/132 (1.5%)	NICE analysis: RR 6.31 (1.45 to 27.42)	80 more per 1000 (from 7 more to 400 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting nausea												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	9/136 (6.6%)	7/132 (5.3%)	NICE analysis: RR 1.25 (0.48 to 3.25)	13 more per 1000 (from 28 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting vomiting												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	2/136 (1.5%)	3/132 (2.3%)	NICE analysis: RR 0.65 (0.11 to 3.81)	8 fewer per 1000 (from 20 fewer to 64 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting diarrhoea												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	3/136 (2.2%)	0/132 (0%)	NICE analysis: RR 6.8 (0.35 to 130.3)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral, 1g once daily for 3 days

[2] Oral, 875/125mg twice daily for 7 days

[3] Paris et al. 2008

[4] Authors judged discrepancy in intention to treat (ITT) and per protocol population to be negligible, therefore only reported ITT analysis

[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with azithromycin

[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

[7] Downgraded 2 levels - very wide confidence intervals

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Table Q7.1. A respiratory fluoroquinolone compared to a B-lactam + macrolide in adults hospitalized with CAP

ATS / IDSA, Page E 41

Frank 2002, Fogarty 2004, Zervos 2004, Portier 2005, Xu 2006, Lin 2007, Lee 2012, Postma 2015 (Cluster RCT)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a respiratory fluoroquinolone	a B-lactam + macrolide	Relative (95% CI)	Absolute (95% CI)		
Clinical response												
7	randomised trials	not serious [a]	not serious	not serious	not serious	none	473/574 (82.4%)	458/593 (77.2%)	**RR 1.05** (1.00 to 1.11)	**39 more per 1,000** (from 0 fewer to 85 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse effect												
7	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	247/584 (42.3%)	269/604 (44.5%)	**RR 0.98** (0.88 to 1.09)	**9 fewer per 1,000** (from 40 more to 53 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
4	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	34/406 (8.4%)	45/423 (10.6%)	**RR 0.57** (0.16 to 2.04)	**46 fewer per 1,000** (from 89 fewer to 111 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality (follow up: 90 days)												
1	randomised trials	not serious	not serious	not serious [c]	serious [b]	none	From Postma 2015, a cluster RCT: BLM vs FQ: adjusted OR 1.37 (95% CI 0.96 - 1.97), in favor of a respiratory fluoroquinolone.				⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
6	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	144/184 (78.3%)	160/213 (75.1%)	**RR 1.02** (0.90 to 1.16)	**15 more per 1,000** (from 75 fewer to 120 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

a. No blinding of participants, personnel; however, not believed to a significant risk for study outcomes
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. 90-day mortality was not pre-specified as an outcome for these PICOs

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Table Q7.2. respiratory fluoroquinolone compared to a B-lactam + macrolide in adults hospitalized with CAP

NICE, Page 131, Table 52

Raz-Pasteur (2015)

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1] versus beta-lactam[2] plus macrolide[3]	Relative (95% CI)		
Mortality (30 days)										
5[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[5]	serious[6]	none	n= 2683[7]	RR 0.99 (0.70 to 1.40)[8]	⊕⊕OO LOW	CRITICAL
Clinical failure (antibiotic modifications related to perceived failure)										
9[4]	randomised trials	serious[9]	no serious inconsistency	serious[5]	serious[10]	none	n= 2441[7]	RR 0.72 (0.57 to 0.91)[8]	⊕OOO VERY LOW	CRITICAL
Clinical failure in pneumococcal pneumonia										
7[4]	randomised trials	serious[9]	no serious inconsistency	serious[5]	serious[11]	none	n= 145[7]	RR 2.03 (0.94 to 4.38)[8]	⊕OOO VERY LOW	CRITICAL
Treatment discontinuation										
6[4]	randomised trials	serious[12]	no serious inconsistency	serious[5]	serious[10]	none	n= 2179[7]	RR 0.65 (0.54 to 0.78)[8]	⊕OOO VERY LOW	CRITICAL
Microbiological failure										
7[4]	randomised trials	serious[12]	no serious inconsistency	serious[5]	very serious[13]	none	n= 35[7]	RR 0.93 (0.63 to 1.38)[8]	⊕OOO VERY LOW	IMPORTANT
Any adverse events										
7[4]	randomised trials	serious[12]	no serious inconsistency	serious[5]	no serious imprecision	none	n= 2727[7]	RR 0.90 (0.81 to 1.00)[8]	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1] versus beta-lactam[2] plus macrolide[3]	Relative (95% CI)		
Diarrhoea										
3[4]	randomised trials	no serious risk of bias	serious[14]	serious[5]	no serious imprecision	none	n= 617[7]	RR 0.13 (0.05 to 0.34)[8]	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk										

[1] Levofloxacin (intravenous or oral, 500 to 750 mg once daily) or moxifloxacin (oral or intravenous 400 mg once daily)
[2] Beta-lactams included ceftriaxone (intravenous 1 to 2 g once daily), co-amoxiclav (intravenous 500/1000 mg once daily; 1000/125 mg three times daily), amoxicillin (intravenous, unreported dosage), penicillin (intravenous, unreported dosage), or cefoperazone (intravenous 2 g once daily)
[3]Macrolides included azithromycin (intravenous or oral 500 mg once daily), erythromycin (intravenous 500 mg to 1 g once daily), clarithromycin (oral 500 mg twice daily), roxithromycin (oral 150 mg twice daily)
[4] Raz-Pasteur et al. 2015
[5] Downgraded 1 level - includes (or very likely to include) antibiotics not licensed in the UK; includes 1 RCT of people with community-acquired pneumonia treated in the community
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[7] Events data for each arm not reported
[8]RR < 1 favours fluoroquinolone monotherapy
[9] Downgraded 1 level - systematic review authors report unclear risk of bias in allocation concealment in majority of studies, and unclear allocation generation in some studies
[10] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with dual therapy
[11] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with monotherapy
[12] Downgraded 1 level - systematic review authors describe low risk of bias in allocation generation and concealment and blinding in only a minority of studies; unclear which studies are high or low risk of bias
[13] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[14] Downgraded 1 level - heterogeneity >50%

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Table Q7.3. Fluroquinolones versus non-fluoroquinolones risk for arrythmia and cardiovascular death
Liu, X et al , 2017

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Floroquinolone	Non Floroquinolone	Relative (95% CI)	Absolute (95% CI)		
Serious arrhythmia												
7	observational studies	serious [a]	serious [b]	not serious	not serious		964/1191786 (0.1%)	4691/4333170 (0.1%)	RR 2.29 (1.20 to 4.36)	1 more per 1,000 (from 0 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cardiac Risk												
3	observational studies	serious [c]	not serious	not serious	not serious		326/521998 (0.1%)	187/2495624 (0.0%)	RR 1.60 (1.17 to 2.20)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
All cause death												
11	observational studies	serious [d]	serious [e]	not serious	not serious		287/1120301 (0.0%)	464/3764523 (0.0%)	RR 1.02 (0.76 to 1.37)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Explanations

a. Allocation concealment bias (Hamms, 2008); Information classification bias; possible miss-classification of significant exposure and outcome (Zambon, 2009)

b. Significant heterogeneity of RRs across the included studies (I2=95%,P<.001)

c. Allocation concealment bias, blinding of participants bias, incomplete outcome data (Cannon, 2005)

d. Allocation concealement (selection bias)

e. Moderate heterogeneity (I2=56%, P<.05)

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Table Q7.4. A B-lactam compared to a B-lactam + macrolide in adults hospitalized with CAP Setting ATS / IDSA, Page E 42

Garin 2014, Postma 2015 (Cluster RCT)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a B-lactam	a B-lactam + macrolide	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 30 days)												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	14/291 (4.8%)	10/289 (3.5%)	**RR 1.39** (0.63 to 3.08)	**13 more per 1,000** (from 13 fewer to 72 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Complicated pleural effusion												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	8/291 (2.7%)	14/289 (4.8%)	**RR 0.57** (0.24 to 1.33)	**21 fewer per 1,000** (from 16 more to 37 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical response												
1	randomised trials	not serious [a]	not serious	not serious	not serious	none	171/291 (58.8%)	192/289 (66.4%)	**RR 0.88** (0.78 to 1.00)	**80 fewer per 1,000** (from 0 fewer to 146 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse effects												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	3/291 (1.0%)	3/289 (1.0%)	**RR 0.99** (0.20 to 4.88)	**0 fewer per 1,000** (from 8 fewer to 40 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	1/291 (0.3%)	3/289 (1.0%)	**RR 0.33** (0.03 to 3.16)	**7 fewer per 1,000** (from 10 fewer to 22 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital readmission (follow up: 30 days)												

1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	23/291 (7.9%)	9/289 (3.1%)	**RR 2.54** (1.19 to 5.39)	**48 more per 1,000** (from 6 more to 137 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ICU admission												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	12/291 (4.1%)	14/289 (4.8%)	**RR 0.85** (0.40 to 1.81)	**7 fewer per 1,000** (from 29 fewer to 39 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital length of stay												
2	randomised trials	not serious [a]	not serious	not serious	not serious	none	Median and IQR provided for both studies. Garin: BL=8 (6-13) days and for BLM=8 (6-12) days. Postma: BL=6 (4-8) days and BLM=6 (4-10) days.				⨁⨁⨁⨁ HIGH	CRITICAL
New pneumonia (follow up: 30 days)												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	10/291 (3.4%)	6/289 (2.1%)	**RR 1.66** (0.61 to 4.49)	**14 more per 1,000** (from 8 fewer to 72 more)	⨁⨁⨁◯ MODERATE	CRITICAL
In-hospital mortality												
1	randomised trials	not serious [a]	not serious	not serious [d]	serious [b,c]	none	8/291 (2.7%)	7/289 (2.4%)	**RR 1.14** (0.42 to 3.09)	**3 more per 1,000** (from 14 fewer to 51 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality (follow up: 90 days)												
2	randomised trials	not serious [a]	not serious	not serious [d]	serious [b,c]	none	One cluster RCT (Postma 2105) reported the absolute difference in the adjusted risk of death with BL strategy compared to BLM strategy: 19 fewer deaths per 1000 patients (90% CI: from 44 fewer to 6 more). Another RCT (Garin 2014) reported 24/291 (8.2%) deaths in BL group and 20/289 (6.9%) in BLM group (RR 1.19, 95% CI: 0.67 to 2.11; risk difference: 13 more per 1000, 95% CI: from 23 fewer to 77 more).				⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Garin 2014 had no blinding of participants or personnel; outcomes assessors were blinded. Not believed to be a significant risk for study outcomes.
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. Few events
d. Not one of the pre-specified outcomes for this group of PICOs

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Table Q7.5. A respiratory fluoroquinolone compared to a B-lactam + macrolide in adults hospitalized with CAP

Liu. et al, 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Floroquinolone	Beta lactam with or without macrolide	Relative (95% CI)	Absolute (95% CI)		
Mortality												
9	randomised trials	not serious	serious [a]	not serious	not serious		114/2198 (5.2%)	191/2670 (7.2%)	RR 0.82 (0.65 to 1.02)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Clinical success												
11	randomised trials	not serious	serious [a]	not serious	not serious		1048/1148 (91.3%)	984/1107 (88.9%)	RR 1.03 (0.99 to 1.08)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Microbiologic success												
18	randomised trials	not serious	serious [a]	not serious	not serious		513/517 (99.2%)	462/542 (85.2%)	RR 1.040 (0.997 to 1.092)	34 more per 1,000 (from 3 fewer to 78 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio **Explanations** a. Non-uniform antibiotic regimen

Question 8: What antibiotics are recommended for the empiric treatment of high-risk CAP?

Table Q8.1 GRADE profile – Empiric treatment of high risk CAP: Should a Beta-lactam/Fluoroquinolone vs Beta-lactam/Macrolide be used for treatment of high risk CAP?

Setting: In-patient

Vardakas 2017

Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta lactam + Fluoroquinolone	Beta lactam + Macrolide	Relative (95% CI)	Absolute (95% CI)		
Mortality												
17	observational studies	not serious	not serious	not serious	not serious	none	624/3982 (15.7%)	1109/12702 (8.7%)	RR 1.33 (1.15 to 1.54)	29 more per 1,000 (from 13 more to 47 more)	⨁⨁◯◯ LOW	CRITICAL

Question 8: What antibiotics are recommended for the empiric treatment of high-risk CAP?

Table Q8.2 GRADE profile –Empiric treatment of high risk CAP: Should fluoroquinolone monotherapy vs beta-lactam +/- macrolides be used for treatment of high risk CAP?

Setting: In-patient

Liu 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone	Beta lactam with or without macrolide	Relative (95% CI)	Absolute (95% CI)		
Mortality												
9	randomised trials	not serious	not serious	serious [a]	not serious	none	114/2198 (5.2%)	191/2670 (7.2%)	RR 0.82 (0.65 to 1.02)	13 fewer per 1,000 (from 25 fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical success (Intention-to-treat population)												
8	randomised trials	not serious	not serious	serious [a]	not serious	none	804/994 (80.9%)	775/988 (78.4%)	RR 1.03 (0.99 to 1.08)	24 more per 1,000 (from 8 fewer to 63 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

a. The comparator group received beta-lactams with macrolides (combination therapy) or without macrolides (monotherapy)

Question 8: What antibiotics are recommended for the empiric treatment of high-risk CAP?

Table Q8.3 GRADE profile –Empiric treatment of high risk CAP: Should Ceftriaxone + Azithromycin vs Ceftriaxone + other macrolides be used for treatment of high risk CAP?

Source: NICE pages 137-140

Setting: In-patient

Tamm 2007

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus azithromycin[1]	Ceftriaxone plus macrolide[2]	Relative (95% CI)	Absolute		
Bacteriological eradication EOT (day 12-16)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	30/41 (73.2%)	31/46 (67.4%)	NICE analysis: RR 1.09 (0.83 to 1.43)	61 more per 1000 (from 115 fewer to 290 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological eradication EOS (day 28-35)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	28/41 (68.3%)	28/46 (60.9%)	NICE analysis: RR 1.12 (0.82 to 1.53)	73 more per 1000 (from 110 fewer to 323 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological eradication EOT, evaluable participants (day 12-16)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	24/31 (77.4%)	25/31 (80.6%)	NICE analysis: RR 0.96 (0.74 to 1.24)	32 fewer per 1000 (from 210 fewer to 194 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological eradication EOS, evaluable participants (day 28-35)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	16/22 (72.7%)	23/31 (74.2%)	NICE analysis: RR 0.98 (0.71 to 1.36)	15 fewer per 1000 (from 215 fewer to 267 more)	⊕⊕OO LOW	IMPORTANT
Clinical success in Streptococcus pneumoniae EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	17/21 (81%)	21/30 (70%)	NICE analysis: RR 1.16 (0.85 to 1.58)	112 more per 1000 (from 105 fewer to 406 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Streptococcus pneumoniae EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	15/20 (75.0%)	20/30 (66.7%)	NICE analysis: RR 1.12 (0.79 to 1.61)	80 more per 1000 (from 140 fewer to 407 more)	⊕⊕OO LOW	IMPORTANT

Clinical success in people with positive blood cultures EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	8/12 (66.7%)	10/17 (58.8%)	NICE analysis: RR 1.13 (0.64 to 1.99)	76 more per 1000 (from 212 fewer to 582 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in people with positive blood cultures EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	8/12 (66.7%)	9/17 (52.9%)	NICE analysis: RR 1.26 (0.69 to 2.3)	138 more per 1000 (from 164 fewer to 688 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[5]	none	44/135 (32.6%)[10]	58/143 (40.6%)[11]	NICE analysis: RR 0.80 (0.59 to 1.10)	81 fewer per 1000 (from 166 fewer to 41 more)	⊕⊕OO LOW	CRITICAL
Gastrointestinal adverse events												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[5]	none	17/135 (12.6%)	26/143 (18.2%)	NICE analysis: RR 0.69 (0.39 to 1.22)	56 fewer per 1000 (from 111 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
Incidence of diarrhoea												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	10/135 (7.4%)	12/143 (8.4%)	NICE analysis: RR 0.88 (0.39 to 1.98)	10 fewer per 1000 (from 51 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Incidence of nausea												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	2/135 (1.5%)	7/143 (4.9%)	NICE analysis: RR 0.30 (0.06 to 1.43)	34 fewer per 1000 (from 46 fewer to 21 more)	⊕OOO VERY LOW	IMPORTANT

Abbreviations: CI – confidence interval; EOT – end of treatment; NA – not applicable; RR – relative risk; EOS – end of study

[1] Intravenous ceftriaxone 1-2g once-daily plus intravenous azithromycin 500mg once-daily for 2-5 days, followed by step down to oral azithromycin 500mg once-daily for a total therapy duration of 7-10 days

[2] Intravenous ceftriaxone 1-2g once-daily plus either intravenous clarithromycin 500mg twice-daily or erythromycin 1g three times for 2-5 days, followed by step down to either oral clarithromycin 500mg twice-daily or erythromycin 1g three times a day for a total of 7-14 days.

[3] Tamm et al. 2007

[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone plus azithromycin

[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone plus erythromycin macrolide

[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

[7] Downgraded 1 level - only modified intention to treat analysis reported, as a non-inferiority study per protocol analysis would also be expected

[8] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone with azithromycin; very wide confidence intervals

[9] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with ceftriaxone plus clarithromycin or erythromycin

[10] All adverse events classified as mild or moderate-severity

[11] Three adverse events classified as severe, comprising injection site inflammation (leading to discontinuation), injection site pain (antibiotics switched) and hepatic enzyme increase

Question 10: Among patients with CAP, who are the patients at risk for MRSA, Pseudomonas aeruginosa, ESBL producing organisms and should receive empiric antibiotic coverage for these organisms?

Table Q10.1 Factors independently associated with MRSA pneumonia

Study	Design	Risk Factor	Odds Ratio	95% CI
Aliberti 2016	Observational	Previous MRSA infection or colonization within 1 year	6.21	3.25-11.85
		Recurrent skin infection	2.87	1.10-7.45
		Severe pneumonia requiring ICU admission and mechanical ventilation	2.39	1.55-3.68
Jung 2013	Observational	Previous MRSA infection within 1 year	6.05	2.99-12.22
		Pneumonia Severity Index score $\geq$ 120	2.40	1.18-4.86
		Intravenous antibiotic treatment within 30 days of pneumonia	2.23	1.15-4.32
Wooten 2012	Observational	Recent IV antibiotic use (90 days)	4.87	2.35-10.1
		COPD	3.76	1.74-8.08
		Tobacco use	2.31	1.23-4.31

Table Q10.2 Factors independently associated with *Pseudomonas aeruginosa* community acquired pneumonia

Study	Design	Risk Factor	Odds Ratio	95% CI
Restrepo 2018	Observational	Previous *Pseudomonas* infection or colonization within 1 year	16.10	9.48-27.35
		Prior Tracheostomy	6.5	2.61-16.19
		Bronchiectasis	2.88	1.65-5.05
		Very severe COPD	2.76	1.25-6.06
		Invasive respiratory vasopressor support (IRVS)	2.33	1.44-3.78
Cilloniz 2016	Observational	Chronic respiratory illness	2.26	1.25-4.10

Table Q10.3 Factors independently associated with pneumonia due to MDR Enterobacteriaceae

Study	Design	Risk Factor	Odds Ratio	95% CI
Villafuerte 2019	Observational	Previous ESBL infection/colonization	8.50	3.12-23.16

Question 10: Among patients with CAP, who are the patients at risk for MRSA, Pseudomonas aeruginosa, ESBL producing organisms and should receive empiric antibiotic coverage for these organisms?

Table Q10.4 GRADE profile – Vancomycin vs Linezoid for MRSA pneumonia

Setting: In-patient HAP/VAP with MRSA

From meta-analysis in IDSA 2016 Guidelines for HAP and VAP supplement

Bibliography: Wunderlink 2012, Kohno 2007, Stevens 2002, Wunderlink 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Linezolid	Vancomycin	Relative (95% CI)	Absolute (95% CI)		
Mortality modified intention to treat												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	67/254 (26.4%)	63/224 (28.1%)	RR 0.83 (0.36 to 1.90)	48 fewer per 1,000 (from 180 fewer to 253 more)	⊕⊕◯◯ LOW	
Clinical cure intention to treat												
2	randomised trials	not serious	not serious	serious [b]	not serious	none	65/132 (49.2%)	31/81 (38.3%)	RR 1.27 (0.83 to 1.95)	103 more per 1,000 (from 65 fewer to 364 more)	⊕⊕⊕◯ MODERATE	
Clinical cure modified intention to treat												

4	randomised trials	not serious	not serious	serious [b]	not serious	none	145/273 (53.1%)	123/270 (45.6%)	RR 1.18 (1.00 to 1.40)	82 more per 1,000 (from 0 fewer to 182 more)	⊕⊕⊕◯ MODERATE	
Adverse event - Nephrotoxicity												
4	randomised trials	not serious	serious [c]	serious [b,d]	not serious	none	25/1010 (2.5%)	52/930 (5.6%)	RR 0.46 (0.29 to 0.74)	30 fewer per 1,000 (from 40 fewer to 15 fewer	⊕⊕◯◯ LOW	

CI: Confidence interval; RR: Risk ratio

Explanations

a. Heterogeneity of 57%

b. Involves patients with HAP/ VAP and not CAP

c. Heterogeneity of 79%

d. Multiple definitions of nephrotoxicity

Question 12: Among adults with CAP, how soon should empiric treatment be started?

Table Q12.1: Summary of Evidence from observational studies with multivariate analysis including timing of antibiotic therapy

Pneumonia Diagnosis and management of community- and hospital-acquired pneumonia in adults Clinical guideline 191 Methods, evidence and recommendations 3 December 2014, Commissioned by the National Institute for Health and Care Excellence, page 168, table 60

Houck 2004, Bader 2011, Dedier 2001, Jo 2012, Lee 2011, Meehan 1997, Mortensen 20-08, Woilson 2005, Bordon 2013, Waterer 2006, Simonetti 2012, Battleman 2002, Huang 2006

Table 60: Summary of evidence from observational studies with multivariate analysis including timing of antibiotic therapy as explanatory factor

Study (design)	Quality assessment					Outcomes					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Study ID	No of patients	Outcome definition	Timing definition (hours)	Adjusted HR/OR/RR (95% CI)	
All-cause mortality											
9 retrospective chart reviews (Houck 2004, Bader 2011, Dedier 2001, Jo 2012, Lee 2011, Meehan 1997, Mortensen 2008, Wilson 2005, Bordon 2013) 2 prospective observational studies (Waterer 2006, Simonetti 2012)	Serious[1]	Serious[2]	No serious	Serious[3]	None	Houck 2004	18, 209	30 days	≤ 4 vs. > 4 h	**Overall**: AOR 0.85 (0.76 to 0.95) **PSI II-III**: AOR 0.62 (0.42 to 0.92) **PSI IV-V**: AOR 0.87 (0.78 to 0.97)	Very low
						Lee 2011	2076	30 days	< 4 vs. ≥ 4 h	AOR 0.7 (0.5 to 1.1)	
						Wilson 2005	96	In-hospital death	≤ 4 vs. > 4 h	AOR 0.29 (0.09 to 0.92) (inverted)	
						Waterer 2006	451	Unclear definition	≤ 4 vs. > 4 h	AOR 0.54 (0.2 to 1.19) (inverted)	
						Simonetti 2012 – CAP	1274	30 days	≤ 4 vs. > 4 h	AOR 1.12 (0.38 to 3.33)	
						Bader 2011	206	In-hospital death	≤ 8 vs. > 8 h	AOR 0.25 (0.08 to 0.83) (inverted)	
						Meehan 1997	14069	30 days	≤ 8 vs. > 8 h	AOR 0.85 (0.75 to 0.96)	
						Mortensen 2008	733	30 days	≤ 8 vs. > 8 h	AOR 1.2 (0.7 to 2.1)	
						Dedier 2001	1062	In-hospital death	≤ 8 vs. > 8 h	AOR 1. 69 (0.78 to 3.66)	
						Houck 2004	18, 209	30 days	≤ 8 vs. > 8 h	AOR 0.85 (0.73 to 0.99)	
						Simonetti 2012 – CAP	1274	30 days	≤ 8 vs. > 8 h	AOR 1.58 (0.64 to 3.88)	

Study (design)	Quality assessment						Outcomes					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Study ID	No of patients	Outcome definition	Timing definition (hours)	Adjusted HR/OR/RR (95% CI)	
							Houck 2004[4]	18, 209	30 days	≤ 12 vs. > 12 h	AOR 0.97 (0.79 to 1.19)	
							Jo 2012	477	28 days	Continuous variable	AOR 1 (0.99 to 1.00)	
							Bordon 2013	372	30 days	Continuous variable	AHR not reported (p = 0.148)	
Length of stay (prolonged)												
5 retrospective chart reviews (Battleman 2002, Dedier 2001, Houck 2004, Lee 2011, Bordon 2013), 1 prospective cohort (Huang 2006)	Serious[1]	No serous	No serious	Serious[5]	None		Houck 2004	18,209	> 5 days (median)	≤ 4 vs. ≥ 4 h	**Overall**: AOR 0.90 (0.83 to 0.96) **PSI II-III**: AOR 0.86 (0.75 to 0.99) **PSI IV-V**: AOR 0.92 (0.84 to 1.01)	Low
							Lee 2011	2076	Unclear – discrete data model	≤ 4 vs. ≥ 4 h	AOR 1.2 (1.1 to 1.4)	
							Dedier 2001	1062	> 4 days (median) LOS	≤ 8 vs. > 8 h	AOR 0.89 (0.65 to 1.22)	
							Battleman 2002	609	> 9 days: (75th percentile)	≤ 8 vs. > 8 h	AOR 0.57 (0.44 to 0.75) (inverted)	
							Huang 2006	2757	> 7 days (median = 6.4 days)	≤ 4 vs. 4 to 8 h	AOR 1.02 (0.83 to 1.25) (inverted)	
							Huang 2006	2757	> 7 days (median = 6.4 days)	≤ 4 vs. > 8 h	AOR 0.78 (0.63 to 0.97) (inverted)	

Study (design)	Quality assessment					Outcomes					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Study ID	No of patients	Outcome definition	Timing definition (hours)	Adjusted HR/OR/RR (95% CI)	
						Bordon 2013	372		Continuous	AHR 0.99 (0.97 to 1.02)	
Re-admission after discharge											
2 retrospective chart reviews (Houck 2004, Lee 2011)	Serious[6]	Serious[7]	No serious	No serious	None	Houck 2004	18,209	30 days	≤ 4 vs. > 4 h	**Overall**: AOR 0.95 (0.85 to 1.06) **PSI II-III**: AOR 0.87 (0.70 to 1.08) **PSI IV-V**: AOR 0.99 (0.88 to 1.11)	Low
						Lee 2011	2076	30 days	≤ 4 vs. ≥ 4 h	AOR 1.4 (0.9 to 2.2)	
Clinical instability at 48 hours											
1 retrospective chart review (Dedier 2001)	Serious[8]	No serious	Serious[9]	No serious	None	Dedier 2001	1062	Objective criteria	≤ 8 vs. > 8 h	AOR 1.04 (0.75 to 1.44)	Low

[1] Not all key confounders adjusted for in majority of studies

[2] Effect estimate range from large effect in favour of earlier antibiotic therapy to no clinically relevant effect (although 95% CIs largely overlap)

[3] Majority of studies small and wide 95% CIs

[4] See also Houck forest plot in Appendix I: for more time-points

[5] 95% CI crosses default MIDs for majority of studies

[6] Both studies < 50% of cases remain included after applying exclusion criteria; larger study (Houck) restricted to age over 65 years. Unclear if patients still representative of the CAP population in UK.

[7] Two studies show opposite direction of effect

[8] Not all key confounders were adjusted for in the analysis

[9] Surrogate outcome measure

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.1: ≤ 7 days of antibiotic therapy compared to > 7 days of antibiotic therapy in adults hospitalized with CAP

Setting: hospitalized patients

IDSA page 52-53

Schonwald 1994; Bohte 1995; Rizzato 1995; Siegel 1999; Leophonte 2002; el Moussaoui 2006; Zhao 2014; Uranga 2016

Author(s):
Date:
Question: ≤ 7 days of antibiotic therapy compared to > 7 days of antibiotic therapy in adults hospitalized with CAP
Setting:
Bibliography: Schonwald 1994; Bohte 1995; Rizzato 1995; Siegel 1999; Leophonte 2002; el Moussaoui 2006; Zhao 2014; Uranga 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	≤ 7 days of antibiotic therapy	> 7 days of antibiotic therapy	Relative (95% CI)	Absolute (95% CI)		
Clinical cure (Follow-up < 30 days)												
7	randomised trials [a]	not serious	not serious	not serious	serious [b]	none	442/580 (76.2%)	391/537 (72.8%)	**RR 1.03** (0.98 to 1.07)	**22 more per 1,000** (from 15 fewer to 51 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical cure (Follow-up >= 30 days)												
2	randomised trials [c,d]	not serious	not serious	not serious	serious [e]	none	In Siegel 1999, relapse was declared if there was initial improvement in signs and symptoms, then new signs symptoms and symptoms appeared after antibiotic completion. In this study, no episodes of relapse were observed in either study arm. In Uranga 2016, 4 of 162 patients who received antibiotics for a minimum of 5 days experienced recurrence compared to 6 of 150 patients in the arm with longer treatment duration.				⨁⨁⨁◯ MODERATE	CRITICAL
Any adverse effect												
6	randomised trials [h]	not serious	not serious	not serious	serious [b]	none	188/430 (43.7%)	192/396 (48.5%)	**RR 0.96** (0.86 to 1.06)	**19 fewer per 1,000** (from 29 more to 68 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse effect												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	29/246 (11.8%)	36/239 (15.1%)	**RR 0.78** (0.51 to 1.20)	**33 fewer per 1,000** (from 30 more to 74 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR**: Risk ratio; **MD**: Mean difference

Explanations

a. Data from studies comparing similar antibiotics. Additional characteristics of note: In Schonwald 1994, patients were hospitalized with atypical pneumonia. In Bohte 1995, data shown here are for the group of patients treated for non-pneumococcal CAP. A separate arm compared azithromycin to benzylpenicillin but this was considered a dissimilar comparison, thus these data are not included here. In Rizzato 1995, a previous antibiotic had been administered unsuccessfully in 20 cases. In Zhao 2014, data for clinical cure includes those who were considered cured and those considered improved, as improvement required no further antibiotic treatment. Although clinicians determined antibiotic type in Uranga 2016, it is included here (as opposed to excluding it due to "dissimilar comparisons"), because the majority (80%) of patients in both groups received a Quinolone.
b. CI does not exclude an appreciable increase or reduction in the absolute risk.
c. Although clinicians determined antibiotic type in Uranga 2016, it is included here (as opposed to excluding it due to "dissimilar comparisons"), because the majority (80%) of patients in both groups received a Quinolone.
d. In Siegel 1999, all included participants were male.
e. Includes very few events.
f. In Rizzato 1995, a previous antibiotic had been administered unsuccessfully in 20 cases.
g. el Moussaoui 2006 also included data about hospital length of stay, but the this was not reported in a standard format (e.g. mean [SD]). It was reported as follows: "the bootstrap estimated mean length of hospital stay was 7.9 days (6.5 to 9.3 days) in the three day treatment group compared with 8.9 days (6.8 to 11 days) in the eight day treatment group, with a bootstrap estimated mean difference of 1.0 day (− 1.3 to 3.2 days)."
h. The large number of adverse effects reported in Leophonte 2002 suggests that in this study, adverse effects were assessed differently compared to the other studies (reported adverse events in over 80% of patients, although only 20 (16%) patients in the 5 day group and 26 (21.8%) patients in the 10 day group presented with an adverse event considered by the investigator as possibly or probably linked to treatment).

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.2 Short vs. long course antibiotics

NICE, Page 145

Table 59

Table 59: GRADE profile – short- versus long-course antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course[2]	Relative (95% CI)	Absolute		
Clinical failure (all antibiotic comparisons)												
15[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	326/1521 (21.4%)	326/1275 (25.6%)	RR 0.89 (0.78 to 1.02)	28 fewer per 1000 (from 56 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (excluding antibiotics not available in UK)												
11[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	206/836 (24.6%)	241/834 (28.9%)	NICE analysis: RR 0.87 (0.75 to 1.02)	38 fewer per 1000 (from 72 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (all antibiotic comparisons)												
8[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	serious[6]	none	-	-	RR 0.81 (0.46 to 1.43)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – risk ratio												

[1] Included: azithromycin, levofloxacin, gemifloxacin, ceftriaxone, cefuroxime or telithromycin, for 3 to 7 days

[2] Included: erythromycin, josamycin, levofloxacin, cefaclor, clarithromycin, co-amoxiclav, ceftriaxone, roxithromycin or cefuroxime (in 1 study unnamed 'multiple antibiotics' given) for 10 to 14 days (majority of studies 10 days, 1 study 14 days)

[3] Li et al. 2007

[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2

[5] Downgraded 1 level - includes antibiotics not licenced in the UK

[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.3 Short vs. long course macrolide

NICE, Page 146

Table 60

Table 60: GRADE profile – short- versus long-course macrolide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course macrolide[2]	Relative (95% CI)	Absolute		
Clinical failure (all antibiotic comparisons)												
10[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	154/893 (17.2%)	131/640 (20.5%)	RR 0.88 (0.71 to 1.09)	27 fewer per 1000 (from 59 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (excluding antibiotics not available in UK)												
7[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	72/375 (19.2%)	78/352 (22.2%)	NICE analysis: RR 0.88 (0.67 to 1.17)	27 fewer per 1000 (from 73 fewer to 38 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Includes: azithromycin and telithromycin (telithromycin used in 1 study) for 3 to 5 days

[2] Includes: erythromycin, josamycin, clarithromycin and roxithromycin (1 study unreported 'multiple antibiotics' given), for 10 to 14 days

[3] Li et al. 2007

[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2

[5] Downgraded 1 level - includes antibiotics not licenced in the UK

[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with long courses

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.4 Short vs. long course beta lactam

NICE, Page 146

Table 61

Table 61: GRADE profile – short versus long course beta-lactam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course[2]	Relative (95% CI)	Absolute		
Clinical failure												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	38/152 (25%)	39/144 (27.1%)	RR 0.92 (0.63 to 1.36)	22 fewer per 1000 (from 100 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Includes: ceftriaxone (5 days) and cefuroxime (7 days)

[2] Includes: ceftriaxone (10 days) and cefuroxime (10 days)

[3] Li et al. 2007

[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2; unclear which studies are high risk of bias

[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.5 short-course azithromycin versus long-course antibiotics

NICE, Page 146-147

Table 62

Table 62: GRADE profile – short-course azithromycin versus long-course antibiotics

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day course azithromycin	10 to 14 day antibiotic course[1]	Relative (95% CI)	Absolute	Quality	Importance
Clinical failure (fixed effect; excluding antibiotics not available in UK)												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	49/298 (16.4%)	60/286 (21%)	NICE analysis: RR 0.82 (0.59 to 1.14)	38 fewer per 1000 (from 86 fewer to 29 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (random effect; all antibiotic comparisons)												
6[2]	randomised trials	serious[3]	serious[4]	serious[5]	serious[6]	none	51/388 (13.1%)	70/346 (20.2%)	RR 0.61 (0.34 to 1.10)	79 fewer per 1000 (from 134 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (random effect; excluding antibiotics not available in UK)												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	49/298 (16.4%)	60/286 (21%)	NICE analysis: RR 0.84 (0.57 to 1.25)	34 fewer per 1000 (from 90 fewer to 52 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Includes: clarithromycin and roxithromycin (1 study unspecified 'multiple antibiotics' given), for 10 to 14 days

[2] Li et al. 2007

[3] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2; unclear which studies are high risk of bias

[4] Downgraded 1 level - heterogeneity >50%

[5] Downgraded 1 level - includes antibiotics not licenced in the UK

[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with long courses

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.6 Short vs. long course beta levofloxacin

NICE, Page 147

Table 63

Table 63: GRADE profile – short- versus long-course levofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course[2]	Relative (95% CI)	Absolute		
Clinical failure												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	73/256 (28.5%)	97/272 (35.7%)	NICE analysis: RR 0.80 (0.62 to 1.03)	71 fewer per 1000 (from 136 fewer to 11 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Levofloxacin for 5 days

[2] Levofloxacin for 10 days

[3] Li et al. 2007

[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2; unclear which studies are high risk of bias

[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with long courses

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Table Q13.7 Short vs. Long course amoxicillin

NICE, Page 148

Table 64

Table 64: GRADE profile – short versus long course amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day[1]	8 day amoxicillin[2]	Relative (95% CI)	Absolute		
Clinical cure (day 10; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	50/54 (92.6%)	56/60 (93.3%)	NICE analysis: RR 0.99 (0.9 to 1.1)	1 fewer per 100 (from 9 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (day 10; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	50/56 (89.3%)	56/63 (88.9%)	NICE analysis: RR 1 (0.89 to 1.14)	0 fewer per 1000 (from 98 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological success (day 10)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	22/25 (88%)	19/20 (95%)	NICE analysis: RR 0.93 (0.78 to 1.10)	66 fewer per 1000 (from 209 fewer to 95 more)	⊕⊕⊕O MODERATE	IMPORTANT
Radiological success (day 10)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	48/56 (85.7%)	52/63 (82.5%)	NICE analysis: RR 1.04 (0.89 to 1.21)	33 more per 1000 (from 91 fewer to 173 more)	⊕⊕⊕O MODERATE	IMPORTANT
Clinical cure (day 28; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	47/52 (90.4%)	49/56 (87.5%)	NICE analysis: RR 1.03 (0.9 to 1.18)	26 more per 1000 (from 88 fewer to 157 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (day 28; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	47/56 (83.9%)	49/63 (77.8%)	NICE analysis: RR 1.08 (0.91 to 1.29)	62 more per 1000 (from 70 fewer to 226 more)	⊕⊕OO LOW	CRITICAL
Bacteriological success (day 28)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	20/25 (80%)	15/20 (75%)	NICE analysis: RR 1.07 (0.77 to 1.47)	53 more per 1000 (from 173 fewer to 353 more)	⊕⊕OO LOW	IMPORTANT
Radiological success (day 28)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	48/56 (85.7%)	50/63 (79.4%)	NICE analysis: RR 1.08 (0.92 to 1.27)	63 more per 1000 (from 63 fewer to 214 more)	⊕⊕OO LOW	IMPORTANT
Length of hospital stay												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	Mean 7.9 days (6.5 to 9.3)	Mean 8.9 days (6.8 to 11)	-	MD 1.00 days (-1.3 to 3.2)	⊕⊕OO LOW	CRITICAL

Question 14: Among patients on empiric antibiotic therapy for CAP, should de-escalation be done?

Table 14.1 De-escalation of antibiotic coverage to no change in antibiotic coverage for adult CAP in-patients with no identified MDR pathogens

IDSA, pE49, table 22

Yamana, 2016; You, 2018

Certainty Assessment							Impact	Certainty	Importance
Nos of studies	Study design	Risk of bias	inconsistency	indirectness	imprecision	Other considerations			
Mortality (15 days)									
1	observational	not serious	not serious	not serious	not serious	none	In propensity-matched patients, 15-day mortality rate was 5.0% in both the de-escalation and continuation groups (14/278; 95% CI of the difference in mortality rate, -3.6 to 3.6).	⊕⊕◯◯ LOW	Critical
In hospital mortality									
2	observational	not serious	not serious	not serious	not serious	none	Both studies had propensity-matched patients. In Yamana,2016, the in-hospital mortality rate was 14.4% (40/278) in the de-	⊕⊕◯◯ LOW	Critical

							escalation group and 13.3% (37/278) in the continuation group; the difference in mortality rate was 1.1% (95% CI, -4.7 to 6.8). For You, 2018, overall survival was estimated in the using Kaplan-Meier (KM) methodology with comparisons accomplished using log-rank statistics and found no significant differences between the de-escalation and continuous group on (log-rank *P* = .86).		

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.1: GRADE Table for pneumococcal polysaccharide vaccine

Moberley 2013, Apolinario, 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pneumococcal polysaccharide vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
Invasive pneumococcal disease												
11	randomised trials	not serious	not serious	serious [a,b]	not serious	none	15/18634 (0.1%)	63/17855 (0.4%)	**OR 0.26** (0.14 to 0.45)	**3 fewer per 1,000** (from 3 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Pneumonia												
9	randomised trials	not serious	not serious [c]	serious [a,b]	serious [d]	none	413/77960 (0.5%)	465/78234 (0.6%)	**RR 0.89** (0.79 to 1.01)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pneumococcal polysaccharide vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
14	randomised trials	not serious	serious [e]	serious [a,b]	serious [d]	none	1018/24018 (4.2%)	1039/23542 (4.4%)	**OR 0.90** (0.74 to 1.09)	**2 fewer per 1,000** (from 5 fewer to 2 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality due to Pneumonia or IPD												
9	randomised trials	not serious	serious [f]	serious [a,b]	not serious	none	140/15592 (0.9%)	222/15131 (1.5%)	**RR 0.62** (0.50 to 0.76)	**6 fewer per 1,000** (from 7 fewer to 4 fewer)	⨁⨁◯◯ LOW	CRITICAL
Pneumonia for high risk groups including age 65 and above												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pneumococcal polysaccharide vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	not serious	not serious [g]	not serious [a]	not serious	none	170/1520 (11.2%)	217/1506 (14.4%)	**RR 0.78** (0.65 to 0.94)	**32 fewer per 1,000** (from 50 fewer to 9 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. different population

b. includes different age groups

c. heterogeneity with I2=28%. may be due to varied population

d. wide confidence interval but with trend towards benefit

e. significant heterogeneity with I2=69%

f. significant heterogeneity with I2=74%

g. no significant heterogeneity with I2=6%

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.2: GRADE Table for pneumococcal conjugate vaccine

Bonten 2015

Certainty assessment							№ of patients		Effect		Certainty	Import
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	placebo	Relative (95% CI)	Absolute (95% CI)		
Invasive pneumococcal disease												
1	randomised trials	not serious	not serious	serious [a,b]	not serious	strong association	34/42240 (0.1%)	66/42256 (0.2%)	**RR 0.52** (0.34 to 0.78)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITI
Pneumonia												
1	randomised trials	not serious	not serious	serious [a,b]	serious [c]	none	747/42240 (1.8%)	787/42256 (1.9%)	**RR 0.95** (0.86 to 1.05)	**1 fewer per 1,000** (from 3 fewer to 1 more)	⊕⊕◯◯ LOW	CRITI
All-cause Mortality												

Certainty assessment							№ of patients		Effect		Certainty	Import
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a,b]	serious [c]	none	3006/42237 (7.1%)	3005/42255 (7.1%)	**RR 1.00** (0.95 to 1.05)	**0 fewer per 1,000** (from 4 fewer to 4 more)	⨁⨁◯◯ LOW	CRITI
Mortality due to pneumonia or IPD												
1	randomised trials	not serious	not serious	serious [a,b]	serious [c,d]	none	6/42240 (0.0%)	7/42256 (0.0%)	**RR 0.86** (0.29 to 2.55)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITI

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Filipinos not represented

b. Mean age of participants is 72

c. wide confidence interval

d. small number of events

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.3 Influenza vaccine compared to placebo or "do nothing" for preventing influenza in healthy adults

Setting: 16-64 adults

Bibliography: Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD001269. DOI: 10.1002/14651858.CD001269.pub6

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	placebo or "do nothing"	Relative (95% CI)	Absolute (95% CI)		
Influenza												
25	randomised trials	serious [a]	not serious	serious [b]	not serious	none	414/39711 (1.0%)	721/31510 (2.3%)	**RR 0.41** (0.36 to 0.47)	**14 fewer per 1,000** (from 15 fewer to 12 fewer)	⊕⊕◯◯ LOW	IMPORTANT
influenza-like illness												
16	randomised trials	serious [a]	serious [c]	not serious	not serious	none	1646/16572 (9.9%)	1442/9223 (15.6%)	**RR 0.84** (0.75 to 0.95)	**25 fewer per 1,000** (from 39 fewer to 8 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Hospitalizations												
3	randomised trials	serious [d]	not serious	not serious	serious [e]	none	272/2840 (9.6%)	1331/9084 (14.7%)	**RR 0.96** (0.85 to 1.08)	**6 fewer per 1,000** (from 22 fewer to 12 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	placebo or "do nothing"	Relative (95% CI)	Absolute (95% CI)		
local harms												
11	randomised trials	serious [a]	serious [c]	not serious	not serious	none	3697/6181 (59.8%)	2188/6126 (35.7%)	**RR 2.44** (1.82 to 3.22.448)	**514 more per 1,000** (from 293 more to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT
systemic harms												
6	randomised trials	serious [a]	not serious	not serious	serious [e]	none	165/1084 (15.2%)	148/1044 (14.2%)	**RR 1.16** (0.87 to 1.53)	**23 more per 1,000** (from 18 fewer to 75 more)	⨁⨁◯◯ LOW	IMPORTANT

a. At least 2 studies had unclear risk of bias especially seen in older studies.
b. Downgraded one level due to uncertainty over definition, surveillance and testing of influenza in older trials.
c. There was unexplained inconsistency that was supported by non-overlapping confidence intervals, high I2 values and statistically significant heterogeneity of effect estimates.
d. Downgraded one level due to serious risk of bias. Meta-analysis heavily influenced by a large study with high risk of bias across several domains.
e. Imprecision is present because the width of confidence interval is consistent with both important benefit and harm.

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.4 Influenza vaccine compared to placebo in preventing pneumonia in the elderly

Setting: all settings RCTs

Bibliography: Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018 Feb 1;2:CD004876 1;2:CD004876. doi:10.1002/14651858.CD004876.pub4.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
pneumonia (follow up: 1 years)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/523 (0.2%)	1/178 (0.6%)	**RR 0.34** (0.02 to 5.43)	**4 fewer per 1,000** (from 6 fewer to 25 more)	⊕◯◯◯ VERY LOW	CRITICAL
Influenza												
3	randomised trials	serious [c]	not serious [d]	serious [e]	not serious	none	16/927 (1.7%)	38/911 (4.2%)	**RR 0.42** (0.27 to 0.66)	**24 fewer per 1,000** (from 30 fewer to 14 fewer)	⊕⊕◯◯ LOW	IMPORTANT
influenza-like illness												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious [c]	not serious [d]	serious [e]	not serious	none	124/3100 (4.0%)	222/3794 (5.9%)	**RR 0.59** (0.47 to 0.73)	**24 fewer per 1,000** (from 31 fewer to 16 fewer)	⨁⨁◯◯ LOW	IMPORTANT
All deaths												
1	randomised trials	serious [f]	not serious	not serious	very serious [g]	none	3/522 (0.6%)	1/177 (0.6%)	**RR 1.02** (0.11 to 9.02)	**0 fewer per 1,000** (from 5 fewer to 45 more)	⨁◯◯◯ VERY LOW	CRITICAL
general malaise												
4	randomised trials	serious [c]	not serious	not serious	not serious	none	85/1291 (6.6%)	70/1269 (5.5%)	**RR 1.18** (0.87 to 1.61)	**10 more per 1,000** (from 7 fewer to 34 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Fever												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [c]	not serious	not serious	serious [h]	none	33/1270 (2.6%)	20/1249 (1.6%)	**RR 1.51** (0.92 to 2.71)	**8 more per 1,000** (from 1 fewer to 27 more)	⊕⊕◯◯ LOW	IMPORTANT
local tenderness/sorearm												
4	randomised trials	serious [c]	not serious	not serious	not serious	none	174/1291 (13.5%)	47/1269 (3.7%)	**RR 3.56** (2.61 to 4.87)	**95 more per 1,000** (from 60 more to 143 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

a. No data provided on the process of blinding the participants to the placebo as well as the rate of follow-up.
b. Downgraded two levels due to very serious imprecision. No events occurred in one study of nearly 700 people.
c. Downgraded since at least one study has unclear risk or high risk in at least 2 domains.
d. Risk for influenza varies as studies were conducted in different settings like outbreak and non-outbreak
e. Population included are in the community, psychiatric hospital and nursing home both in an outbreak setting and no outbreak setting.
f. Downgraded since the study has unclear risk of bias in two domains (blinding and follow-up rate)
g. Downgraded two levels since there are very few events and the CI includes appreciable benefits and harm.
h. Pooled studies have appreciable benefit and harm.

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.5: Influenza vaccine compared to no vaccination in preventing pneumonia in the elderly

Setting: all settings, observational studies

Bibliography: Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018 Feb 1;2:CD004876 1;2:CD004876. doi:10.1002/14651858.CD004876.pub4.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	no vaccination	Relative (95% CI)	Absolute (95% CI)		
Pneumonia												
2	observational studies	not serious	not serious	not serious	serious [a]	none	75/9099 (0.8%)	83/8991 (0.9%)	**RR 0.88** (0.64 to 1.20)	**1 fewer per 1,000** (from 3 fewer to 2 more)	⊕◯◯◯ VERY LOW	CRITICAL
Hospitalization for flu or pneumonia												
9	observational studies	serious [b]	serious [c]	not serious	serious [a]	none	2604/308732 (0.8%)	7766/475911 (1.6%)	**RR 0.73** (0.62 to 0.85)	**4 fewer per 1,000** (from 6 fewer to 2 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Deaths from flu or pneumonia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	no vaccination	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	not serious	none	90/29346 (0.3%)	472/134045 (0.4%)	**RR 0.87** (0.70 to 1.09)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Influenza												
2	observational studies	serious [d]	not serious	serious [e]	serious	none	17/9129 (0.2%)	51/9120 (0.6%)	**RR 0.19** (0.02 to 2.01)	**5 fewer per 1,000** (from 5 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
Influenza-like illness												
4	observational studies	serious [f]	serious [g]	not serious	serious [a]	none	63/7027 (0.9%)	36/2586 (1.4%)	**RR 0.75** (0.42 to 1.43)	**3 fewer per 1,000** (from 8 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hospitalization for any respiratory disease												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	no vaccination	Relative (95% CI)	Absolute (95% CI)		
5	observational studies	serious [b]	serious [h]	not serious	serious [a]	none	3997/233604 (1.7%)	5163/333695 (1.5%)	**RR 0.88** (0.54 to 1.43)	**2 fewer per 1,000** (from 7 fewer to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL
Deaths from flu or pneumonia												
1	observational studies	not serious	not serious	not serious	not serious	none	2585/147294 (1.8%)	3720/279374 (1.3%)	**RR 1.32** (1.25 to 1.39)	**4 more per 1,000** (from 3 more to 5 more)	⨁⨁◯◯ LOW	CRITICAL

a. Imprecision is present because of the width of confidence interval that contains both important benefit and harm.
b. All studies had unclear risk of selection bias.
c. There was unexplained inconsistency that was supported by nonoverlapping confidence intervals, high I2 values and statistically significant heterogeneity of effect estimates. Heterogeneity: Tau2 = 0.04; Chi2 = 61.76, df = 8 (P<0.00001); I2 =87%.
d. The studies used different detection of influenza outcome (laboratory-confirmed influenza and clinical diagnosis of influenza)
e. The two studies were done in different settings: one was done in an outbreak setting and the other in low epidemic season.
f. Three of the studies were prospective cohort and one study was retrospective cohort.
g. The was inconsistency that was supported by high I2 values and statistically significant heterogeneity of effect estimates (Test for subgroup differences: Chi2 = 4.15, df = 2 (P = 0.13), I2 =52%)
h. There was inconsistency that was supported by high 12 values and statistically signifcant heterogeneity of effect estimates.

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.6 Influenza vaccine compared to no vaccination in preventing pneumonia and complications in the elderly without risks

Setting: elderly without risks

Bibliography: Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018 Feb 1;2:CD004876 1;2:CD004876. doi:10.1002/14651858.CD004876.pub4.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	no vaccination	Relative (95% CI)	Absolute (95% CI)		
Pneumonia												
1	observational studies	not serious	not serious	not serious	not serious	none	28/5349 (0.5%)	54/6050 (0.9%)	**RR 0.59** (0.37 to 0.92)	**4 fewer per 1,000** (from 6 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Hospitalization for influenza or pneumonia												
1	observational studies	not serious	not serious	not serious	not serious	none	126/57058 (0.2%)	196/44561 (0.4%)	**RR 0.50** (0.40 to 0.63)	**2 fewer per 1,000** (from 3 fewer to 2 fewer)	⊕⊕◯◯ LOW	CRITICAL
Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccine	no vaccination	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious [a]	none	11/5349 (0.2%)	22/6050 (0.4%)	**RR 0.57** (0.27 to 1.17)	**2 fewer per 1,000** (from 3 fewer to 1 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Deaths from respiratory disease												
1	observational studies	not serious	not serious	not serious	not serious	none	932/78912 (1.2%)	1691/202512 (0.8%)	**RR 1.41** (1.31 to 1.53)	**3 more per 1,000** (from 3 more to 4 more)	⨁⨁◯◯ LOW	CRITICAL
Combined outcome: all deaths or severe respiratory disease												
2	observational studies	serious	not serious	not serious	not serious	none	365/71848 (0.5%)	521/63332 (0.8%)	**RR 0.62** (0.54 to 0.70)	**3 fewer per 1,000** (from 4 fewer to 2 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.7: Influenza vaccines compared to no vaccination in preventing pneumonia in elderly with risks

Setting: elderly with risks

Bibliography: Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018 Feb 1;2:CD004876 1;2:CD004876. doi:10.1002/14651858.CD004876.pub4.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccines	no vaccination	Relative (95% CI)	Absolute (95% CI)		
Pneumonia												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	44/3562 (1.2%)	29/2861 (1.0%)	**RR 1.22** (0.76 to 1.94)	**2 more per 1,000** (from 2 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hospitalization for influenza or pneumonia												
1	observational studies	serious [c]	not serious	not serious	not serious	none [b]	419/30840 (1.4%)	278/15092 (1.8%)	**RR 0.74** (0.63 to 0.86)	**5 fewer per 1,000** (from 7 fewer to 3 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	influenza vaccines	no vaccination	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious [a]	none [b]	5/3562 (0.1%)	10/2861 (0.3%)	**RR 0.40** (0.14 to 1.17)	**2 fewer per 1,000** (from 3 fewer to 1 more)	⨁◯◯◯ VERY LOW	CRITICAL
Deaths from any respiratory disease												
1	observational studies	not serious	not serious	not serious	not serious	none	1653/66850 (2.5%)	2029/75614 (2.7%)	**RR 0.92** (0.86 to 0.98)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
Combined all deaths or severe respiratory disease												
2	observational studies	serious [d]	not serious	not serious	not serious	none	1824/91158 (2.0%)	1806/55090 (3.3%)	**RR 0.60** (0.49 to 0.74)	**13 fewer per 1,000** (from 17 fewer to 9 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

a. The study was imprecise as the CI has both benefit and harm estimates.
b. Suspected selective availability of data from published or unpublished studies as only one study was involved.
c. There was unclear risk of selection bias.
d. One study had unclear risk of selection bias.

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.8: Pneumococcal vaccine with influenza vaccine compared to no vaccine for elderly

Setting: community dwellers, elderly

Bibliography: Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018 Feb 1;2:CD004876 1;2:CD004876. doi:10.1002/14651858.CD004876.pub4.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pneumococcal vaccine with influenza vaccine	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Hospitalization for influenza or pneumonia or respiratory diseases												
3	observational studies	serious [a]	not serious	not serious	not serious	none	2504/225249 (1.1%)	4961/293499 (1.7%)	**RR 0.67** (0.64 to 0.70)	**6 fewer per 1,000** (from 6 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Deaths from influenza or pneumonia												
1	observational studies	not serious	not serious	not serious	not serious	none	67/100242 (0.1%)	245/159385 (0.2%)	**RR 0.43** (0.33 to 0.57)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
All deaths												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pneumococcal vaccine with influenza vaccine	no vaccine	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	serious [b]	not serious	not serious	serious [c]	none	1517/100547 (1.5%)	5531/159454 (3.5%)	**RR 0.44** (0.41 to 0.46)	**19 fewer per 1,000** (from 20 fewer to 19 fewer)	⨁◯◯◯ VERY LOW	

a. Two studies had unclear risk of bias however both contributed the most to the pooled relative risk.
b. Unclear risk of selection bias.
c. Downgraded one level due to serious imprecision based on high heterogeneity.

Question 16: Among adult patients, how effective are pneumococcal and influenza vaccines in preventing pneumonia and its complications?

Table Q16.9: Combination of influenza and pneumococcal vaccine compared to influenza vaccine alone for the prevention of pneumonia in the elderly

Setting: combination of community dwellers and nursing homes

Bibliography: Zhang YY, Tang X, Du C, Wang B, Bi Z, Dong B. Comparison of influenza and pneumococcal polysaccharide vaccine and influenza vaccination alone for preventing pneumonia and reducing mortality among the elderly: A meta-analysis. Human vaccines and immunotherapies. 2016. 12(12): 3056-3064

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Pneumonia									
4	observational studies	not serious	not serious	serious	not serious	none	There was no evidence of heterogeneity among the 4 studies. The study revealed that the combination of influenza and pneumococcal vaccine can lower the incidence of pneumonia (RR 0.74, 95% CI 0.62-0.88)	⊕◯◯◯ VERY LOW	CRITICAL
All-caused mortality (follow up: range 1 years to 2 years)									
4	observational studies	not serious	not serious	serious [a]	not serious	none	There was evidence that the combination of influenza+pneumococcal vaccination significantly decreased the all-cause mortality rate than influenza alone (RR = 0.84, 95% CI: 0.62-0.88)	⊕◯◯◯ VERY LOW	CRITICAL

b. Combination of elderly from nursing home and community dwelling.

APPENDIX C: FOREST PLOTS AND SUMMARY OF FINDING TABLES

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6. 1 Cephalosporin vs Co-amoxiclav
Page 1072, Figure 1c
Maimon 2008,

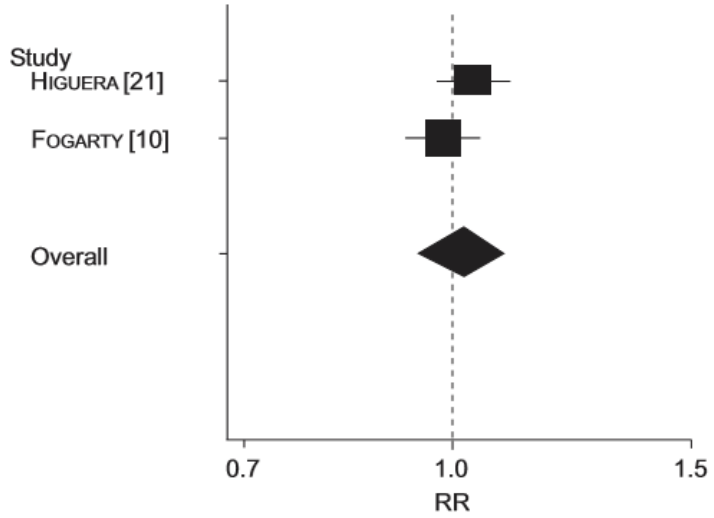

Figure Q6.1 Clinical success of cephalosporins (treatment) versus b-lactams/beta- lactamase inhibitors (control)

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6.2 Clarithromycin vs Erythromycin

Page 55, Analysis 8.1

Pakhale 2014

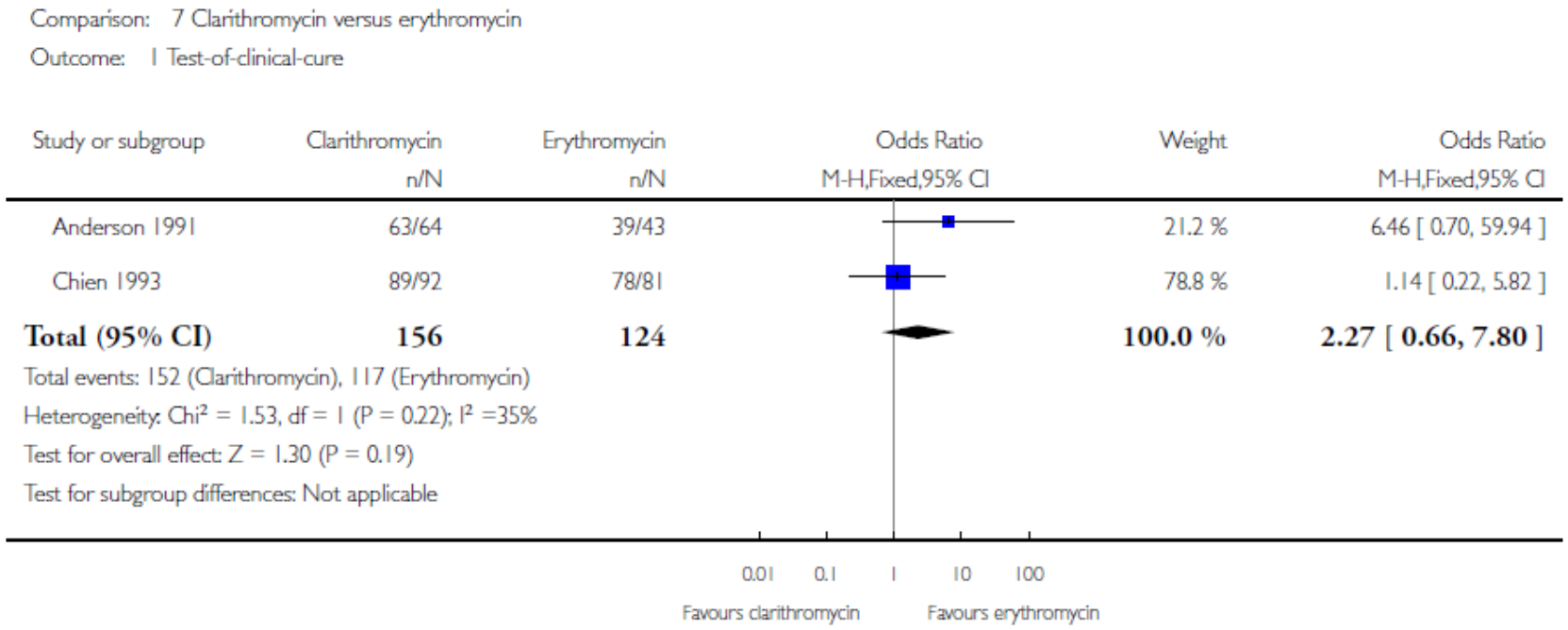

Figure Q6.2 Test of Clinical Cure between Clarithromycin and Erythromycin

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6.3 Clarithromycin vs Erythromycin

Page 54, Analysis 7.1

Pakhale 2014

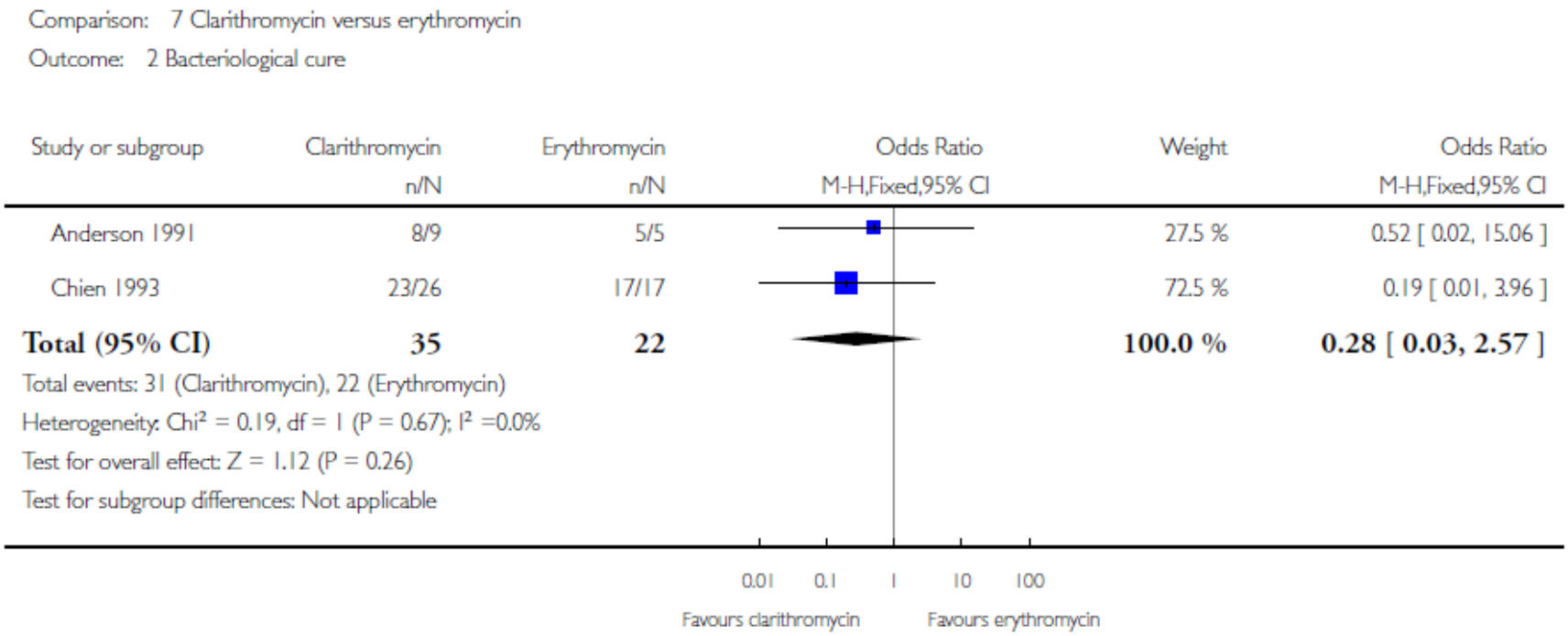

Figure Q6.3 Bacteriologic cure between Clarithromycin and Erythromycin

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6.4 Clarithromycin vs Erythromycin

Page 54, Analysis 7.3

Pakhale 2014

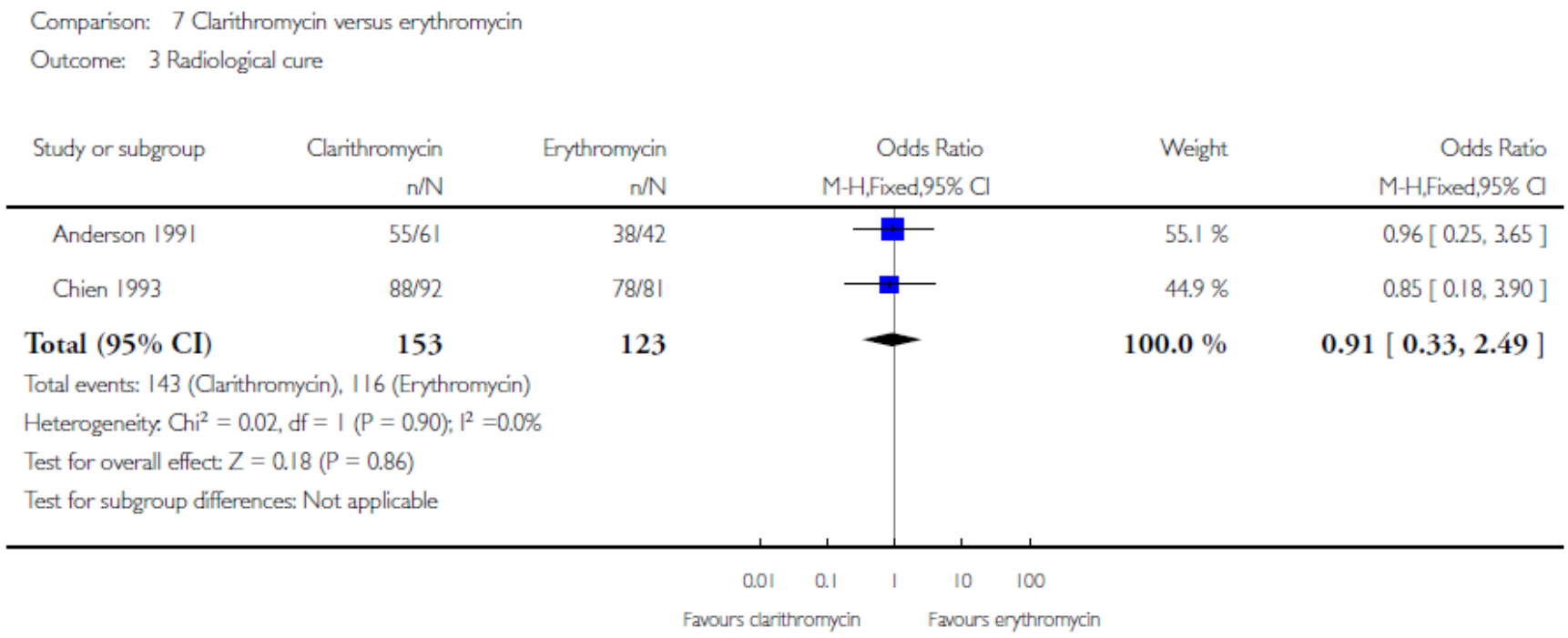

Figure Q6.4 Radiologic cure between Clarithromycin and Erythromycin

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6.5 Azithromycin vs Clarithromycin

Page 57, Analysis 9.1

Pakhale 2014

Comparison: 9 Azithromycin microspheres versus clarithromycin

Outcome: 1 Test-of-clinical-cure

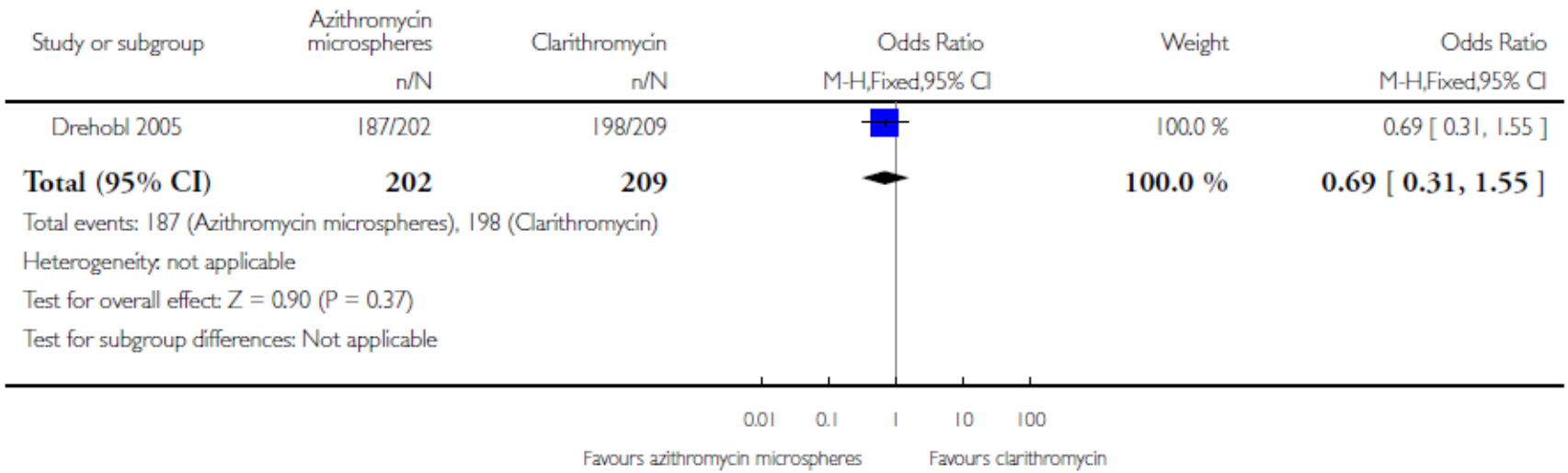

Figure Q6.5 Test of Clinical cure between Azithromycin and Clarithromycin

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6.6 Azithromycin vs Clarithromycin

Page 57, Analysis 9.2

Pakhale 2014

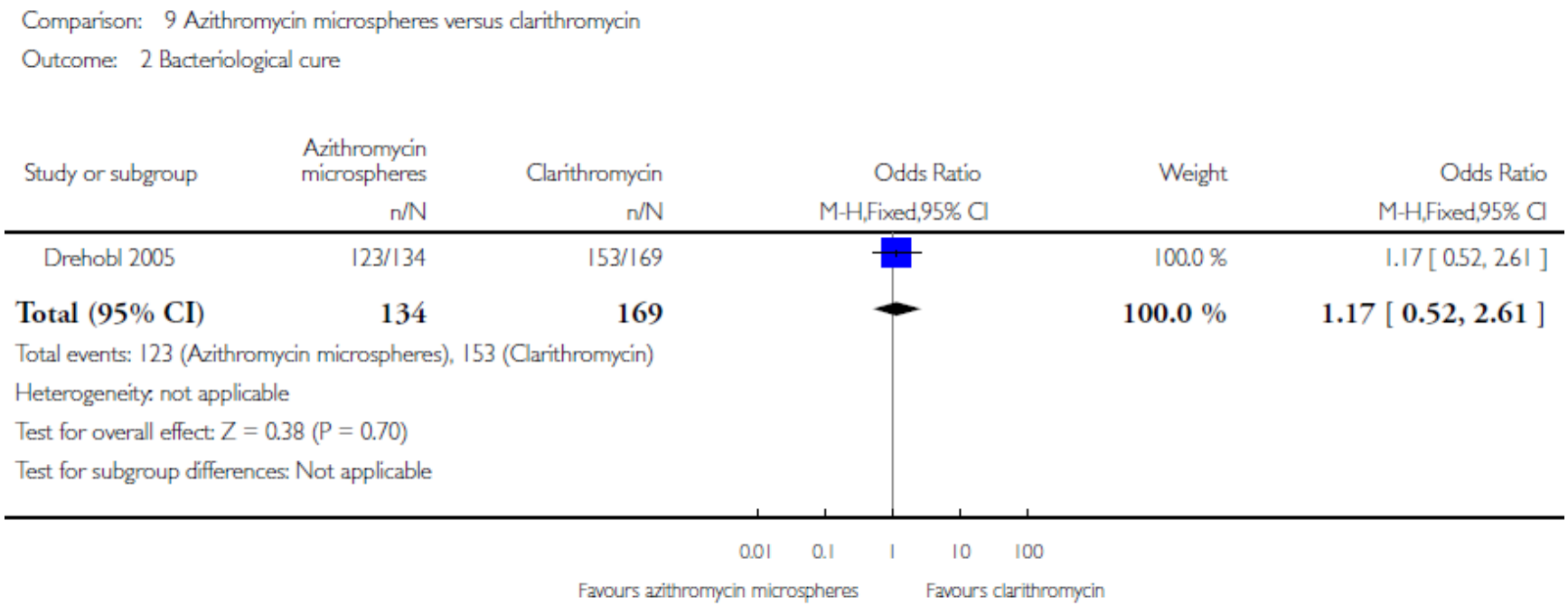

Figure Q6.6 Bacteriologic cure between Azithromycin and Clarithromycin

Question 6: What antibiotics are recommended for the empiric treatment of low-risk CAP?

Figure Q6.7 Azithromycin vs Clarithromycin

Page 58, Analysis 9.3

Pakhale 2014

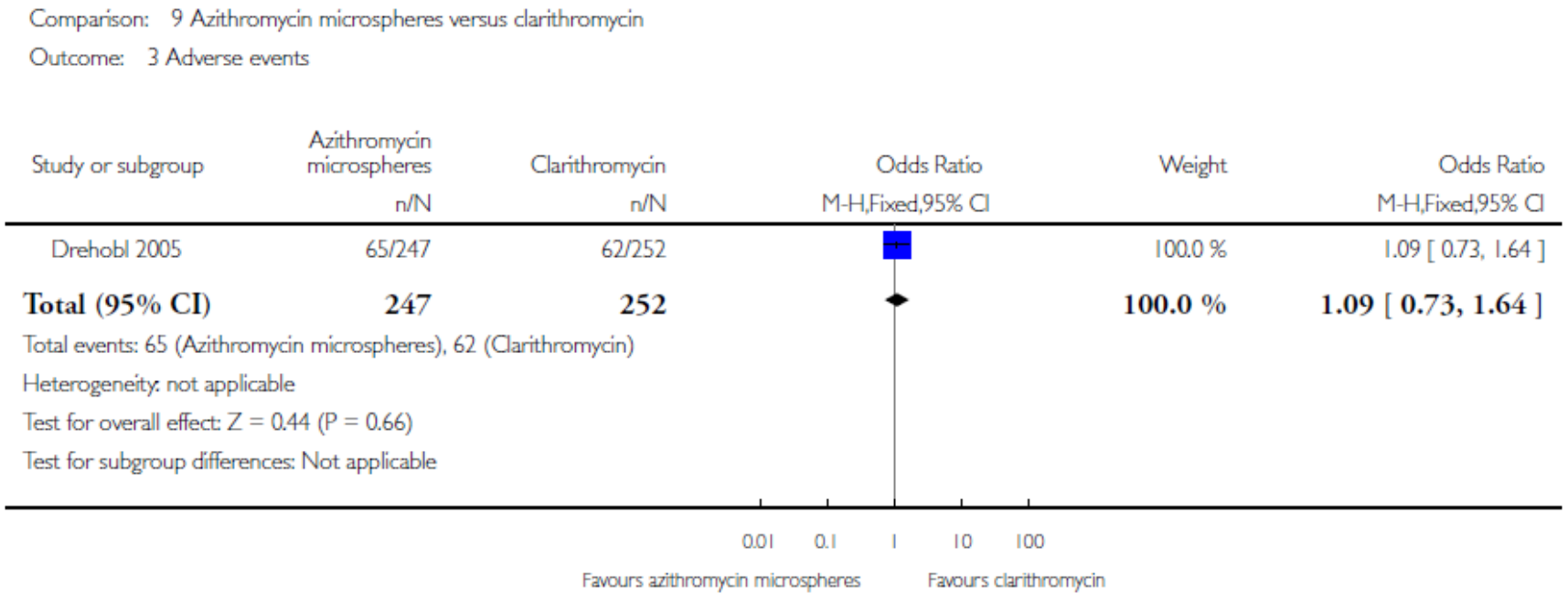

Figure Q6.7 Adverse events between Azithromycin and Clarithromycin

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Figure Q7.1. Clinical failure for Fluoroquinolone monotherapy versus Beta-lactam plus macrolide

Page 5

Raz-Pasteur 2015

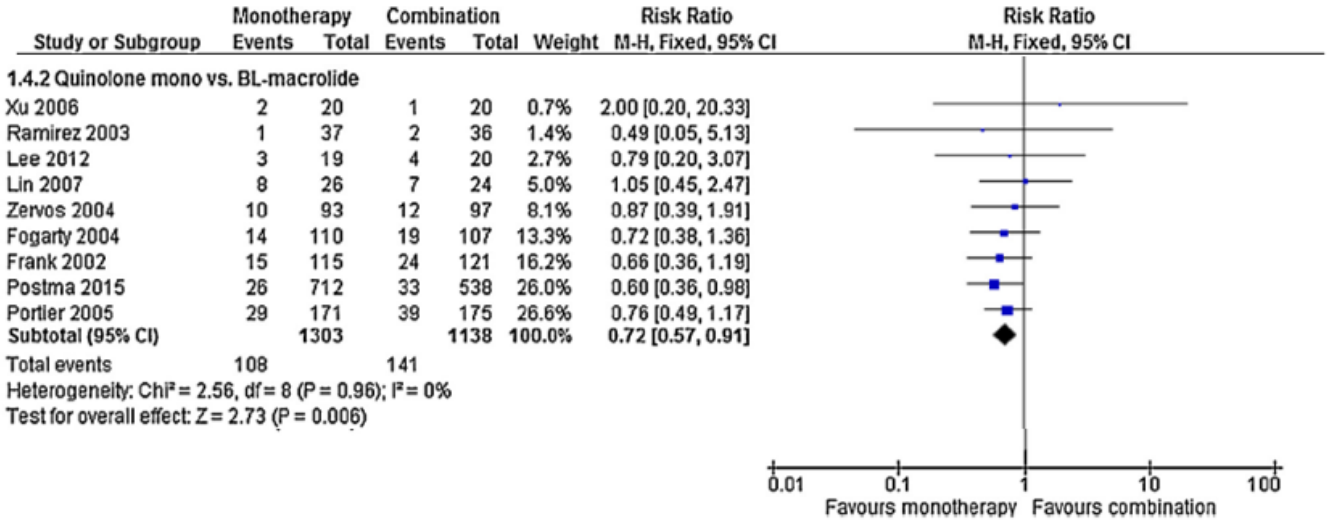

Figure Q7.1 Clinical failure for Fluoroquinolone monotherapy versus Beta-lactam plus macrolide (Raz-Pasteur 2015)

Question 7: What antibiotics are recommended for the empiric treatment of moderate-risk CAP?

Figure Q7.2. Serious arrhythmia, cardiovascular death, and all-cause death associated with FQs compared to no FQs use

Page 5

Liu, X et al, 2017

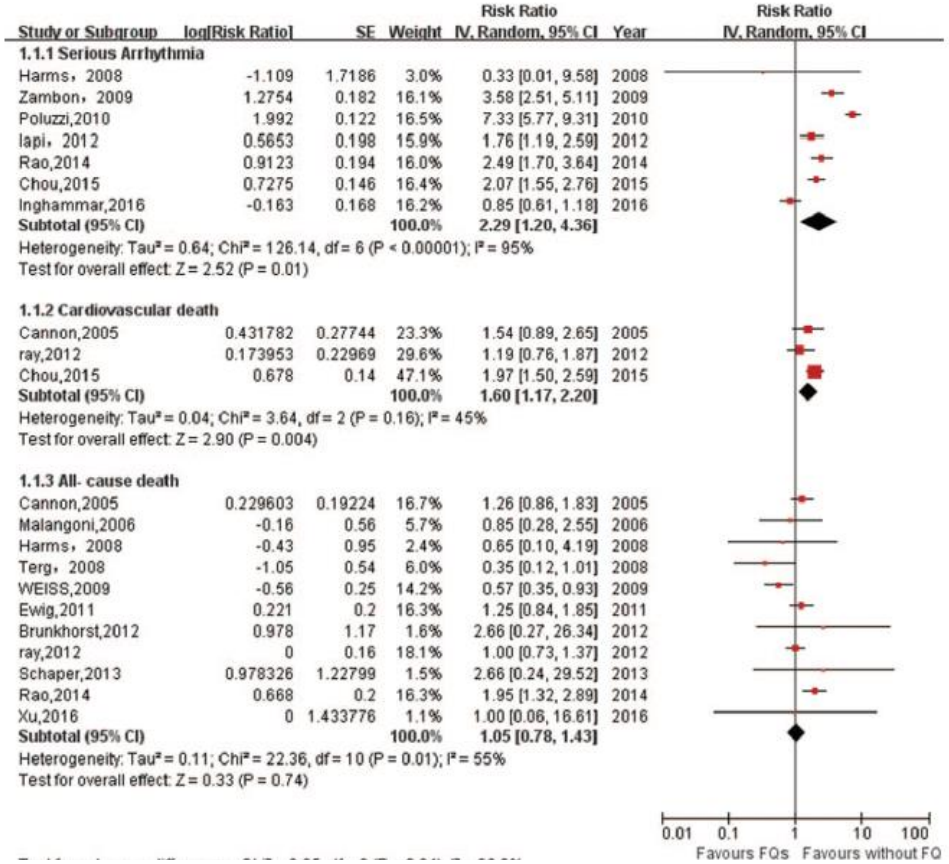

Figure Q7.2 Serious arrhythmia, cardiovascular death, and all-cause death associated with FQs compared to no FQs use. CI=confidence interval, FQs=fluoroquinolones, IV=inverse of the variance, RR=relative risks, SE=standard error.

Question 8: What antibiotics are recommended for the empiric treatment of high-risk CAP?

Table Q8.4 Percentage change from baseline to end point in percentage of susceptibility to fluoroquinolones, by pathogen
Setting: In-patient
(Zervos 2003)

Pathogen	No. of hospitals	Change in percentage of susceptibility, %	
		Mean ± SD	Range
Escherichia coli	10	– 6.8 ± 5.5	– 16.1 to – 1.0
Pseudomonas aeruginosa	10	– 25.1 ± 20.7	– 16.7 to 18.2
Klebsiella pneumoniae	10	– 1.3 ± 9.5	– 11.8 to 22.5
Proteus mirabilis	10	– 11.9 ± 12.4	– 43.7 to 0.0
Enterobacter cloacae	10	– 6.6 ± 5.8	– 15.0 to 3.7
Enterobacter aerogenes	8	1.4 ± 10.45	– 8.2 to 17.4
Acinetobacter species	9	– 17.0 ± 105.8	– 34.3 to 296.9
Serratia marcescens	9	– 3.8 ± 5.27	– 13.2 to 3.3
Citrobacter species	9	3.2 ± 33.11	– 31.0 to 87.5
Stenotrophomonas maltophilia	10	– 17.4 ± 30.08	– 60.7 to 32.6
Staphylococcus aureus	9	– 26.8 ± 23.34	– 57.0 to 9.0

Question 12: Among adults with CAP, how soon should empiric treatment be started?

Figure Q12.1: Studies Assessing Initiation of Antibiotic Therapy and MORTALITY for Patients Hospitalized With Community-Acquired Pneumonia

National Clinical Guideline Centre Forest plots Pneumonia Diagnosis and management of community- and hospital-acquired pneumonia in Adults Clinical guideline 191 Appendix I 3 December 2014, page 24, Figure 62

Houck 2004, Lee 2011, Simonetti 2012, Waterer 2005, Wilson 2005, Bader 2011, Dedier 2001, Meehan 1997, Mortensen 2008, Jo 2012

Figure 62: Mortality

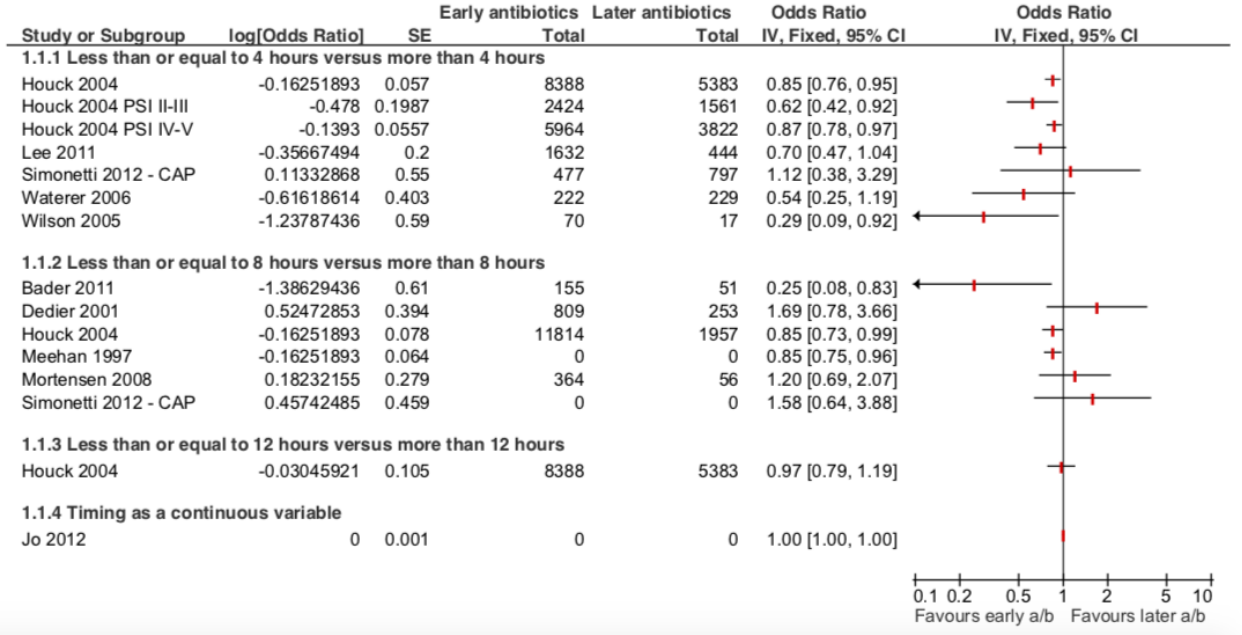

Figure Q12.1: Forest plot for studies Assessing Initiation of Antibiotic Therapy and MORTALITY for Patients Hospitalized With Community-Acquired Pneumonia

Question 12: Among adults with CAP, how soon should empiric treatment be started?

Figure Q12.2: Studies Assessing Initiation of Antibiotic Therapy and PROLONGED LENGTH OF STAY for Patients Hospitalized With Community-Acquired Pneumonia

National Clinical Guideline Centre Forest plots Pneumonia Diagnosis and management of community- and hospital-acquired pneumonia in adults Clinical guideline 191 Appendix I 3 December 2014, page 26, Figure 64

Houck 2004, Lee 2011, Dedier 2001, Huang 2006

Figure 64: Prolonged length of stay (above median)

Study or Subgroup	log[Odds Ratio]	SE	Early antibiotics Total	Later antibiotics Total	Odds Ratio IV, Fixed, 95% CI
1.3.1 Less than or equal to 4 hours versus more than 4 hours					
Houck 2004	-0.10536052	0.036	8388	5383	0.90 [0.84, 0.97]
Houck 2004 PSI II-III	-0.1508	0.0698	2424	1561	0.86 [0.75, 0.99]
Houck 2004 PSI IV-V	-0.0834	0.0464	5964	3822	0.92 [0.84, 1.01]
Lee 2011	0.1823	0.0464	1632	444	1.20 [1.10, 1.31]
1.3.2 Less than or equal to 8 hours versus more than 8 hours					
Dedier 2001	-0.11653382	0.16	809	253	0.89 [0.65, 1.22]
1.3.3 Less than or equal to 4 hours versus 4-8 hours					
Huang 2006	0.01980263	0.105	0	0	1.02 [0.83, 1.25]
1.3.4 Less than or equal to 4 hours versus more than 8 hours					
Huang 2006	-0.24846136	0.11	0	0	0.78 [0.63, 0.97]

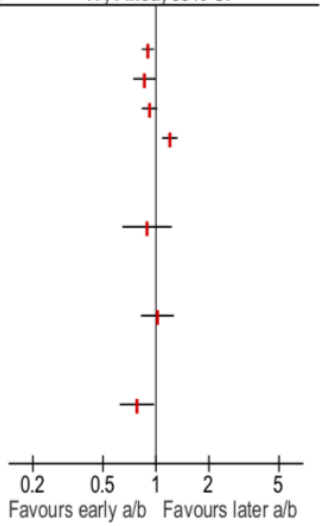

Figure Q12.2: Forest plot of Studies Assessing Initiation of Antibiotic Therapy and PROLONGED LENGTH OF STAY for Patients Hospitalized With Community-Acquired Pneumonia

Question 12: Among adults with CAP, how soon should empiric treatment be started?

Figure Q12.3: Studies assessing initiation of antibiotic therapy within 4 hours versus more than 4 hours and RE-ADMISSION AFTER DISCHARGE for Patients Hospitalized With Community-Acquired Pneumonia

National Clinical Guideline Centre Forest plots Pneumonia Diagnosis and management of community- and hospital-acquired pneumonia in adults Clinical guideline 191 Appendix I 3 December 2014, page 26, Figure 66

Houck 2004, Lee 2011

Figure 66: Re-admission after discharge

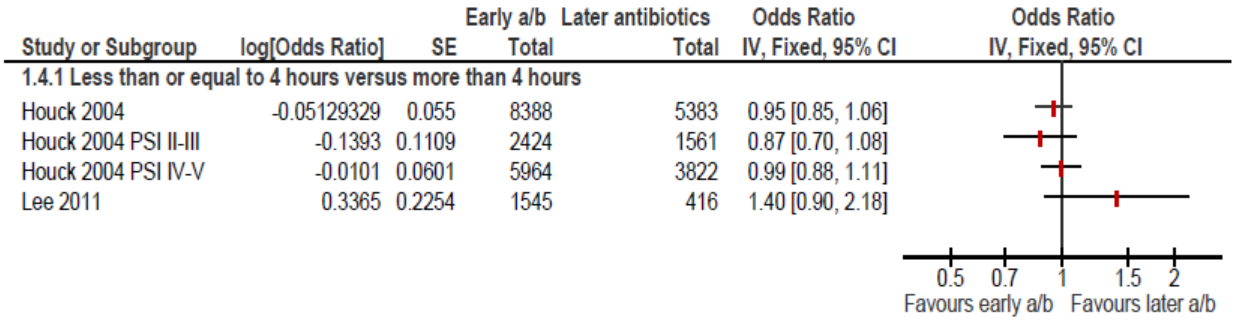

Figure Q12.3: Forest plot for studies assessing initiation of antibiotic therapy within 4 hours versus more than 4 hours and RE-ADMISSION AFTER DISCHARGE for Patients Hospitalized With Community-Acquired Pneumonia

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Figure Q13.1 Clinical cure of short-course vs. long course antibiotic treatments for community-acquired pneumonia in adults

Page 6, Figure 2

Tansarli GS, Mylonakis E. 2018.

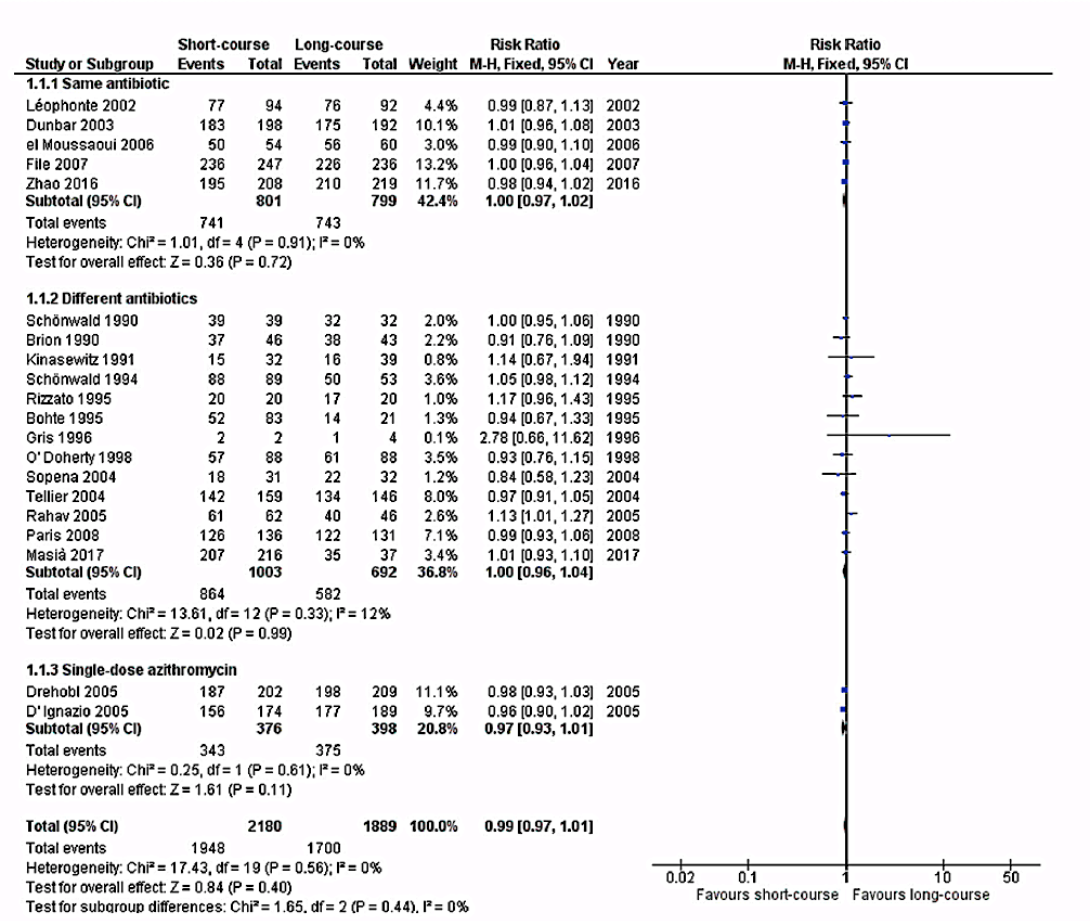

Figure Q13.1: Forest plot depicting the risk ratios of clinical cure for clinically evaluable patients receiving antibiotic treatment for ≤6 days versus ≥7 days in clinical trials, stratified by type of regimen

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Figure Q13.2 Mortality of short-course vs. long course antibiotic treatments for community-acquired pneumonia in adults
Tansarli GS, Mylonakis E. 2018.
Page 7, figure 3

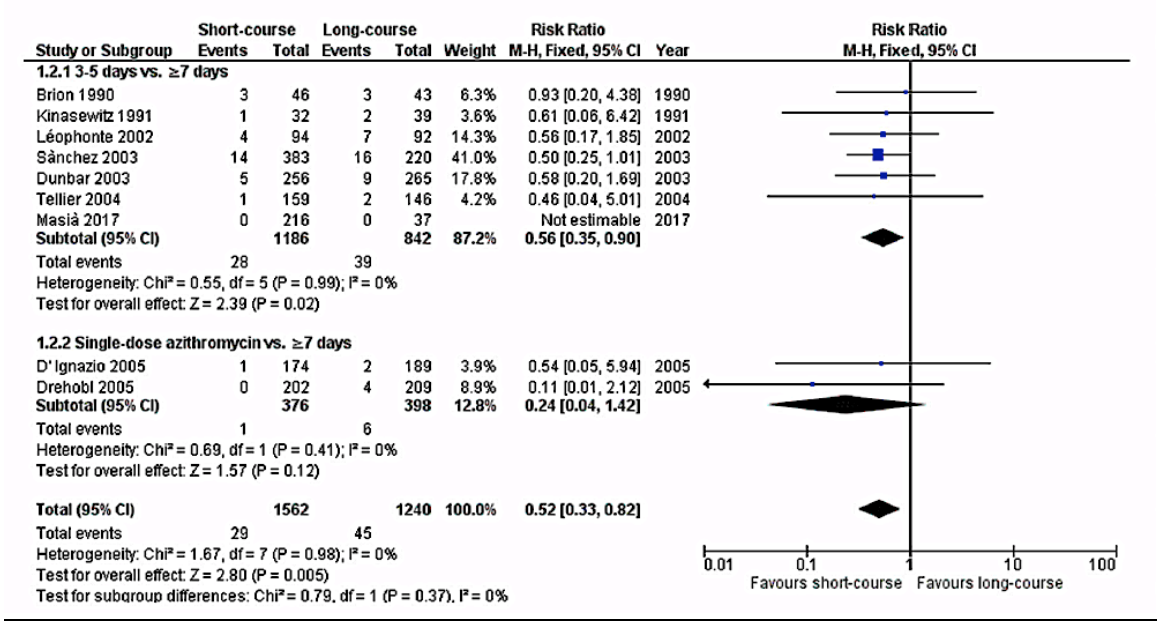

Figure Q13.2: Forest plot depicting the risk ratios of mortality for patients receiving antibiotic treatment for ≤6 days versus ≥7 days clinical trials, stratified by duration of therapy.

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Figure Q13.3. Antibiotic related adverse events of short-course vs. long course antibiotic treatments for community-acquired pneumonia in adults

Tansarli GS, Mylonakis E. 2018.

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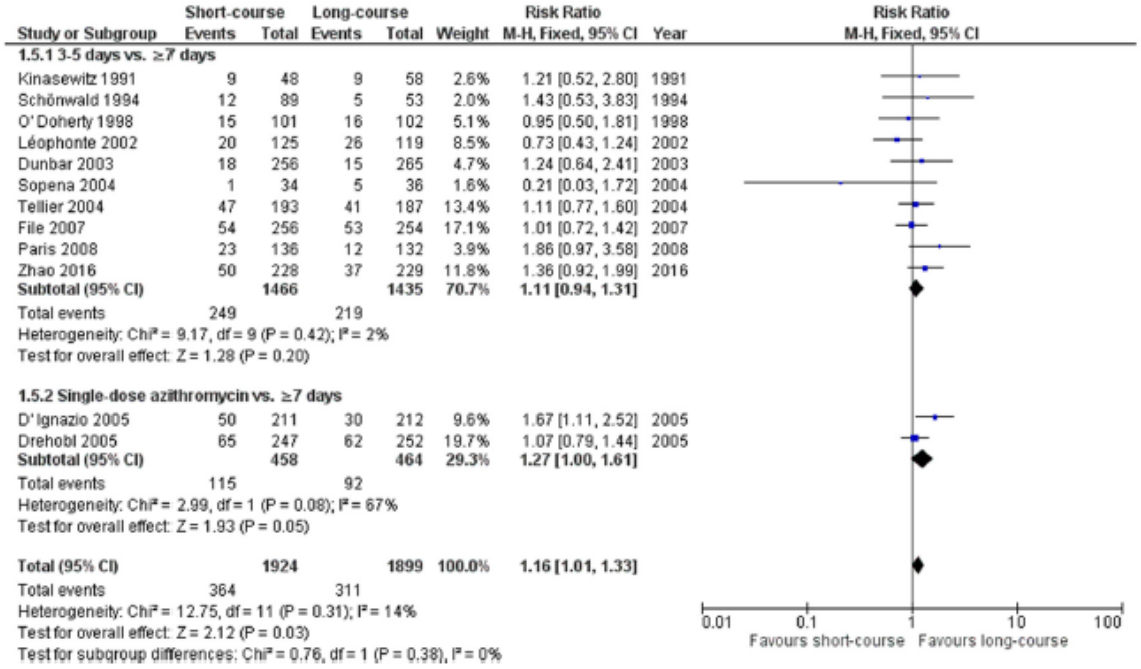

Figure Q13.3: Forest plot depicting the risk ratios of antibiotic related adverse events for patients receiving antibiotic treatment for ≤6 days versus ≥7 days clinical trials, stratified by duration of therapy

Question 13: Among adult patients with CAP, what is the appropriate duration of treatment?

Figure Q13.4. Serious adverse events of short-course vs. long course antibiotic treatments for community-acquired pneumonia in adults Tansarli GS, Mylonakis E. 2018.

Page 8, figure 4

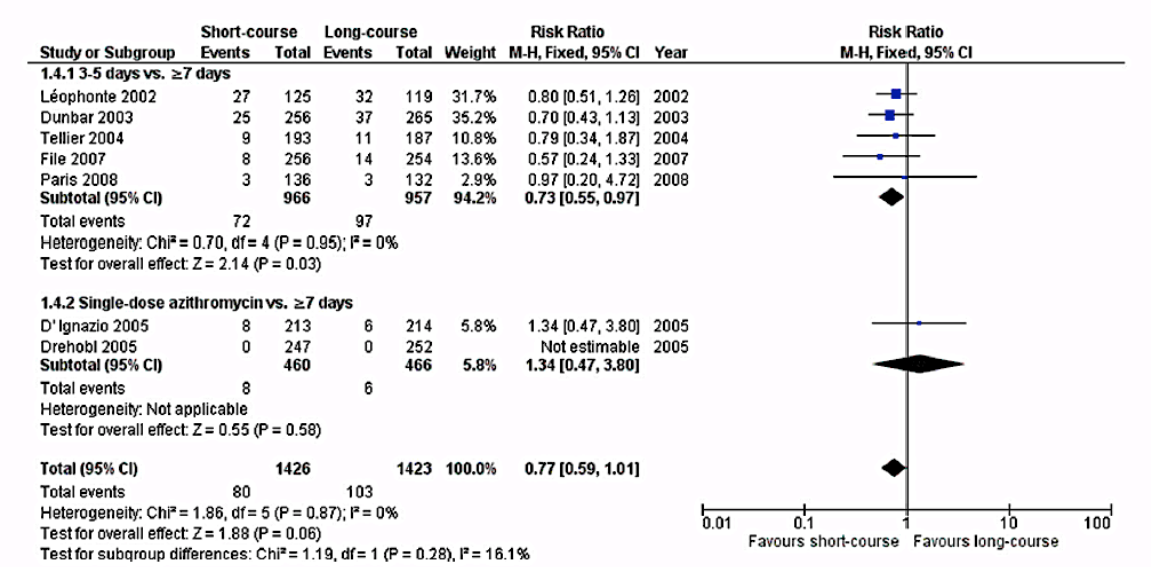

Figure Q13.4: Forest plot depicting the risk ratios of serious adverse events for patients receiving antibiotic treatment for ≤6 days versus ≥7 days clinical trials, stratified by duration of therapy

Question 15A: Among patients with clinical improvements while ongoing treatment, should the chest xray be performed to monitor response to treatment?

Figure Q15A.1. Outcome of recommendations for radiographic follow-up of pneumonia on outpatient chest radiography
Little BP, Gilman MD, Humphrey KL, Alkasab TK, Gibbons FK, Shepard JA, Wu CC. Journal of Roentgenology. 2014 Jan;202(1):54-9
Figure 2

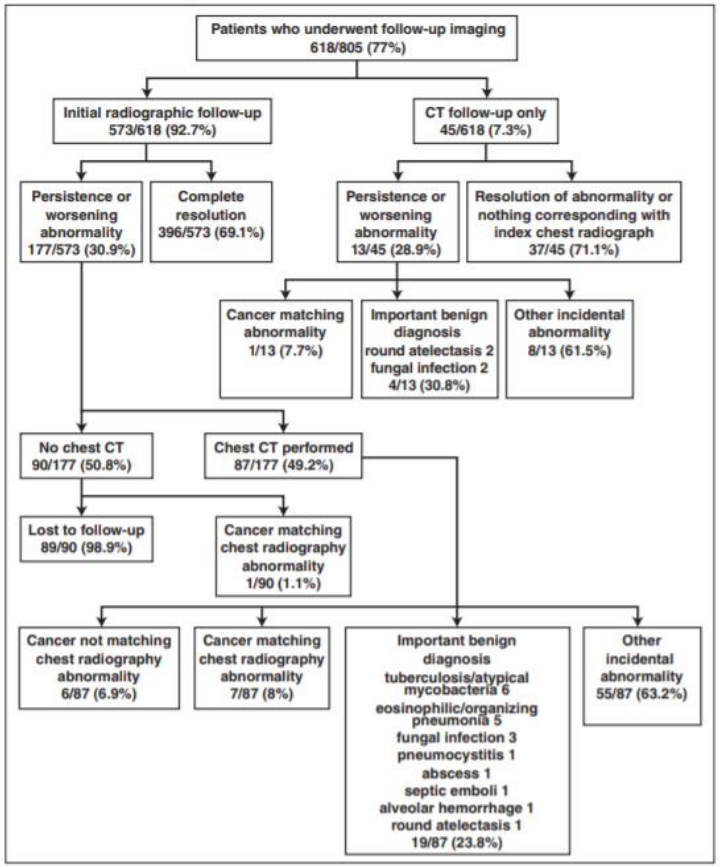

Fig. 2—Flowchart shows outcome of patients who underwent follow-up imaging.

Figure Q15A.1. Outcome of recommendations for radiographic follow-up of pneumonia on outpatient chest radiography

Question 15A: Among patients with clinical improvements while ongoing treatment, should the chest xray be performed to monitor response to treatment?

Figure Q15A.2. Clinical symptoms rated by patients (CAP score) according to radiographic resolution of CAP

Bruns AH, Oosterheert JJ, El Moussaoui R, Opmeer BC, Hoepelman AI, Prins JM. Journal of general internal medicine. 2010 Mar 1;25(3):203-6.

Figure 1

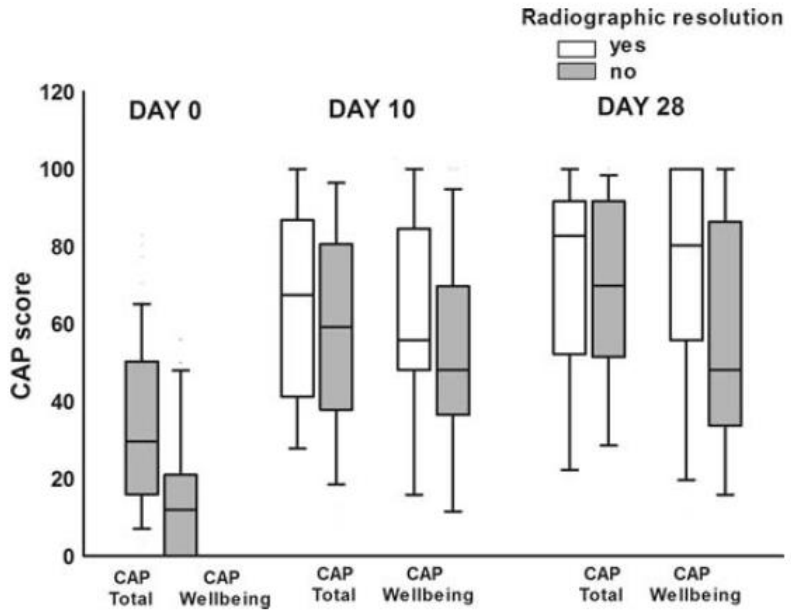

Figure 1. Clinical symptoms rated by patients (CAP score) according to radiographic resolution of CAP.

Figure Q15A.2. Pneumonia recovery; discrepancies in perspectives of the radiologist, physician and patient.