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**PAPP PERSPECTIVE**

# 2012 PAPP Update

# in the

# Evaluation and Management of

# Pediatric Community-Acquired Pneumonia

**2012 PAPP Task Force on pCAP**

**Philippine Academy of Pediatric Pulmonologists, Inc. [PAPP, Inc.]**
PAPP Task Force on pCAP: 2012 PAPP Update in the Evaluation and Management of Pediatric Community-Acquired Pneumonia

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## FOREWORD

In 2004, the Philippine Pediatric Society spearheaded the publication of the Clinical Practice Guidelines in the Evaluation and Management of Pediatric Community Acquired Pneumonia (pCAP). It identified key issues on the diagnosis and management of the disease in immunocompetent children aged 3 months – 19 years, using the available local and foreign data. While most of the important concerns were addressed, gaps in knowledge emerged.

Recognizing these important unresolved issues and the evidences gathered in the following years, the Philippine Academy of Pediatric Pulmonologists (PAPP) drafted the 2008 PAPP Update in the Evaluation and Management of pCAP. It included new developments and answers to some of the previously identified issues.

Once again, the PAPP takes another look at the disease. The Task Force on PCAP reviewed the relevant researches in the past four years and came up with the 2012 PAPP Update in the Evaluation and Management of pCAP. We are optimistic that the document will assist clinicians in making rational medical decisions and, in the process, improve the quality of care for Filipino children.

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President
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## PREFACE

Being the third document dealing with pediatric community-acquired pneumonia, the 2012 PAPP Task Force on pCAP has made revisions on several recommendations based on recent evidence from local and foreign literature. The decision to revise was based on the strength of evidence and consultation with major stakeholders as to acceptability and relevance to clinical practice. The final revision was reached through consensus among the members of the Task Force, and was approved by the Board of Directors of the Philippine Academy of Pediatric Pulmonologists, Inc.

The main difficulty encountered by the members of the 2012 Task Force has remained to be the lack of relevant and high quality studies that specifically address the clinical questions at hand. This makes any changes in policy recommendation to be highly dependent upon consensus decision based on expert opinion. A welcome offshoot of this difficulty is identification of gaps in knowledge in this field, which hopefully can stimulate local researches that will answer specific concerns .

Cristan Q Cabanilla, MD FPPS FPAPP
Chair
2012 PAPP Task Force on pCAP

# METHODOLOGY OVERVIEW

**A. Scope**

The 2012 PAPP Update in the Evaluation and Management of Pediatric Community-Acquired Pneumonia deals with [1] recognition of community-acquired pneumonia, [2] identification of appropriate and practical diagnostic procedures, and [3] initiation of rational management and preventive measures in an immunocompetent patient aged 3 months to 19 years.

**B. Intended target users**

The intended users are medical practitioners who are involved in the day-to-day care of pediatric patients with community-acquired pneumonia.

**C. Technical Working Group**

A technical working group has been designated by the PAPP 2012 Task Force on pCAP to search and appraise relevant clinical evidence.

**D. Conflict of interest**

The following have been resource speakers in continuing medical education activities dealing with pediatric community-acquired pneumonia sponsored by a pharmaceutical company, a medical society, or a hospital facility: Cristan Q. Cabanilla, Emily B. Gaerlan-Resurreccion, Gari D. Astrologio, Amelia G. Cunanan, Anjanette R. de Leon, Roslyn Marie K. Dychiao, Mary Genevieve M. Estrada, Jean Marie E. Jamero, Grace V. Malayan, Raymund Anthony L. Manuel, Catherine S. Palaypayon, Anna Marie S. Putulin, Galilee G. Ramos, Ernesto Z. Salvador, Marion O. Sanchez, and Rozaida R. Villon.

**E. Clinical questions pertaining to evaluation, treatment and prevention**

The 2012 PAPP Task Force on pCAP has decided to maintain the same clinical questions that were formulated in the 2004 Clinical Practice Guideline in the Evaluation and Management of Pediatric Community-acquired Pneumonia, and 2008 Update in the Evaluation and Management of Pediatric Community-acquired Pneumonia:

1. Who shall be considered as having community-acquired pneumonia?
2. Who will require admission?
3. What diagnostic aids are initially requested for ambulatory patients?
4. What diagnostic aids are initially requested for in-patients?
5. When is antibiotic recommended?
6. What empiric treatment should be administered if a bacterial etiology is strongly considered?
7. What treatment should be initially given if a viral etiology is strongly considered?
8. When can a patient be considered as responding to the current antibiotic?
9. What should be done if a patient is not responding to current antibiotic therapy?
10. When can switch therapy in bacterial pneumonia be started?
11. What ancillary treatment can be given?
12. How can pneumonia be prevented?

## F. Literature search and appraisal of evidence

Local researches submitted to the Philippine Pediatric Society [PPS] and Philippine Academy of Pediatric Pulmonologists [PAPP], and foreign literature identified using the PubMed database were searched and limited to the following: [1]. Source of data from January 1, 2008 to December 31, 2011; [2]. 3 months to 19 years of age; and [3]. immunocompetent host. Publication bias potentially exists since published local articles other than what had been submitted to PPS and PAPP and unpublished local or foreign articles were not searched.

Appraisal of evidence and interpretation of results were done based on Dans AL, Dans LF, Silvestre MAA: *Painless Evidence-Based Medicine* 2008, England John Wiley and Sons & Ltd.

## G. Reporting of results of studies in the Summary of Evidence

The results of studies as outlined in the Summary of Evidence include the following: subject population, study design, outcome measure and result. Please see appendix for definition of terms and interpretation of results.

## H. Grade recommendation with level of evidence

The 2012 PAPP Task Force on pCAP formulated the recommendations in an en-banc meeting according to the strength of evidence that was originally used in the 2004 Clinical Practice Guideline in the Evaluation and Management of Pediatric Community Acquired Pneumonia.

| GRADE | LEVEL OF EVIDENCE | THERAPY | DIAGNOSIS |
|---|---|---|---|
| A | 1a | Systematic review with homogeneity of RCT | Systematic review of level 1 diagnostic studies or a clinical practice guideline validated on a test set |
| | 1b | Individual RCT with narrow confidence interval | Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard |
| | 1c | All or none | SpIN and SnOut |
| B | 2a | Systematic review with homogeneity of cohort studies | Systematic review with homogeneity of level 2 diagnostic studies |
| | 2b | | Independent blind comparison but either in nonconsecutive patients or confined to a narrow spectrum of study individuals [or both], all of whom have undergone both the diagnostic test and the reference standard, or a diagnostic clinical practice guideline not validated in a test set |
| | 2c | "Outcomes" research | |
| | 3a | Systematic review with homogeneity of case control studies | |
| | 3b | Individual case control studies | Independent blind comparison of an appropriate spectrum but reference standard was not applied to all study patients |
| C | 4 | Case series or poor quality cohort | Reference standard was not applied independently or not applied blindly |
| D | 5 | Expert opinion | Expert opinion |

## I. Stakeholder's consultation

The 2012 PAPP Update has been been presented to the following stakeholders who have been preselected by the PAPP 2012 Task Force on pCAP for opinion as to acceptability and applicability in individual clinical practice: public health officer, general pediatrician, infectious disease pediatrician, ambulatory pediatrician, general medical practitioner, family physician, municipal or city health officer, rural health physician, medical officer employed in a government hospital, pediatric radiologist, pathologist, medical insurance officer, private hospital administrator and postgraduate medical trainee.

Any opinion expressed by the individual stakeholder does not necessarily reflect that of the medical society or institution he/she is affiliated with.

**J. Formulation of the final draft**

The 2012 PAPP Task in pCAP met en-banc to finalize the draft of the 2012 PAPP Update. Each recommendation was approved by at least three-fourths of the members of the Task Force.

**K. Approval by the 2012-2013 PAPP Board of Directors**

The final draft was approved by the 2012-2013 PAPP Board of Directors through a board resolution.

**L. Dissemination and periodic evaluation**

Dissemination is through the Philippine Academy of Pediatric Pulmonologists [PAPP]. Digital version can be downloaded free at the PAPP website, while a hard copy is available at the PAPP office.

Periodic evaluation using a questionnaire survey as to acceptability by the end-user, utilization in clinical practice, and identification of gaps in knowledge will be developed each year by the PAPP Task Force on pCAP, and distributed to clinicians during the PAPP Annual Convention**.** Results of the periodic evaluation will be used for formulating the 2016 PAPP Update in the Evaluation and Management of Pediatric Community Acquired Pneumonia.


## ACKNOWLEDGMENT

Gratitude is extended to the following for reviewing the document and providing invaluable comments: Alberto P. Herrerra MD [City Health Officer, Marikina City]; Melanie C. Santillan MD DPPS [Medical Specialist III, Head of Special Products Development Team, Philippine Health Insurance Corporation]; Joel G. Julian MD DPPS [Hospital administrator, Marikina Valley Medical Center, Marikina City]; Violeta N. Acorda MD FPPS [General pediatrician, Department of Pediatrics Mary Johnston Hospital]; Rochelle C. Cedeno MD DPPS [General pediatrician, Ospital ng Makati]; Yadnee V. Estrera MD DPPS [General pediatrician, Metro Davao Medical and Research Center]; Juanita T. Lu MD FPPS [General pediatrician, Philippine Children's Medical Center]; Delfin B. Santos MD FPPS [General pediatrician, The Medical City]; Jaime A. Santos MD FPPS FPIDSP [Pediatric Infectious Disease, Department of Microbiology Fatima University College of Medicine]; Liza V. Santos MD FPPS FPAPA [Ambulatory pediatrician, Philippine Children's Medical Center]; Rey Cesar R. Anunciacion MD FPCP FPCCP [Adult pulmonologist, World Citi Medical Center]; Roy Allan A. Loreto MD DFM [Family medicine practitioner, Quezon City General Hospital]; Joann B. de Guzman MD DPPS [Rural health physician, Marikina City]; Viola Leah S. Navarro MD [Medical officer, Ynares Municipal Hospital, Jala-jala Rizal]; Grace R. Bausa MD [General practitioner, St Vincent Hospital, Marikina City]; Maricar R. Paguia MD FPCR [Pediatric radiologist, St. Luke's Medical Center]; Arnold M. Fernandez MD FPSP [Pathologist, Capitol Medical Center]; and Gemmalyn D. Esguerra MD, Kristine Elisa M. Kionisala MD, Vianney Marie C. Mandapat MD and Josy Naty M. Venturina MD [Postresidency medical fellows-in-training, Philippine Children's Medical Center].

Our thank you to Elmer G. Punzalan MD [Assistant Secretary for Special Concerns, Department of Health] for reviewing the document.

## DISCLAIMER

The recommendations presented in this update are limited to options in the evaluation, management and prevention of pediatric community-acquired pneumonia in an immunocompetent patient aged 3 months to 19 years. Each recommendation should not be presumed to be always applicable to every individual patient. It should complement but not replace individual clinical judgement.

## 2012 SUMMARY OF RECOMMENDATIONS

## PEDIATRIC COMMUNITY ACQUIRED PNEUMONIA

**CLINICAL QUESTION 1. WHO SHALL BE CONSIDERED AS HAVING COMMUNITY-ACQUIRED PNEUMONIA?**

1. The presence of pneumonia **may be** considered **even without** a chest radiograph in a patient presenting with cough and/or respiratory difficulty *[Recommendation Grade D]* plus any of the following predictors of radiographic pneumonia:
   1.1. At the Emergency Room as the site-of-care,
      1.1.1. tachypnea as defined by World Health Organization [WHO] in a patient aged 3 months to 5 years *[Recommendation Grade B];* or
      1.1.2. fever at any age *[Recommendation Grade B];* or
      1.1.3. oxygen saturation less than or equal to 92% at room air at any age *[Recommendation Grade B]* in the absence of any co-existing illness (neurologic, musculoskeletal, or cardiac condition) that may potentially affect oxygenation *[Recommendation Grade D].*
   1.2. At the Out-Patient Clinic as the site-of-care,
      1.2.1. tachypnea as defined by World Health Organization [WHO] in a patient aged 3 months to 5 years *[Recommendation Grade D];* or
      1.2.2. fever at any age *[Recommendation Grade D].*
2. The presence of pneumonia **should be** determined using a chest radiograph in a patient presenting with
   2.1. cough and/or respiratory difficulty *[Recommendation Grade D]* in the following situations:
      2.1.1. Presence of dehydration aged 3 months to 5 years *[Recommendation Grade B].*
      2.1.2. Presence of severe malnutrition aged less than 7 years *[Recommendation Grade B].*
   2.2. high grade fever and leukocytosis aged 3 to 24 months without respiratory symptoms *[Recommendation Grade C].*

**Clinical Question 2. WHO WILL REQUIRE ADMISSION?**

1. Revised risk classification for pneumonia-related mortality[a] [*Recommendation Grade D*]

| **CLASSIFICATION PROVIDED BY**<br>Philippine Academy of Pediatric Pulmonologists<br>Philippine Health Insurance Corp<br>World Health Organization | **pCAP A or B**<br>---<br>Nonsevere | | **pCAP C**<br>Pneumonia I<br>Severe | **pCAP D**<br>Pneumonia II<br>Very severe |
|---|---|---|---|---|
| **VARIABLES**[b] | | | | |
| **Clinical** | | | | |
| 1. Dehydration[c] | None | Mild | Moderate | Severe |
| 2. Malnutrition[d] | None | | Moderate | Severe |
| 3. Pallor | None | | Present | Present |
| 4. Respiratory rate<br>3 to12 months[e]<br>1 to 5 years[e]<br>> 5 years | <br>≥50/min to ≤60/min<br>≥40/min to ≤50/min<br>≥30/min to ≤35/min | | <br>>60/min to ≤70<br>>50/min<br>>35/min | <br>>70/min<br>>50/min<br>>35/min |
| 5. Signs of respiratory failure<br>a. Retraction<br>b. Head bobbing<br>c. Cyanosis<br>d. Grunting<br>e. Apnea<br>f. Sensorium | <br>None<br>None<br>None<br>None<br>None<br>None | | <br>IC/subcostal<br>Present<br>Present<br>None<br>None<br>Irritable | <br>Supraclavicular/IC/SC<br>Present<br>Present<br>Present<br>Present<br>Lethargic/stuporous/comatose |
| **Diagnostic aid at site-of-care**[f] | | | | |
| 1. Chest x ray findings of any of the following: effusion; abscess; air leak or lobar consolidation | None | | Present | Present |
| 2. Oxygen saturation at room air using pulse oximetry | 95% | | <95% | <95% |
| **ACTION PLAN** | | | | |
| 1. Site-of-care | Outpatient | | Admit to ward | Admit to a critical care facility |
| 2. Follow-up | End of treatment | | | |

[a] In order to classify to a higher risk category, at least 2 variables (clinical and diagnostic aid) should be present. In the absence of a diagnostic aid variable, clinical variables will suffice.

[b] Risk factors for mortality based on evidence and/or expert opinion among members of the 2012 PAPP Task Force on pCAP.

[c] Weight for Height [WFH] SD score < -2 moderate; SD score < -3 severe. WHO management of severe malnutrition: a manual for physicians and other health workers. Geneva. World Health Organization 1999

[d] Grading of dehydration adapted from Nelson's Textbook of Pediatrics: MILD [thirsty, normal or increased pulse rate, decreased urine output and normal physical examination]; MODERATE [tachycardia, little or no urine output, irritable/lethargic, sunken eyes and fontanel, decreased tears, dry mucus membranes, mild tenting of the skin, delayed capillary refill, cool and pale]; SEVERE [rapid and weak pulse, decreased blood pressure, no urine output, very sunken eyes and fontanel, no tears, parched mucous membranes, tenting of the skin, very delayed capillary refill, cold and mottled]

[e] World Health Organization age specific-criteria for tachypnea for children under 5 years old.

[f] Chest x ray and pulse oximetry are desirable variables but not necessary as determinants of admission at site-of-care.

2. Patients under 5 years old *[Recommendation Grade B]* and more than 5 years old *[Recommendation Grade D]* who are classified as pCAP C but whose chest x-ray is without any of the following: effusion, lung abscess, air leak or multilobar consolidation, and whose oxygen saturation is ≥ 95% at room air **can be** managed initially on an outpatient basis.

**Clinical Question 3. WHAT DIAGNOSTIC AIDS ARE INITIALLY REQUESTED FOR A PATIENT CLASSIFIED AS EITHER pCAP A or pCAP B BEING MANAGED IN AN AMBULATORY SETTING?**

1. Chest x-ray **may be** requested to rule out pneumonia-related complications or pulmonary conditions simulating pneumonia *[Recommendation Grade D]*.
    1.1. It **should not be** routinely requested to predict end-of-treatment clinical outcome *[Recommendation Grade A].*
2. Chest x-ray, complete blood count, C-reactive protein, erythrocyte sedimentation rate, procalcitonin, or blood culture **should not be routinely** requested to determine appropriateness of antibiotic usage *[Recommendation Grade D].*

**Clinical Question 4. WHAT DIAGNOSTIC AIDS ARE INITIALLY REQUESTED FOR A PATIENT CLASSIFIED AS EITHER pCAP C or pCAP D BEING MANAGED IN A HOSPITAL SETTING?**

1. For pCAP C,
    1.1. The following ancillary/diagnostic procedures **should be** done.
        1.1.1. to determine etiology:
            1.1.1.1. Gram stain and/or culture and sensitivity of pleural fluid when available *[Recommendation Grade D]*
        1.1.2. to assess gas exchange:
            1.1.2.1. Oxygen saturation using pulse oximetry *[Recommendation Grade D]*
            1.1.2.2. Arterial blood gas *[Recommendation Grade D]*
    1.2. The following ancillary/diagnostic procedures **may be** done
        1.2.1. to confirm clinical suspicion of multilobar consolidation, lung abscess, pleural effusion, pneumothorax or pneumomediastinum:
            1.2.1.1. Chest x-ray PA-lateral
        1.2.2. to determine appropriateness of antibiotic usage:
            1.2.2.1. C-reactive protein (CRP) *[Recommendation Grade A]*
            1.2.2.2. Procalcitonin (PCT) *[Recommendation Grade B]*
            1.2.2.3. Chest x-ray PA-lateral *[Recommendation Grade C]*
            1.2.2.4. White Blood Cell (WBC) count *[Recommendation Grade D]*
            1.2.2.5. Gram stain of sputum or nasopharyngeal aspirate *[Recommendation Grade D]*
        1.2.3. to determine etiology
            1.2.3.1. Sputum culture and sensitivity *[Recommendation Grade C]*
            1.2.3.2. Blood culture and sensitivity *[Recommendation Grade C]*
        1.2.4. to predict clinical outcome:
            1.2.4.1. Chest x-ray PA-lateral *[Recommendation Grade B]*
            1.2.4.2. Pulse oximetry *[Recommendation Grade B]*
        1.2.5. to determine the presence of tuberculosis if clinically suspected:
            1.2.5.1. Mantoux test (PPD 5-TU) *[Recommendation Grade D]*
            1.2.5.2. Sputum smear for aid fast bacilli
        1.2.6. to determine metabolic derangement:
            1.2.6.1. Serum electrolytes *[Recommendation Grade C]*
            1.2.6.2. Serum glucose *[Recommendation Grade C]*
2. For pCAP D, a referral to a specialist **should be** done *[Recommendation Grade D].*

**Clinical Question 5. WHEN IS ANTIBIOTIC RECOMMENDED?**

1. For pCAP A or B, an antibiotic **may be** administered if a patient is
    1.1. beyond 2 years of age *[Recommendation Grade D]*; or
    1.2. with high grade fever without wheeze *[Recommendation Grade D].*
2. For pCAP C, an antibiotic
    2.1. **should be** administered if alveolar consolidation on chest x-ray is present *[Recommendation Grade C].*
    2.2. **may be** administered if a patient is with any of the following:
        2.2.1. Elevated serum C-reactive protein [CRP] *[Recommendation Grade A]*
        2.2.2. Elevated serum procalcitonin level [PCT] *[Recommendation Grade B]*
        2.2.3. Elevated white cell count *[Recommendation Grade D].*
        2.2.4. High grade fever without wheeze *[Recommendation Grade D].*
        2.2.5. Beyond 2 years of age *[Recommendation Grade D].*
3. For pCAP D, a specialist **should be** consulted *[Recommendation Grade D].*

**Clinical Question 6. WHAT EMPIRIC TREATMENT SHOULD BE ADMINISTERED IF A BACTERIAL ETIOLOGY IS STRONGLY CONSIDERED?**

1. For a patient who has been classified as pCAP A or B without previous antibiotic,
    1.1. amoxicillin [40-50 mg/kg/day, maximum dose of 1500 mg/day in 3 divided doses for at most 7 days] is the drug of choice *[Recommendation Grade B].*
        1.1.1. Amoxicillin may be given for a minimum of 3 days *[Recommendation Grade A].*
        1.1.2. Amoxicillin may be given in 2 divided doses for a minimum of 5 days *[Recommendation Grade B].*
    1.2. azithromycin [10 mg/kg/day OD for 3 days or 10mg/kg/day at day 1 then 5 mg/kg/day for days 2 to 5, maximum dose of 500mg/day], or clarithromycin [15 mg/kg/day, maximum dose of 1000 mg/day in 2 divided doses for 7 days] may be given to those patients with known hypersensitivity to amoxicillin *[Recommendation Grade D].*
2. For a patient who has been classified as pCAP C, without previous antibiotic,
    2.1. requiring hospitalization and
        2.1.1. has completed the primary immunization against *Haemophilus influenza* type *b*, penicillin G [100,000 units/kg/day in 4 divided doses] administered as monotherapy is the drug of choice *[Recommendation Grade B].*
        2.1.2. has not completed the primary immunization or immunization status unknown against *Haemophilus influenza* type *b*, ampicillin [100 mg/kg/day in 4 divided doses] administered as monotherapy is the drug of choice *[Recommendation Grade B].*
        2.1.3. above15 years of age *[Recommendation Grade D]*, a parenteral non-antipseudomonal β-lactam (β-lactam/β-lactamase inhibitor combination (BLIC), cephalosporin or carbapenem] + extended macrolide [azithromycin or chlarithromycin], or a parenteral non-antipseudomonal β-lactam [β-lactam/ β-lactamase inhibitor combination (BLIC], cephalosporin or carbapenem] + respiratory fluoroquinolones [levofloxacin or moxifloxacin] administered as combination therapy may be given *[Recommendation Grade A].*
    2.2. and who can tolerate oral feeding and does not require oxygen support, amoxicillin [40-50 mg/kg/day, maximum dose of 1500 mg/day in 3 divided doses for at most 7 days] may be given on an outpatient basis *[Recommendation Grade B].*
3. For a patient classified as pCAP C who is severely malnourished or suspected to have methicillin-resistant *Staphylococcus aureus,* or classified as pCAP D, referral to a specialist is highly recommended *[Recommendation Grade D].*
4. For a patient who has been established to have *Mycobacterium tuberculosis* infection or disease*,* antituberculous drugs should be started *[Recommendation Grade D].*

**Clinical Question 7. WHAT TREATMENT SHOULD BE INITIALLY GIVEN IF A VIRAL ETIOLOGY IS STRONGLY CONSIDERED?**

1. Oseltamivir (30 mg twice a day for ≤15 kg body weight, 45 mg twice a day for >15-23 kg, 60 mg twice a day for >23-40 kg, and 75 mg twice a day for >40 kg) remains to be the drug of choice for laboratory confirmed *[Recommendation Grade A]*, or clinically suspected *[Recommendation Grade D]* cases of influenza.
2. The use of immunomodulators for the treatment of viral pneumonia is not recommended *[Recommendation Grade D].*
3. Ancillary treatment as provided in Clinical Question 11 may be given *[Recommendation Grade D].*

**Clinical Question 8. WHEN CAN A PATIENT BE CONSIDERED AS RESPONDING TO THE CURRENT ANTIBIOTIC?**

1. Decrease in respiratory signs and/or defervescense within 72 hours after initiation of antibiotic are predictors of favorable response *[Recommendation Grade D].*
2. If clinically responding, further diagnostic aids to assess response such as chest x-ray, C-reactive protein and complete blood count **should not be** routinely requested *[Recommendation Grade D]*

**Clinical Question 9. WHAT SHOULD BE DONE IF A PATIENT IS NOT RESPONDING TO CURRENT ANTIBIOTIC THERAPY?**

1. If an outpatient classified as either pCAP A or pCAP B is not responding to the current antibiotic within 72 hours, consider any of the following *[Recommendation Grade D]*:
    1.1. Other diagnosis.
        1.1.1. Coexisting illness.
        1.1.2. Conditions simulating pneumonia.
    1.2. Other etiologic agents for which C-reactive protein, chest x-ray or complete blood count may be used to determine the nature of the pathogen.
        1.2.1. May add an oral macrolide if atypical organism is highly considered.
        1.2.2. May change to another antibiotic if microbial resistance is highly considered.

2. If an inpatient classified as pCAP C is not responding to the current antibiotic within 72 hours, consider any of the following *[Recommendation Grade D]*:
    2.1. Other diagnosis:
        2.1.1. Coexisting illness.
        2.1.2. Conditions simulating pneumonia.
    2.2. Consider other etiologic agents for which C-reactive protein, chest x-ray or complete blood count may be used to determine the nature of the pathogen.
        2.2.1. May add an oral macrolide if atypical organism is highly considered.
        2.2.2. May change to another antibiotic if microbial resistance is highly considered.
    2.3 . May refer to a specialist.
3. If an inpatient classified as pCAP D is not responding to the current antibiotic within 72 hours, immediate consultation with a specialist **should be** done *[Recommendation Grade D].*

**Clinical Question 10. WHEN CAN SWITCH THERAPY IN BACTERIAL PNEUMONIA BE STARTED?**

1. For pCAP C,
    1.1. switch from intravenous antibiotic administration to oral form 3 days after initiation of current antibiotic is recommended in a patient who should fulfill all of the following *[Recommendation Grade D]*:
        1.1.1. Responsive to current antibiotic therapy as defined in Clinical Question 8.
        1.1.2. Tolerance to feeding and without vomiting or diarrhea.
        1.1.3. Without any current pulmonary (effusion/empyema; abscess; air leak, lobar consolidation, necrotizing pneumonia) or extrapulmonary complications; and
        1.1.4. Without oxygen support.
    1.2. switch therapy from three [3] days of parenteral ampicillin to
        1.2.1. amoxicillin [40-50 mg/kg/day for 4 days] *[Recommendation Grade B].*
2. For pCAP D, referal to a specialist **should be** considered *[Recommendation Grade D].*

**Clinical Question 11. WHAT ANCILLARY TREATMENT CAN BE GIVEN?**

1. For pCAP A or B,
    1.1. cough preparation *[Recommendation Grade A]*, elemental zinc *[Recommendation Grade B]*, vitamin A *[Recommendation Grade D]*, vitamin D *[Recommendation Grade D]*, probiotic *[Recommendation Grade D]* and chest physiotherapy *[Recommendation Grade D]* **should not be** routinely given during the course of illness.
    1.2. a bronchodilator **may be** administered in the presence of wheezing *[Recommendation Grade D].*
2. For pCAP C,
    2.1. oxygen and hydration **should be** administered whenever applicable [*Recommendation Grade D*].
        2.1.1. Oxygen delivery through nasal catheter is as effective as using nasal prong *[Recommendation Grade A].*
    2.2. a bronchodilator **may be** administered only in the presence of wheezing. *[Recommendation Grade D].*
        2.2.1. Steroid **may be** added to a bronchodilator *[Recommendation Grade B].*
    2.3. a probiotic **may be** administered *[Recommendation Grade B].*
    2.4. cough preparation, elemental zinc, vitamin A, vitamin D and chest physiotherapy **should not be** routinely given during the course of illness *[Recommendation Grade A].*
3. For pCAP D, referal to a specialist **should be** considered *[Recommendation Grade D].*

**Clinical Question 12. HOW CAN PNEUMONIA BE PREVENTED?**

1. The following **should be** given to prevent pneumonia:
    1.1. Vaccine against
        1.1.1. *Streptococcus pneumonia* (conjugate type) *[Recommendation Grade A].*
        1.1.2. *Influenza [Recommendation Grade A].*
        1.1.3. *Diphtheria, Pertussis, Rubeola, Varicella, Haemophilus Influenzae* type *b [Recommendation Grade A].*
    1.2. Micronutrient.
        1.2.1. Elemental zinc for ages 2 to 59 months to be given for 4 to 6 months *[Recommendation Grade A].*
2. The following **may be** given to prevent pneumonia:
    2.1. Micronutrient.
        2.1.1. Vitamin D3 supplementation *[Recommendation Grade B].*
3. The following **should not be** given to prevent pneumonia:
    3.1. Micronutrient
        3.1.1. Vitamin A *[Recommendation Grade A].*

## 2012 UPDATE RECOMMENDATION AND SUMMARY OF EVIDENCE

## CLINICAL QUESTION 1. WHO SHALL BE CONSIDERED AS HAVING COMMUNITY-ACQUIRED PNEUMONIA?

## BACKGROUND.

**2004 SUMMARY RECOMMENDATION.**

Predictors of community-acquired pneumonia in a patient with cough

1. for ages 3 months to 5 years are tachypnea and/or chest indrawing *[Recommendation Grade B].*
2. for ages 5 to 12 years are fever, tachypnea, and crackles *[Recommendation Grade D].*
3. beyond 12 years of age are the presence of the following features *[Recommendation Grade D]*:
   - 3.1. fever, tachypnea, and tachycardia; and
   - 3.2. at least one abnormal chest findings of diminished breath sounds, rhonchi, crackles or wheezes.

**2008 UPDATE SUMMARY HIGHLIGHT,**

The likelihood of radiologic pneumonia at the Emergency Room in a patient with cough is highest at ages 3 months to 5 years if any of the following is present: [a] RR≥50 /min, nasal flaring, and oxygen saturation ≤ 96%; or [b] tachypnea and chest indrawing; or [c] chest indrawing.

## 2012 SUMMARY RECOMMENDATION.

1. The presence of pneumonia **may be** considered **even without** a chest radiograph in a patient presenting with cough and/or respiratory difficulty *[Recommendation Grade D]* plus any of the following predictors of radiographic pneumonia:
   - 1.1. At the Emergency Room as the site-of-care,
     - 1.1.1. tachypnea as defined by World Health Organization [WHO] in a patient aged 3 months to 5 years *[Recommendation Grade B];* or
     - 1.1.2. fever at any age *[Recommendation Grade B]*; or
     - 1.1.3. oxygen saturation less than or equal to 92% at room air at any age *[Recommendation Grade B]* in the absence of any co-existing illness (neurologic, musculoskeletal, or cardiac condition) that may potentially affect oxygenation *[Recommendation Grade D].*
   - 1.2. At the Out-Patient Clinic as the site-of-care,
     - 1.2.1. tachypnea as defined by World Health Organization [WHO] in a patient aged 3 months to 5 years *[Recommendation Grade D]*; or
     - 1.2.2. fever at any age *[Recommendation Grade D].*

2. The presence of pneumonia **should be** determined using a chest radiograph in a patient presenting with
   - 2.1. cough and/or respiratory difficulty *[Recommendation Grade D]* in the following situations:
     - 2.1.1. Presence of dehydration aged 3 months to 5 years *[Recommendation Grade B]*.
     - 2.1.2. Presence of severe malnutrition aged less than 7 years *[Recommendation Grade B]*.
   - 2.2. high grade fever and leukocytosis aged 3 to 24 months without respiratory symptoms *[Recommendation Grade C]*.

## SUMMARY OF EVIDENCE

### 1. Initial presentation.

The PAPP Task Force on pCAP has retained the position statement of previous PAPP pCAP Update that a patient presenting initially with cough and/or respiratory difficulty should be evaluated for possible presence of pneumonia.

The addition of respiratory difficulty as an initial presentation has been recommended, as pneumonia may manifest without cough in 3% to 11% of cases with radiographic evidence of a pneumonic process [Cevey-Macherel M,2009; Neuman MI,2011; Korppi M,2008]. In addition, occult pneumonia radiographically identified among infants who presented with high grade fever and leukocytosis in the absence of any respiratory symptom was identified in 6.8% [95% Confidence Interval [CI]: 4-10.6%] to 15% [95% CI:12%-19%] of cases [Shah S,2010;Minteqi S,2010; Rutman MS,2009].

### 2. Chest radiograph as the reference standard for pneumonia.

The Task Force has retained the position statement of previous PAPP pCAP Update that chest x-ray is the reference standard in establishing the presence of pneumonia. The Task Force acknowledges the limitations of chest x-ray as a diagnostic tool, as there are no studies evaluating its accuracy in comparison with microbiology as the gold standard in differentiating pneumonia from mimics of pneumonia.

### 3. Predictors of radiographic pneumonia at the Emergency Room as the site-of-care.

3.1. Positive predictors of radiographic community-acquired pneumonia are as follows:

3.1.1. For ages 3 months to 5 years:

| PREDICTORS | PATIENTS [n] | ODDS RATIO [95% CI] | SENSITIVITY SPECIFICITY | p VALUE at <0.05 | AUTHOR |
|---|---|---|---|---|---|
| Cough with oxygen saturation ≤ 92% | 1901 | 3.6 [2.0-6.8] | | | Neuman MI 2011 |
| Clinical suspicion of pneumonia with age-specific tachypnea as defined by World Health Organization | 1622 | | | Statistically significant | Shah S 2010 |
| Clinical suspicion of pneumonia with fever | 389 | | ------ 44-50% | | Cardoso M 2011 |

3.1.2. Less than 21 years of age:

| PREDICTORS | PATIENTS [n] | ODDS RATIO [95% CI] | SENSITIVITY; SPECIFICITY | AUTHOR |
|---|---|---|---|---|
| Clinical suspicion of pneumonia with | 2574 | | | Neuman MI 2011 |
| O2 sat < 92% at ER | | 3.57 [2.28-5.64] | | |
| fever ≥ 3 days | | 3.35 [2.24-5.00] | | |
| focal rales | | 1.66 [1.14-2.42] | | |
| chest pains | | 1.52 [1.08-2.16] | | |
| decreased breath sounds | | 1.32 [0.96-1.82] | | |
| cough ≥ 3 days | | 1.26 [0.78-2.04] | | |
| grunting | | 1.25 [0.65-2.39] | | |
| fever ≥ 38 at ER | | 1.24 [0.97-1.58] | | |
| retraction | | 1.17 [0.83-1.66] | | |
| tachypnea at ER | | 1.17 [0.88-1.55] | | |
| respiratory distress | | 0.91 [0.66-1.27] | | |
| Clinical suspicion of pneumonia with | 526 | | | Mathews B 2009 |
| fever at ER | | 3.42 [1.44-8.16] | | |
| abdominal pain | | 3.06 [1.15-8.16] | | |
| low oxygen saturation at ER | | 2.85 [1.08-7.54] | | |
| focal crackles or rales | | 1.96 [0.85-4.51] | | |
| respiratory distress | | 0.82 [0.50-1.34] | | |
| retraction | | 0.60 [0.32-1.14] | | |
| Clinical suspicion of pneumonia with | 526 | | | Mathews B 2009 |
| wheezing | | 1.42 [0.56-3.63] | | |
| Clinical suspicion of pneumonia and fever with | 257 | | | Bilkis MD 2010 |
| decreased breath sounds | | | 53% ; 73% | |
| rales | | | 61% ; 50% | |
| tachypnea | | | 71% ; 48% | |
| decreased breath sounds and/or tachypnea | | | 93% ; 19% | |

3.2. Negative predictors for radiographic pneumonia.

The Task Force has not made any recommendation dealing with negative predictors for radiographic pneumonia because of inherent difficulty in excluding pneumonia using chest radiograph in a patient clinically presenting with lower respiratory tract infection.

**4. Predictor of radiographic pneumonia at the Out-Patient Clinic as site-of-care**

There is no study pertaining to this situation.

**5. Specific clinical situations.**

5.1. Impact of dehydration on clinical predictors of radiographic pneumonia

Subjects: patients aged 2-59 months with radiographic pneumonia and dehydration [n=67] versus without dehydration as controls [n=101] [Chisti MJ, 2010]

Study design: cohort

Outcome measure: fast breathing or lower chest wall indrawing

Result: fast breathing [60%] versus controls [88%],
*p* value statistically significant at less than 0.05
lower chest wall indrawing [67%] versus controls [82%],
*p* value statistically significant at less than 0.05

5.2. Impact of malnutrition on clinical predictors of radiographic pneumonia

a. Subjects: patients less than 7 years old with radiographic pneumonia and severe malnutrition [Chisti MJ, 2010]

Study design: meta-analysis

Clinical predictor: fast breathing and/or chest wall indrawing

Result: fast breathing: sensitivity 14-76%; specificity 66-100%
chest indrawing: sensitivity 17-87%; specificity 95-98%
fast breathing and chest indrawing:
sensitivity 39-87%; specificity 97-100%

b. Subjects: patients less than 1 year old with radiographic pneumonia and severe malnutrition [n=48] [Chisti MJ,2010]

Study design: cohort

Clinical predictor: fast breathing or lower chest indrawing

Result: fast breathing among cases with malnutrition [58%]
versus those without malnutrition [82%]:
RR 0.69 [95% CI 0.46-1.02]
lower chest indrawing among cases with malnutrition [36%]
versus those without malnutrition [88%]:
RR 0.47 [95% CI 0.29-74]

**Clinical Question 2.** **WHO WILL REQUIRE ADMISSION?**

## BACKGROUND.

**2004 SUMMARY RECOMMENDATION.**

1. A patient at moderate to high risk to develop pneumonia-related mortality should be admitted [*Recommendation Grade D*].
2. A patient at minimal to low risk can be managed on an outpatient basis [*Recommendation Grade D*].

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. Additional variables for considering admission include lack of measles and *Hi*b vaccination, high oxygen requirement on admission, and chest indrawing.
2. Admissible patients may be managed in a day care setting.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. Revised risk classification for pneumonia-related mortality[a] *[Recommendation Grade D]*

| **CLASSIFICATION PROVIDED BY**<br>Phil Academy of Pediatric Pulmonologists<br>Philippine Health Insurance Corporation<br>World Health Organization | **pCAP A or B**<br>---<br>Nonsevere | | **pCAP C**<br>Pneumonia I<br>Severe | **pCAP D**<br>Pneumonia II<br>Very severe |
|---|---|---|---|---|
| **VARIABLES**[b] | | | | |
| **Clinical** | | | | |
| 1. Dehydration[c] | None | Mild | Moderate | Severe |
| 2. Malnutrition[d] | None | | Moderate | Severe |
| 3. Pallor | None | | Present | Present |
| 2. Respiratory rate<br>3 to12 months[e]<br>1 to 5 years[e]<br>>5 years | ≥50/min to ≤60/min<br>≥40/min to ≤50/min<br>≥30/min to ≤35/min | | >60/min to ≤70<br>>50/min<br>>35/min | >70/min<br>>50/min<br>>35/min |
| 3. Signs of respiratory failure<br>a. Retraction<br>b. Head bobbing<br>c. Cyanosis<br>d. Grunting<br>e. Apnea<br>f. Sensorium | <br>None<br>None<br>None<br>None<br>None<br>None | | <br>IC/subcostal<br>Present<br>Present<br>None<br>None<br>Irritable | <br>Supraclavicular/IC/SC<br>Present<br>Present<br>Present<br>Present<br>Lethargic/stuporous/comatose |
| **Diagnostic aid at site-of-care**[f] | | | | |
| 1. Chest x-ray findings of any of the following: effusion; abscess; air leak or lobar consolidation | None | | Present | Present |
| 2. Oxygen saturation at room air using pulse oximetry | 95% | | <95% | <95% |
| **ACTION PLAN** | | | | |
| 1. Site-of-care | Outpatient | | Admit to ward | Admit to a critical care facility |
| 2. Follow-up | End of treatment | | | |

[a] In order to classify to a higher risk category, at least 2 variables (clinical and diagnostic aid) should be present. In the absence of a diagnostic aid variable, clinical variables will suffice.

[b] Risk factors for mortality based on evidence and/or expert opinion among members of the 2012 PAPP Task Force on pCAP.

[c] Weight for Height [WFH] SD score < -2 moderate; SD score < -3 severe. WHO management of severe malnutrition: a manual for physicians and other health workers. Geneva. World Health Organization 1999

[d] Grading of dehydration adapted from Nelson's Textbook of Pediatrics: MILD [thirsty, normal or increased pulse rate, decreased urine output and normal physical examination]; MODERATE [tachycardia, little or no urine output, irritable/lethargic, sunken eyes and fontanel, decreased tears, dry mucus membranes, mild tenting of the skin, delayed capillary refill, cool and pale]; SEVERE [rapid and weak pulse, decreased blood pressure, no urine output, very sunken eyes and fontanel, no tears, parched mucous membranes, tenting of the skin, very delayed capillary refill, cold and mottled]

[e] World Health Organization age specific-criteria for tachypnea for children under 5 years old.

[f] Chest x ray and pulse oximetry are desirable variables but not necessary as determinants of admission at site-of-care.

2. Patients under 5 years old *[Recommendation Grade B]* and more than 5 years old *[Recommendation Grade D]* who are classified as pCAP C but whose chest x-ray is without any of the following: effusion, lung abscess, air leak or multilobar consolidation, and whose oxygen saturation is ≥95% at room air **can be** managed initially on an outpatient basis.

**SUMMARY OF EVIDENCE.**

**1. Rationale for revision.**
The Task Force has revised the 2004 Clinical Practice Guideline in the Evaluation and Management of Pediatric Community Acquired Pneumonia risk classification scheme for pneumonia-related mortality to be congruent with the classification provided by the Philippine Health Insurance Corporation and World Health Organization.

**2. Variables for pneumonia related mortality.**

| VARIABLE | STUDY DESIGN | ODDS OR RISK RATIO [95% CI] | AUTHOR |
|---|---|---|---|
| Malnutrition | | | |
| Moderate | Meta analysis | 4.03 [2.67-6.08] | Chisti M,2009 |
| Severe | Meta analysis | 8.09 [4.36-15.01] | Chisti M,2009 |
| Severe | Cohort | 16.50 [4.20-62.50] | Nantanda R,2008 |
| Severe | Cohort | 5·20 [1·20-22.0] | Chisti M,2010 |
| Severe | Cohort | 4.60 [2.90-7.40] | Naheed A,2009 |
| Severe | Cohort | 1.71 [1.30-2.20] | Chisti M,2010 |
| Signs of resp failure | | | |
| a. Retraction | Cohort | 36.80 [8.14-166.7] | Salilig MG,2009 |
| b. Head bobbing | Cohort | 8.34 [2.71-12.77] | Tiewsoh K,2009 |
| c. Cyanosis | Cohort | 29.60 [----------] | Salilig MG,2009 |
| Pallor | Cohort | 10.88 [2.95-20.40] | Tiewsoh K,2009 |
| Chest x-ray: multilobar consolidation | Cohort | 30.86 [10.82-88] | Salilig MG,2009 |
| Chest x-ray: multilobar consolidation | Cohort | 11·90 [2·3-61·60] | Chisti M,2010 |
| Pulse oximetry: O2 sat <70% | Cohort | 41.62 [5.31-321.42] | Salilig MG,2009 |
| Pulse oximetry: O2 sat <92% | Cohort | 4.90 [1.2-19.5] | Nantanda R,2008 |
| Pulse oximetry: O2 sat <90% | Cohort | 4.50 [3.8-5.3] | Mwaniki M,2009 |

**3. Alternative action plan** for patients classified as pCAP C: management on an outpatient basis.

Subjects: patients aged 2-59 months with WHO-defined severe pneumonia [Ashraf H,2010]
Study design: randomized controlled trial
Site-of-care clinically important endpoint: improvement in clinical condition
Intervention: day care without hospital admission versus hospital admission
Result: daycare (87.7% [95% CI: 80.9–90.9%]) versus
hospital admission (96.1% [95% CI: 92.2–98.1%]):
relative benefit: 0.90

**Clinical Question 3.** **WHAT DIAGNOSTIC AIDS ARE INITIALLY REQUESTED FOR A PATIENT CLASSIFIED AS EITHER pCAP A or pCAP B BEING MANAGED IN AN AMBULATORY SETTING?**

## BACKGROUND.

**2004 CLINICAL PRACTICE GUIDELINE SUMMARY RECOMMENDATION.**

No diagnostic aids are initially requested for a patient classified as either pCAP A or pCAP B who is being managed in an ambulatory setting *[Recommendation Grade D].*

**2008 UPDATE SUMMARY HIGHLIGHT.**

The low risk for bacteremia [1.6% (95% CI 0.7-2.9) among patients aged 2-24 months with nonsevere pneumonia does not warrant blood culture determination.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. Chest x ray **may be** requested to rule out pneumonia-related complications or pulmonary conditions simulating pneumonia *[Recommendation Grade D]**.***

    1.1. It **should not be** routinely requested to predict end-of-treatment clinical outcome *[Recommendation Grade A].*

2. Chest x-ray, complete blood count, C-reactive protein, erythrocyte sedimentation rate, procalcitonin, or blood culture **should not be routinely** requested to determine appropriateness of antibiotic usage *[Recommendation Grade D].*

## SUMMARY OF EVIDENCE.

**1. Clinically important endpoint**: pneumonia-related complications, or pulmonary conditions simulating pneumonia using chest x-ray

There are no studies pertaining to these situations.

**2. Clinically important endpoint**: clinical outcome using chest x-ray

Study design: meta-analysis [Swingler GH,2008]
Clinically important endpoint: predictor of clinical outcome
Intervention: chest x-ray versus no chest x ray
Result: recovery on 7th day:
RR 1.01 [95% CI 0.79-1.31]
hospital visit within 4th week after recovery:
RR 1.02 [95% CI 0.79-1.30]
admission within 4th week after recovery:
RR 1.02 [95% CI 0.41-2.52]

**3. Clinically important endpoint**: appropriateness of antibiotic usage using chest x-ray, complete blood count, C-reactive protein, erythrocyte sedimentation rate, procalcitonin and blood culture

There are no studies pertaining to these situations.

## Clinical Question 4. WHAT DIAGNOSTIC AIDS ARE INITIALLY REQUESTED FOR A PATIENT CLASSIFIED AS EITHER pCAP C or pCAP D BEING MANAGED IN A HOSPITAL SETTING?

## BACKGROUND.

**2004 SUMMARY RECOMMENDATION.**

1.The following should be routinely requested:
- 1.1. Chest x-ray PA-lateral *[Recommendation Grade B].*
- 1.2. White blood cell count *[Recommendation Grade C].*
- 1.3. Culture and sensitivity of
  - 1.3.1. Blood for pCAP D *[Recommendation Grade D].*
  - 1.3.2. Pleural fluid [*Recommendation Grade D].*
  - 1.3.3. Tracheal aspirate upon initial intubation *[Recommendation Grade D].*
- 1.4. Blood gas and/or pulse oximetry *[Recommendation Grade D].*

2.The following may be requested:

Culture and sensitivity of sputum for older children *[Recommendation Grade D].*

3. The following should not be routinely requested:
- 3.1. Erythrocyte sedimentation rate *[Recommendation Grade A].*
- 3.2. C-reactive protein *[Recommendation Grade A].*

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. Chest radiographic evaluation is primarily utilized as an integral part of a clinical prediction rule in identifying the presence of a bacterial pathogen. As an individual tool, it can be used to assess severity and presence of complications, and to predict subsequent course of illness.
2. WBC or CRP has a limited value as an individual test in differentiating bacterial from viral pneumonia. A CRP level [≥ 12 mg/dl] is associated with necrotizing pneumonia and/or empyema.
3. Single evidence suggests a 63 mm/h value for ESR in predicting the presence of a bacterial pathogen.
4. The microbiologic yield for blood culture ranged from 1.2% to 6.2%.
5. High oxygen requirement on admission is one of the variables associated with mortality.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. For pCAP C,
- 1.1. The following ancillary/diagnostic procedures **<u>should be</u>** done
  - 1.1.1. to determine etiology:
    - 1.1.1.1. Gram stain and/or culture and sensitivity of pleural fluid when available *[Recommendation Grade D].*
  - 1.1.2. to assess gas exchange:
    - 1.1.2.1. Oxygen saturation using pulse oximetry *[Recommendation Grade D].*
    - 1.1.2.2. Arterial blood gas *[Recommendation Grade D].*
- 1.2. The following ancillary/diagnostic procedures **<u>may be</u>** done
  - 1.2.1. to confirm clinical suspicion of multilobar consolidation, lung abscess, pleural effusion, pneumothorax or pneumomediastinum:
    - 1.2.1.1. Chest x-ray PA-lateral.
  - 1.2.2. to determine appropriateness of antibiotic usage:
    - 1.2.2.1. C-reactive protein (CRP) *[Recommendation Grade A].*
    - 1.2.2.2. Procalcitonin (PCT) *[Recommendation Grade B].*
    - 1.2.2.3. Chest x-ray PA-lateral *[Recommendation Grade C].*
    - 1.2.2.4. White Blood Cell (WBC) count *[Recommendation Grade D].*
    - 1.2.2.5. Gram stain of sputum or nasopharyngeal aspirate *[Recommendation Grade D].*

1.2.3. to determine etiology:
1.2.3.1. Sputum culture and sensitivity *[Recommendation Grade C].*
1.2.3.2. Blood culture and sensitivity *[Recommendation Grade C].*
1.2.4. to predict clinical outcome:
1.2.4.1. Chest x-ray PA-lateral *[Recommendation Grade B].*
1.2.4.2. Pulse oximetry *[Recommendation Grade B].*
1.2.5. to determine the presence of tuberculosis if clinically suspected:
1.2.5.1. Mantoux test (PPD 5-TU) *[Recommendation Grade D].*
1.2.5.2. Sputum smear for acid-fast bacilli *[Recommendation Grade D].*
1.2.6. to determine metabolic derangement:
1.2.6.1. Serum electrolytes *[Recommendation Grade C].*
1.2.6.2. Serum glucose *[Recommendation Grade C].*

2. For pCAP D,
a referral to a specialist **should be** done *[Recommendation Grade D].*

## SUMMARY OF EVIDENCE

**1. Commonly available diagnostic aids** and clinically important endpoints at initial site-of-care.

1.1. Predictor of bacterial pathogen with microbiology as the reference standard:

| DIAGNOSTIC AID<br>PATHOGEN<br>STUDY DESIGN | ODDS RATIO [95% CI] | *p* VALUE at <0.05 | REMARKS | AUTHOR |
|---|---|---|---|---|
| C-reactive protein >30-60 mg/L<br>Bacterial versus nonbacterial pathogen<br>Meta analysis | 2.5 [1.2-5.5] | | | Flood RG,2008 |
| C-reactive protein [median value] mg/l<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Statistically significant | | Cevey-Macherel M,2009 |
| Procalcitonin [median value] ng/ml<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Statistically significant | | Cevey-Macherel M,2009 |
| Procalcitonin [median value] ng/ml<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Statistically significant | | Nascimento-Carvalho CM,2010 |
| Blood culture<br>Bacterial yield<br>Cross sectional | | | 2.6% [1%-5.6%] | Shah SS,2011 |
| Induced sputum culture<br>Bacterial yield<br>Cross sectional | | | 90% | Lahti E,2009 |
| Chest x-ray: upper lobe infiltrate<br>Pneumococcal infection<br>Cross sectional | 1.8 [1.3-2.7] | | | Ferrero F,2010 |
| Chest x-ray: consolidation<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Not statistically significant | | Korppi M,2008<br>Don M,2009<br>Cevey-Macherel M,2009 |
| White Blood Cell count [median value]<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Not statistically significant | | Cevey-Macherel M,2009 |

1.2. Predictor of clinical outcome:

| DIAGNOSTIC AIDS FINDINGS STUDY DESIGN | CLINICAL OUTCOME | RR or OR [95% CI] | *p* VALUE at <0.05 | AUTHOR |
|---|---|---|---|---|
| Chest x-ray Consolidation Cohort | Treatment failure within 48 hr<br>Treatment failure during hospitalization | 3.58 [1.47–8.75]<br>3.02 [1.45–6.31] | | Patel A,2008 |
| Chest x-ray Consolidation Cohort | Prolonged hospitalization | | Statistically significant | Bharti B,2008 |
| Pulse oximetry $0_2$ sat < 90% Cohort | Prolonged hospitalization | 2.06 [1.42-2.42] | | Tiewsoh K,2009 |

**2. Special considerations** at initial site-of-care.

2.1. Tuberculosis and community-acquired pneumonia.

Tuberculosis as an important pathogen in pCAP has been previously cited [Murdoch DR,2009], and to be present in 8.2% of children with acute lower respiratory tract infection [Rijal P,2011]. In a cross sectional study of 572 adolescents with pulmonary tuberculosis, radiographic manifestations compatible with pneumonia include consolidation [27%] and segmental collapse [0.3%] [Sant´Anna C,2009].

2.2. Metabolic derangement.

2.2.1. Serum sodium derangement.

a. Subjects: 108 patients with radiographic pneumonia [Don M, 2008]
Study design: cohort
Outcome measure: incidence of low serum sodium
Result: serum sodium 130-135 mmol/l: 45.4%

b. Subjects: 30 patients with pneumonia [Uy MA, 2009]
Study design: cross-sectional
Outcome measure: incidence of serum sodium abnormality
Result : hyponatremia: 23%
hypernatremia:17%

2.2.2. Serum glucose derangement.

Subjects: 108 patients with radiographic pneumonia [Don M, 2008]
Study design: cohort
Outcome measure: incidence blood glucose abnormality
Result: hyperglycemia ( 167 mg/dl): 0.9%
hypoglycemia (<60 mg/dl) : 3.7%

## Clinical Question 5. WHEN IS ANTIBIOTIC RECOMMENDED?

## BACKGROUND.

**2004 SUMMARY RECOMMENDATION.**

An antibiotic is recommended

1. for a patient classified as either pCAP A or B and is
   - 1.1. beyond 2 years of age *[Recommendation Grade B]*; or
   - 1.2. having high grade fever without wheeze *[Recommendation Grade D].*
2. for a patient classified as pCAP C and is
   - 2.1. beyond 2 years of age *[Recommendation Grade B];* or
   - 2.2. having high grade fever without wheeze *[Recommendation Grade D]*; or
   - 2.3. having alveolar consolidation on the chest x-ray *[Recommendation Grade B]*; or
   - 2.4. having white blood cell count >15,000 *[Recommendation Grade C].*
3. for a patient classified as PCAP D *[Recommendation Grade D].*

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. Epidemiology.
   - 1.1. Recent epidemiologic trend shows that more than 50% of hospitalized cases of pCAP will require antibiotic.
   - 1.2. The importance of mixed infection as causative agents should be clarified as it is responsible for about one-third of all identified causes of hospitalized pCAP.
2. Microbiologic tests.
   The yield in detecting bacteremia in pCAP remains to be low at 1.2% to 26%.
3. Predictors of bacterial pathogen.
   - 3.1. A clinical prediction rule that makes use of a bacterial pneumonia score [BPS] of $\geq$ 4 can predict the presence of a bacterial pathogen in hospitalized patients aged one month to five years.
   - 3.2. Other individual parameters include the following.
     - 3.2.1. Increasing age generally correlates with the presence of antibiotic-requiring pathogen. Identifying a specific age as to when an antibiotic should be started is difficult.
     - 3.2.2. There is single evidence in the use of ESR with a value of 63 mm/h in predicting the presence of a bacterial pathogen.
     - 3.3.3. There is weak evidence in the use of clinical symptomatology, chest x-ray, WBC and CRP as predictors of bacterial pathogen.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. For pCAP A or B, an antibiotic **may be** administered if a patient is
   - 1.1. beyond 2 years of age *[Recommendation Grade D]*; or
   - 1.2. with high grade fever without wheeze *[Recommendation Grade D].*

2. For pCAP C, an antibiotic
   - 2.1. **should be** administered if alveolar consolidation on chest x-ray is present *[Recommendation Grade C].*
   - 2.2. **may be** administered if a patient is with any of the following:
     - 2.2.1. Elevated serum C-reactive protein [CRP] *[Recommendation Grade A]*
     - 2.2.2. Elevated serum procalcitonin level [PCT] *[Recommendation Grade B]*
     - 2.2.3. Elevated white cell count *[Recommendation Grade D].*
     - 2.2.4. High grade fever without wheeze *[Recommendation Grade D].*
     - 2.2.5. Beyond 2 years of age *[Recommendation Grade D].*

3. For pCAP D, a specialist **should be** consulted *[Recommendation Grade D].*

**SUMMARY OF EVIDENCE.**

**1. Clinically important endpoint**: microbiologic determination of pathogen.

1.1. The Task Force recognizes the importance of identifying bacterial etiology through conventional culture of blood and/or lower respiratory tract specimens as basis for antibiotic therapy [Lynch,2010], despite its limitations in timeliness [longer waiting time], accuracy [colonization versus infection], and sensitivity [potentially low yield among antibiotic pretreated patients] [Nolte F,2008].

1.2. Although novel approaches [quantitative real-time polymerase chain reaction of respiratory secretions, urinary antigen detection and pneumococcal surface adhesin A, serological analysis for *Streptococcus* infection [Klugman K 2008], molecular diagnostic tests [Nolte F,2008;Deng J,2009] are currently available, their role as surrogates vis-a-vis conventional culture in initiating antibiotic therapy remains to be established [Murdoch DR,2009].

**2. Clinically relevant information**: epidemiology of all-cause pathogen.

2.1. There has been no epidemiological study done among ambulatory patients.

2.2. The following table shows the epidemiological studies done on hospitalized patients in developed and developing economies.

There has been no study done in the Philippine setting.

| INPATIENT | | | | | AGENT NOT REQUIRING ANTIBIOTIC | AGENT REQUIRING ANTIBIOTIC | | |
|---|---|---|---|---|---|---|---|---|
| Author Year Country | Age months | Subjects N | Methods used | Yield N [%] | Virus % | Bacteria % | Atypical Pathogen % | Mixed Infection % |
| Hasegawa K 2008 Japan | | 1700 | PCR | | 25.8% | 34.4% | 16.2% | 15.2% |
| C-Macherel M 2009 Switzerland | 17-48 | 99 | Culture, PCR, Antigen detection and Immunofluorescence | 85 [85.8%] | 38.8% | 14.1% | 2.3% | 33% |
| P-Ygreda J 2010 Peru | 2-59 | 193 | Culture, PCR, ELISA and immunofluorescence | 123 [63.7%] | 55.0% | 21% | 1.6% | 12% |
| Johnson AW 2008 Nigeria | <59 | 419 | Culture and serology | 127 [30.3%] | 50.0% | 29% | Not tested | 40% |
| Carvalho CM 2008 Brazil | | 184 | | 144 [78.2%] | 60.0% | 42% | Not tested | 28% |

**3. Clinically important endpoint** at site-of-care: ancillary aids as surrogate predictors of bacterial pathogen.

3.1. There has been no study done among ambulatory patients.

3.2. The following table shows studies done among hospitalized patients.

| **DIAGNOSTIC AIDS WITH FINDINGS**<br>**ENDPOINT**<br>**STUDY DESIGN** | **ODDS RATIO**<br>**[95% CI]** | ***p* VALUE at <0.05** | **AUTHOR** |
|---|---|---|---|
| C-reactive protein [CRP]: >30-60 mg/L<br>Bacterial versus nonbacterial pathogen<br>Meta-analysis | 2.58 [1.20-5.55] | | Flood RG, 2008 |
| C-reactive protein [CRP]: median value mg/L<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Statistically significant | Cevey-Macherel M,2009 |
| Procalcitonin [PCT]: median value ng/ml<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Statistically significant | Cevey-Macherel M,2009 |
| Procalcitonin [PCT]: median value ngml<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Statistically significant | Nascimento-Carvalho CM,2010 |
| Chest x-ray: upper lobe infiltrate<br>Pneumococcal infection<br>Cross sectional | 1.80 [1.30-2.70] | | Ferrero F,2010 |
| Chest x-ray: consolidation<br>Bacterial versus nonbacterial pathogen<br>Cohort | | Not statistically significant | Korppi M,2008<br>Don M,2009<br>Cevey-Macherel M,2009 |

3.3. The Task Force has agreed, on consensus, that a WBC count greater than 15,000 with neutrophilia **may** indicate the presence of bacterial infection.

## Clinical Question 6. WHAT EMPIRIC TREATMENT SHOULD BE ADMINISTERED IF A BACTERIAL ETIOLOGY IS STRONGLY CONSIDERED?

## BACKGROUND.

**2004 SUMMARY RECOMMENDATION.**

1. For a patient classified as pCAP A or B without previous antibiotic, amoxicillin [40-50 mg/kg/day in 3 divided doses] is the drug of choice *[Recommendation Grade D]*.
2. For a patient classified as pCAP C without previous antibiotic and who has completed the primary immunization against *Haemophilus influenza* type b, penicillin G [100,000 units/kg/day in 4 divided doses] is the drug of choice *[Recommendation Grade D].* If a primary immunization against *Hib* has not been completed, ampicillin [100 mg/kg/day in 4 divided doses] should be given *[Recommendation Grade D]*.
3. For a patient classified as pCAP D, a specialist should be consulted *[Recommendation Grade D].*

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. Epidemiology
   - 1.1. Epidemiologic trend in developed economies suggests that *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* appear to be the most common pathogens causing community-acquired pneumonia across all ages.
   - 1.2 An important emerging pathogen is community-acquired methicillin resistant *Staphylococcus aureus* [CA-MRSA].
2. Antibiotic resistance

   Data on 2006 Antimicrobial Resistance Surveillance Program showed resistance rate of less than 10% for penicillin and chloramphenicol with *Streptococcus pneumoniae* infection, and for ampicillin with *Haemophilus influenzae*.
3. Empiric antibiotic therapy

   3.1. For pCAP A and B [nonsevere pneumonia], there is evidence for the use of amoxicillin [45 mg/kg/day in three divided doses] for a minimum duration of three days. For those with known hypersensitivity to amoxicillin, a macrolide may be considered. The use of cotrimoxazole is discouraged because of high failure and resistance rates.

   3.2. For pCAP C [severe pneumonia], equal efficacies were noted between oral amoxicillin and parenteral penicillin among patients who can tolerate feeding, and between monotherapy and combination therapy for those who cannot tolerate feeding. Among monotherapy available for use, ampicillin is the best choice considering its cost.

   3.3. For a patient classified as pCAP D, a specialist should be consulted.

## 2012 UPDATE SUMMARY RECOMMENDATION

1. For a patient who has been classified as pCAP A or B without previous antibiotic,
   - 1.1. amoxicillin [40-50 mg/kg/day, maximum dose of 1500 mg/day in 3 divided doses for at most 7 days] is the drug of choice *[Recommendation Grade B].*
     - 1.1.1. Amoxicillin may be given for a minimum of 3 days *[Recommendation Grade A].*
     - 1.1.2. Amoxicillin may be given in 2 divided doses for a minimum of 5 days *[Recommendation Grade B].*
   - 1.2. azithromycin [10 mg/kg/day OD for 3 days or 10mg/kg/day at day 1 then 5 mg/kg/day for days 2 to 5, maximum dose of 500mg/day], or clarithromycin [15 mg/kg/day, maximum dose of 1000 mg/day in 2 divided doses for 7 days] may be given to those patients with known hypersensitivity to amoxicillin *[Recommendation Grade D].*

2. For a patient who has been classified as pCAP C, without previous antibiotic,
    2.1. requiring hospitalization, and
        2.1.1. has completed the primary immunization against *Haemophilus influenza* type *b*, penicillin G [100,000 units/kg/day in 4 divided doses] administered as monotherapy is the drug of choice *[Recommendation Grade B].*
        2.1.2. has not completed the primary immunization or immunization status unknown against *Haemophilus influenza* type *b*, ampicillin [100 mg/kg/day in 4 divided doses] administered as monotherapy is the drug of choice *[Recommendation Grade B].*
        2.1.3. above15 years of age *[Recommendation Grade D]*, a parenteral non-antipseudomonal β-lactam (β-lactam/β-lactamase inhibitor combination (BLIC), cephalosporin or carbapenem] + extended macrolide [azithromycin or clarithromycin], or a parenteral non-antipseudomonal β-lactam [β-lactam/ β-lactamase inhibitor combination (BLIC], cephalosporin or carbapenem] + respiratory fluoroquinolones [levofloxacin or moxifloxacin] administered as combination therapy may be given *[Recommendation Grade A].*
    2.2. who can tolerate oral feeding and does not require oxygen support,
        amoxicillin [40-50 mg/kg/day, maximum dose of 1500 mg/day in 3 divided doses for at most 7 days] may be given on an outpatient basis *[Recommendation Grade B].*

3. For a patient classified as pCAP C who is severely malnourished or suspected to have methicillin-resistant *Staphylococcus aureus,* or classified as pCAP D, referral to a specialist is highly recommended *[Recommendation Grade D].*

4. For a patient who has been established to have *Mycobacterium tuberculosis* infection or disease*,* antituberculous drugs should be started *[Recommendation Grade D].*

## SUMMARY OF EVIDENCE.

The Task Force considers any or a combination of the following as decision guides in what empiric treatment should be started:

### 1. Epidemiology of antibiotic-requiring pathogen

1.1. in the general pediatric population

| AUTHOR YEAR COUNTRY | AGE | +BACTERIAL YIELD/ SUBJECTS [%] | PATIENT WITH ANTIBIOTIC REQUIRING PATHOGEN N | *Streptococcus pneumoniae* N [%] | ATYPICAL AGENT N [%] | OTHER ORGANISMS N [%] |
|---|---|---|---|---|---|---|
| C-Macherel M 2009 Switzerland | 17-48 mo | 83/99 [83.8%] | 83 | 45/83 [54.2%] Culture:1; PCR/Serology: 44 Alone : 12 Co infection with atypical agent : 4 | 29 [34.9%] | 2 [2.4%] |
| Lassmann B 2008 Gabon | 2 mo-15 yrs | 78/99 [78.7%] | 78 | 42 [ 53.8%] Culture:0; PCR:42 Alone 35 Coinfection with atypical agent : 7 | 36 [46.1%] | 0 |
| Hasegawa K 2008 Japan | | 833/1700 [49.0%] | 833 | 203 [14.8%] | 133 [15.9%] | 94 [11.2%] |
| Ygreda J 2010 Peru | 2-59 mo | 41/193 [21.2%] | 41 | 37 [90.2 %] Culture:1;PCR:36 Alone:21 Co infection with atypical agent: 16 | 2 [4.8%] | 2 [4.8%] *Hib*: 2 |
| Johnson AW 2008 Nigeria | <5yrs | 59/419 [14.08%] | 59 | 3/59 [5%] | Not tested | 56 [95%] *Staph a*: 22 *Klebsiella*: 9 *Salmonella*: 5 Others: 20 |
| Calado C 2010 Portugal | <2yrs | 5/63 [7.9%] | 5 | 2/5 [[40%] | Not tested | 3/5 [60%] |
| Shah SS 2011 USA | <18yrs | 6/291 [2.0%] | 6 | 4/6 [67%] Culture: 6 | Not tested | 2/6 [33%] |
| Wang H 2008 China | <5yrs | 23/100 [23%] | 100 | 14/14 [100%] Culture: 14 | Not tested | *Hib*: 5 *Staph a*: 4 |
| Carvalho C 2008 Brazil | | 16/184 [8.6%] | 77 | 16 [21%] | | |

1.2. among severely malnourished children.

Children with pneumonia and severe/very severe malnutrition [Chisti MJ,2009]
Study design: meta-analysis [11 studies]
Bacterial isolation in 215 cases

| | |
|---|---|
| *Klebsiella sp* | 26% |
| *Staphyloccocus aureus* | 25% |
| *Streptococcus pneumoniae* | 18% |
| *Escherichia coli* | 8% |
| *Haemophilus influenzae* | 8% |
| *Salmonella sp* | 5% |
| Others | 10% |

1.3. Methicillin-resistant *Staphylococcus aureus.*

2008-2011 local hospital data reported by Antimicrobial Resistance Surveillance Program showed antimicrobial resistance rates of methicillin-resistant *Staphylococcus aureus* as follows: 31% [2008]; 45% [2009]; and 54% [2010] [Carlos CC,2008; Carlos CC, 2009; Carlos CC,2010].

1.4. *Mycobacterium tuberculosis.*

Tuberculosis as an important pathogen in pCAP has been cited [Murdoch DR,2009] and noted to be present in 8.2% of children with acute lower respiratory tract infection [Rijal P,2011]. In a cross sectional study of 572 adolescents with pulmonary tuberculosis, radiographic manifestations compatible with pneumonia include consolidation [27%] and segmental collapse [0.3%] [Sant´Anna C,2009].

**2. Pattern of antibiotic resistance** among antibiotic-requiring pathogens.

2.1. Local data.

2008-2011 local hospital data reported by Antimicrobial Resistance Surveillance Program [Carlos CC,2008; Carlos CC,2009; Carlos CC,2010; Carlos CC,2011] showed antimicrobial resistance rates as follows

2.1.1. *Streptococcus pneumoniae*

| | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|
| Penicillin | 0% | 0% | 0% | 4% |
| Chloramphenicol | 5% | 5% | 5% | 2% |
| Cotrimoxazole | 22% | 21% | 34% | 16% |

2.1.2. *Haemophilus influenzae*

| | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|
| Chloramphenicol | 21% | 21% | 12% | 31% |
| Cotrimoxazole | 22% | 39% | 34% | 14% |
| Ampicillin | 10% | 17% | 16% | 14% |

2.2. Asian data.

In Japan, 13.2% resistant rate of *Mycoplasma pneumoniae* to macrolide has been reported among 3678 clinical samples of children with pCAP from April 2002 to December 2006 [Morozumi M,2008].

**3. Clinical trials** with either clinical treatment failure [or cure] rate or relapse rate as clinically important endpoints:

3.1. Antibiotic regimen for pCAP A or B.

3.1.1. STANDARD OF CARE: ORAL AMOXICILLIN X 7 DAYS.

3.1.1.1. Efficacy trial.

a. Study design: randomized clinical trial, placebo-controlled [Hazir T,2011]
Endpoint: failure rate at day 3 among 873 patients aged 2-59 months
Intervention: amoxicillin versus placebo
Result: amoxicillin [7.2%] versus placebo [8.3%]: OR 0.85 [CI 95% 0.5-1.43]

b. Study design: randomized clinical trial, placebo-controlled [Awasthi S,2008]
Endpoint: failure rate at end of treatment among 836 patients aged 2-59 months with wheezing
Intervention: amoxicillin+bronchodilator versus placebo+bronchodilator
Result: amoxicillin+bronchodilator [19.9%] versus placebo+bronchodilator [24%]: RR 0.82

c. Study design: randomized noninferiority clinical trial [Awasthi S,2008]
Endpoint: failure rate at end of treatment among 836 patients aged 2-59 months
Intervention: amoxicillin x 3 days versus cotrimoxazole x 5 days
Result: amoxicillin [13.8%] versus cotrimoxazole [9.5%]: RR 0.68

d. Study design: noncomparative clinical trial [Fontoura MC, 2010]
Endpoint: failure rate beyond 48 hours among 192 patients aged 2-59 months
Intervention: amoxicillin
Result: failure rate 3.1%

3.1.1.2. Treatment regimen clinical trial.

a. Study design: meta-analysis [Haider BA,2011]
Endpoint: cure rate at end of treatment
Intervention: amoxicillin 3-day versus 5-day duration
Result: RR 0.99 [95% CI 0.97-10.01]

b. Study design: meta analysis [Haider BA,2011]
Endpoint: relapse rate after 7 days of clinical cure
Intervention: amoxicillin 3-day versus 5-day duration
Result: RR 1.09 [95% CI 0.84-1.42]

c. Study design: randomized double-blind clinical trial [Ocampo FP,2008]
Endpoint: cure rate
Intervention: amoxicillin 3-day versus 5-day duration
Result: 3-day [86.9%] versus 5-day [86.0%]; *p* value not statistically significant

d. Study design: randomized clinical trial [Juliansen Andry,2009]
Endpoint: treatment failure rate by day 5
Intervention: amoxicillin BID versus TID
Result: BID [30%] versus TID [60%]; RR 0.5 [95% CI.048-5.22]

3.1.2 ANTIBIOTIC OPTION OTHER THAN AMOXICILLIN.

There is no study pertaining to this situation.

3. 2. Antibiotic regimen for pCAP C.

3.2.1. STANDARD OF CARE: PARENTERAL PENICILLIN [OR AMPICILLIN].

3.2.1.1. Efficacy clinical trial.

Study design: noncomparative clinical trial [Simbalista R, 2011]
Endpoint: treatment failure rate on 48$^{th}$ hour
Intervention: parenteral penicillin
Result: failure rate 18%

3.2.1.2. Treatment regimen clinical trial.

There is no study pertaining to this situation.

3.2.2. Antibiotic options other than parenteral penicillin

3.2.2.1. Efficacy clinical trial.

a. Study design: randomized clinical trial [Asghar R,2008]
Endpoint: treatment failure rate by day 5
Intervention: chloramphenicol versus ampicillin+gentamycin
Result: chloramphenicol [16%] versus ampicillin+gentamycin[11%]:
RR 1.43 [95% CI 1.03-1.97]

b. Study design: randomized clinical trial [Rosario DS Ana,2009]
Endpoint: treatment failure rate by day 3
Intervention: chloramphenicol versus chloramphenicol+penicillin
Result: *p* value not statistically significant at 0.05

c. Study design: randomized clinical trial [Ramos-Bugay J,2009]
Endpoint: treatment failure rates by end of treatment
Intervention: 3-day oral azithromycin versus 3-day ampicillin followed by 4-day amoxicillin
Result: *p* value not statistically significant

3.2.2.2. Treatment regimen clinical trial.

There is no study pertaining to this situation.

3.2.3. Treatment outside hospital facility

3.2.3.1. Efficacy clinical trial

a. Study design: randomized clinical trial [Hazir T,2008]
Endpoint: treatment failure rate by day 6
Intervention: hospital–based ampicillin [100 mg/kg/day] x 2 days followed by amoxicillin [80-90 mg/kg/day] x 3 days versus home-based group on amoxicillin [80-90 mg/kg/day] x 5 days
Result: hospital–based [7.0%] versus home-based [4.5%]: RR 1.5

b. Study design: randomized clinical trial [Hazir T,2008]
Endpoint: relapse rate by day 14
Intervention: hospital–based ampicillin [100 mg/kg/day] x 2 days followed by amoxicillin [80-90 mg/kg/day] x 3 days versus home-based group on amoxicillin [80-90 mg/kg/day] x 5 days
Result: hospital–based [3.3%] versus home-based [2.7%]; RR 1.2

c. Study design: randomized clinical trial [Bari A,2011]
Endpoint: treatment failure rate by day 6
Intervention: first dose cotrimoxazole then referral to hospital care facility versus home-based community case management
Result: first dose cotrimoxazole [18%] versus home-based community case management [9%]: RR: 0.5

d. Study design: randomized clinical trial [Bari A,2011]
Endpoint: relapse rate between day 6 and 14
Intervention: first dose cotrimoxazole then referral to hospital care facility versus home-based community case management
Result: first dose cotrimoxazole [2%] versus home-based community case management [2%]: RR: 1.0

3.3. Antibiotic regimen for pCAP D.

The Task Force did not search for any evidence in this situation as initial empiric treatment will be very much dependent upon the clinician's evaluation.

## Clinical Question 7. WHAT TREATMENT SHOULD BE INITIALLY GIVEN IF A VIRAL ETIOLOGY IS STRONGLY CONSIDERED?

## BACKGROUND.

**2004 SUMMARY OF RECOMMENDATION.**

1. Ancillary treatment should only be given *[Recommendation Grade D]*.
2. Oseltamivir [2 mg/kg/dose BID for 5 days] or amantadine [4.4-8.8 mg/kg/day for 3-5 days] may be given for influenza that is either confirmed by laboratory *[Recommendation Grade B]* or occurring as an outbreak *[Recommendation Grade D].*

**2008 UPDATE SUMMARY HIGHLIGHT.**

Oseltamivir remains to be the drug of choice for laboratory confirmed cases of influenza.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. Oseltamivir (30 mg twice a day for ≤15 kg body weight, 45 mg twice a day for >15-23 kg, 60 mg twice a day for >23-40 kg, and 75 mg twice a day for >40 kg) remains to be the drug of choice for laboratory confirmed *[Recommendation Grade A]*, or clinically suspected *[Recommendation Grade D]* cases of influenza.

2. The use of immunomodulators for the treatment of viral pneumonia is not recommended *[Recommendation Grade D].*

3. Ancillary treatment as provided in Clinical Question 11 may be given *[Recommendation Grade D].*

## SUMMARY OF EVIDENCE.

The Task Force has considered the result of clinical trials as basis for initiating therapeutic intervention:

1. Definitive treatment.
   a. Study design: meta-analysis [Falagas M,2010]
      Endpoint: influenza-related complication among influenza-confirmed infection
      Intervention: neuraminidase inhibitor versus placebo
      Result: neuraminidase inhibitor [16.2%] versus placebo [25.6%]:
      RR 0.63 [95% CI 0.48-0.84]
   b. Study design: cohort [Higuera Iglesias AL,2011]
      Endpoint: incidence rate of severe pneumonia among influenza-confirmed infection
      Intervention: oseltavimir administration given less than 2 days after onset of symptoms versus that given greater than 3 days after onset of symptoms
      Result: severe pneumonia among those given less than 2 days [2.2%] versus that given greater than 3 days [97.8%]: *p* value statistically significant

2. Ancillary treatment.
   Please refer to Clinical Question 11 for recommendation pertaining to ancillary treatment.

## Clinical Question 8. WHEN CAN A PATIENT BE CONSIDERED AS RESPONDING TO THE CURRENT ANTIBIOTIC?

## BACKGROUND.

**2004 CLINICAL PRACTICE GUIDELINE SUMMARY RECOMMENDATION.**

1. Decrease in respiratory signs [particularly tachypnea] and defervescence within 72 hours after initiation of antibiotic are predictors of favorable therapeutic response *[Recommendation Grade D].*
2. Persistence of symptoms beyond 72 hours after initiation of antibiotics requires reevaluation *[Recommendation Grade B].*
3. End of treatment chest x-ray [*Recommendation Grade B*], WBC, ESR or CRP should not be done to assess therapeutic response to antibiotic *[Recommendation Grade D].*

**2008 UPDATE SUMMARY HIGHLIGHT**

1. In children with nonsevere pneumonia, clinical index suggestive of good therapeutic response is a respiratory rate >5 breaths/min slower than baseline recording at the 72$^{nd}$ hour.
2. In children with severe pneumonia, clinical indices suggestive of good therapeutic response are defervescense, decrease in tachypnea and chest indrawing, increase in oxygen saturation, and ability to feed within 48 hours.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. Decrease in respiratory signs and/or defervescense within 72 hours after initiation of antibiotic are predictors of favorable response *[Recommendation Grade D].*
2. If clinically responding, further diagnostic aids to assess response such as chest x-ray, C-reactive protein and complete blood count **should not be** routinely requested *[Recommendation Grade D]*

## SUMMARY OF EVIDENCE

There is no study pertaining to this situation.

## Clinical Question 9. WHAT SHOULD BE DONE IF A PATIENT IS NOT RESPONDING TO CURRENT ANTIBIOTIC THERAPY?

## BACKGROUND.

**2004 CLINICAL PRACTICE GUIDELINE SUMMARY RECOMMENDATION.**

1. If an outpatient classified as either pCAP A or pCAP B is not responding to the current antibiotic within 72 hours, consider any one of the following *[Recommendation Grade D]* :
    a. change the initial antibiotic; or
    b. start an oral macrolide; or
    c. reevaluate diagnosis.
2. If an inpatient classified as pCAP C is not responding to the current antibiotic within 72 hours, consider consultation with a specialist because of the following possibilities *[Recommendation Grade D]* :
    a. penicillin-resistant *Streptococcus pneumoniae*; or
    b. presence of complications [pulmonary or extrapulmonary]; or
    c. other diagnosis.
3. If an inpatient classified as pCAP D is not responding to the current antibiotic within 72 hours, consider immediate re-consultation with a specialist *[Recommendation Grade D].*

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. There are no studies dealing with therapeutic interventions following treatment failure among children having community-acquired pneumonia.
2. A definition of treatment failure for nonsevere pneumonia is as follows:
    a. Same status. This is defined as RR > age-specific range but + 5 breaths/min to the baseline reading and *without* lower chest indrawing or any danger signs;
    b. Worse status. This is defined as developing lower chest indrawing or *with* any of the danger signs.
3. The causes of treatment failure include coinfection with respiratory syncytial virus or mixed infection, non-adherence to treatment for nonsevere pneumonia, resistance to antibiotics, clinical sepsis, and progressive pneumonia.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. If an outpatient classified as either pCAP A or pCAP B is not responding to the current antibiotic within 72 hours, consider any of the following *[Recommendation Grade D]*:
    1.1. Other diagnosis.
        1.1.1. Coexisting illness.
        1.1.2. Conditions simulating pneumonia.
    1.2. Other etiologic agents for which C-reactive protein, chest x ray or complete blood count may be used to determine the nature of the pathogen.
        1.2.1. May add an oral macrolide if atypical organism is highly considered.
        1.2.2. May change to another antibiotic if microbial resistance is highly considered.

2. If an inpatient classified as pCAP C is not responding to the current antibiotic within 72 hours, consider any of the following *[Recommendation Grade D]*:

- 2.1. Other diagnosis.
  - 2.1.1. Coexisting illness
  - 2.1.2. Conditions simulating pneumonia
- 2.2. Consider other etiologic agents for which C-reactive protein, chest x-ray or complete blood count may be used to determine the nature of the pathogen.
  - 2.2.1. May add an oral macrolide if atypical organism is highly considered.
  - 2.2.2. May change to another antibiotic if microbial resistance is highly considered.
- 2.3 . May refer to a specialist.

3. If an inpatient classified as pCAP D is not responding to the current antibiotic within 72 hours, immediate consultation with a specialist **should be** done *[Recommendation Grade D].*

**SUMMARY OF EVIDENCE**

There is no study pertaining to this situation.

## Clinical Question 10. WHEN CAN SWITCH THERAPY IN BACTERIAL PNEUMONIA BE STARTED?

## BACKGROUND.

**2004 CLINICAL PRACTICE GUIDELINE SUMMARY RECOMMENDATION.**

Switch from intravenous antibiotic administration to oral form 2-3 days after initiation of antibiotic is recommended in a patient [*Recommendation Grade D*] who

1. is responding to the initial antibiotic therapy,
2. is able to feed with intact gastrointestinal absorption; and
3. does not have any pulmonary or extrapulmonary complications.

**2008 UPDATE SUMMARY HIGHLIGHT.**

Switch therapy from three [3] days of IV ampicillin to four [4] days of either amoxicillin or cotrimoxazole *may be used* among patients admitted because of community-acquired pneumonia. Amoxicillin is preferred because of high failure and resistance rates reported in the use of cotrimoxazole.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. For pCAP C,
    - 1.1. switch from intravenous antibiotic administration to oral form 3 days after initiation of current antibiotic is recommended in a patient who should fulfill all of the following *[Recommendation Grade D]*:
        - 1.1.1. Responsive to current antibiotic therapy as defined in Clinical Question 8
        - 1.1.2. Tolerance to feeding, and without vomiting or diarrhea
        - 1.1.3. Without any current pulmonary (effusion/empyema; abscess; air leak, lobar consolidation, necrotizing pneumonia) or extrapulmonary complications; and
        - 1.1.4. Without oxygen support
    - 1.2. switch therapy from three [3] days of parenteral ampicillin to
        - 1.2.1. amoxicillin [40-50 mg/kg/day for 4 days] *[Recommendation Grade B].*

2. For pCAP D, referal to a specialist **<u>should be</u>** considered *[Recommendation Grade D].*

## SUMMARY OF EVIDENCE.

**Clinical trial** with clinical cure rate as endpoint.

Study design: randomized controlled trial [Aliman O, 2008]
Outcome measure: cure rate at end of treatment
Intervention: 7-day IV ampicillin versus 3-day IV ampicillin then shift to oral amoxicillin
Result: 7-day IV ampicillin [63.3%] versus 3-day IV ampicillin then shift to oral amoxicillin [80%]: RR 1.26

## Clinical Question 11. WHAT ANCILLARY TREATMENT CAN BE GIVEN?

## BACKGROUND.

**2004 CLINICAL PRACTICE GUIDELINE SUMMARY RECOMMENDATION.**

1. Among inpatients, oxygen and hydration should be given if needed [*Recommendation Grade D*].
2. Cough preparations, chest physiotherapy, bronchial hygiene, nebulization using normal saline solution, steam inhalation, topical solution, bronchodilators and herbal medicines are not routinely given in community-acquired pneumonia [*Recommendation Grade D*].
3. In the presence of wheezing, a bronchodilator may be administered [*Recommendation Grade D*].

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. There is no evidence to support the use of hydration or fluid restriction and cough preparation in the management of pneumonia.
2. The value of elemental zinc or vitamin A is inconclusive.
3. Single study demonstrated benefit for either virgin coconut oil or probiotic as adjunct therapy in pneumonia.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. For pCAP A or B,
   - 1.1. cough preparation *[Recommendation Grade A]*, elemental zinc *[Recommendation Grade B]*, vitamin A *[Recommendation Grade D]*, vitamin D *[Recommendation Grade D]*, probiotic *[Recommendation Grade D]* and chest physiotherapy *[Recommendation Grade D]* **should not be** routinely given during the course of illness.
   - 1.2. a bronchodilator **may be** administered in the presence of wheezing *[Recommendation Grade D].*

2. For pCAP C,
   - 2.1. oxygen and hydration **should be** administered whenever applicable [*Recommendation Grade D*].
     - 2.1.1. Oxygen delivery through nasal catheter is as effective as using nasal prong *[Recommendation Grade A].*
   - 2.2. a bronchodilator **may be** administered only in the presence of wheezing *[Recommendation Grade D].*
     - 2.2.2. Steroid **may be** added to a bronchodilator *[Recommendation Grade B].*
   - 2.3. a probiotic **may be** administered *[Recommendation Grade B].*
   - 2.4. cough preparation, elemental zinc, vitamin A, vitamin D and chest physiotherapy **should not be** routinely given during the course of illness *[Recommendation Grade A]*.

3. For pCAP D,
   - referal to a specialist **should be** considered *[Recommendation Grade D].*

**SUMMARY OF EVIDENCE.**

**1. Intervention of proven benefit.**

1.1. Oxygen delivery system.

Study design: meta analysis [Rojas MX,2009]
Endpoint: treatment failure to achieve adequate $SaO_2$
. Intervention: nasal prong versus nasopharyngeal catheter
Result: OR 0.96 [95% CI 0.48-1.93]

**2. Intervention of potential benefit.**

2.1. Steroid.

Study design: cohort [Weiss AK, 2011]
Endpoint: length of stay
Intervention: systemic corticosteroids
Result: HR [hazard ratio] 1.24 [95% CI 1.18-1.30]

2.2. Probiotic.

a. Study design: randomized placebo-controlled trial [Magno GV, 2010]
Endpoint: length of hospital stay
Intervention: probiotic versus placebo
Result: 5 days versus 6 days, *p* value statistically significant

b. Study design: randomized controlled trial [Bonus RV,2010 ]
Endpoint: length of hospital stay
Intervention: symbiotic versus no treatment
Result: *p* value statistically significant but sample population requires larger sample size

c. Study design: randomized controlled trial [Manigbas DC,2009]
Endpoint: length of hospital stay
Intervention: probiotic
Result: 4 days vs 6 days, *p* value statistically significant

**3. Intervention of doubtful benefit.**

3.1. Cough preparation.

Study design: meta analysis [children, adolescents and adults] [Chang CC, 2010]
Endpoint: not cured or not improved
Intervention: cough preparation versus placebo
Result: OR 0.85 [95% CI 0.40-1.80]

3.2. Micronutrients.

3.2.1. Vitamin A.

a. Study design: meta analysis [NI J,2010]
Endpoint: mortality
Intervention: vitamin A versus placebo
Result: OR 1.29 [95% CI 0.63-2.66]

b. Study design: meta analysis [Mathew J, 2010]
Endpoint: mortality
Intervention: vitamin A versus placebo
Result: RR 1.15 [95% CI 0.62-2.14]

3.2.2. Zinc sulfate.

a. Study design: meta-analysis [Haider BA, 2011]
Endpoint: cure rate
Intervention: zinc versus placebo
Result: RR 1.02 [95% CI 0.93-1.11]

b. Study design randomized double-blind controlled trial [Valavi E,2011]
Endpoint: failure rate
Intervention: zinc versus placebo
Result: OR for nonsevere pneumonia: 0.95 [95% CI 0.78-1.2]
OR for severe pneumonia : 0.97 [95% CI 0.42, 2.2]

c. Study design: randomized controlled trial [Ganguly A,2011]
Endpoint: cure rate
Intervention: zinc versus placebo
Result: *p* value not statiscally significant

d. Study design: randomized double-blind controlled trial [Maddara IP,2008]
Endpoint: length of hospital stay
Intervention: zinc versus placebo
Result: *p* value not statistically significant

e. Study design: randomized controlled trial [Branganza K,2009]
Endpoint: length of stay
Intervention: zinc
Result: *p* value not statistically significant

f. Study design: case control [Thiam-Tuazon J,2010]
Endpoint: length of hospital stay
Intervention: zinc
Result: *p* value not statistically significant

g. Study design: case control [Honeley HO,2011]
Endpoint: length of hospital stay
Intervention: zinc
Result: *p* value statistically significant

3.2.3. Vitamin D.

a. Study design: randomized placebo-controlled trial [Choudhary N, 2011]
Endpoint: median time to resolution of severe pneumonia
Intervention: Oral vitamin D (1000 IU for <1 yr, 2000 IU for >1 year) versus placebo once a day for 5 days
Result: *p* value not statisticallly significant

b. Study design: randomized, double-blind,placebo-controlled trial [Manaseki-Holland S, 2010]
Endpoint: mean number of days to recovery
Intervention: vitamin D(3) versus placebo
Result: *p* value not statistically significant

3.3. Chest physiotherapy.

Study design: randomized controlled trial [Paludo C,2008]
Endpoint: time to clinical resolution
Intervention: Chest physical therapy+standard treatment versus standard treatment alone
Result: *p* value not statistically significant

## Clinical Question 12. HOW CAN PNEUMONIA BE PREVENTED?

## BACKGROUND.

**2004 SUMMARY RECOMMENDATION.**

1. Vaccines recommended by the Philippine Pediatric Society should be routinely administered to prevent pneumonia [*Recommendation Grade B*].
2. Zinc supplementation [10 mg for infants and 20 mg for children beyond two years of age given for a total of 4 to 6 months] may be administered to prevent pneumonia [*Recommendation Grade A*].
3. Vitamin A [Recommendation *Grade A*], immunomodulators [*Recommendation Grade D*] and vitamin C [*Recommendation Grade D*] should not be routinely administered as a preventive strategy.

**2008 UPDATE SUMMARY HIGHLIGHT.**

1. A meta-analysis on immunomodulators showed a general reduction of rates in acute respiratory tract infection through the use of immunostimulants.
2. There are evidences to suggest that handwashing using antibacterial soaps, pneumococcal and Hib vaccination, elemental zinc, and breastfeeding are effective in preventing pneumonia.
3. Single study showed that patients on gastric acid inhibitors are at an increase risk to have pneumonia.

## 2012 UPDATE SUMMARY RECOMMENDATION.

1. The following **should be** given to prevent pneumonia:
    - 1.1. Vaccine against
        - 1.1.1. *Streptococcus pneumonia* (conjugate type) *[Recommendation Grade A].*
        - 1.1.2. *Influenza [Recommendation Grade A].*
        - 1.1.3. *Diphtheria, Pertussis, Rubeola, Varicella, Haemophilus Influenzae* type *b [Recommendation Grade A].*
    - 1.2 Micronutrient.
        - 1.2.1. Elemental zinc for ages 2 to 59 months to be given for 4 to 6 months *[Recommendation Grade A].*
2. The following **may be** given to prevent pneumonia:
    - 2.1 Micronutrient.
        - 2.1.1. Vitamin D3 supplementation *[Recommendation Grade B].*
3. The following **should not be** given to prevent pneumonia:
    - 3.1 Micronutrient.
        - 3.1.1. Vitamin A *[Recommendation Grade A].*

## SUMMARY OF EVIDENCE.

### 1. Rationale for prevention: burden of illness.

1.1. Local incidence rate.

Mean admission rate per year of patients under 18 years of age admitted to training hospitals accredited by the Philippine Pediatric Society because of pneumonia [ICD code J19] from January 2008 to December 2011: 19.8% [range 17.7-20.3%]

[Registry of Diseases Philippine Pediatric Society]

1.2. Economic burden.

Amount of claims for patients aged 3 months to 18 years admitted to hospitals accredited by the Philippine Health Insurance Corporation because of pneumonia [ICD code J12-J18 excluding J18.9,Y95] from January 2008 to June 2011:

Total amount: PhP 2,283,691,132.88 [355,022 claims]
Government sector: PhP 608,277,552.62 [106,381 claims]
Private sector PhP 1,675,413,770.26 [248,191 claims]
[Insurance claims MIS Database Philippine Health Insurance Corporation]

**2. Intervention of proven benefit to prevent pneumonia.**

2.1. Vaccine against

2.1.1. *Streptococcus pneumonia.*

a. Study design: randomized controlled trial, placebo-controlled, double-blind [Lucero MG, 2009]

Endpoint: first episode of community-acquired radiographic pneumonia in the first 2 years of life [vaccine efficacy (VE)]

Intervention: 11-valent PCV (Sanofi Pasteur, Lyon, France) versus saline placebo

Result: Per protocol analysis:

3-23 months old: RR 22.9% (95% CI: -1.1-41.2; *p*=0.06)
3-11 months old: RR 34.0% (95% CI: 4.8-54.3; *p*=0.02)
12-23 months old: RR 2.7% (95% CI: -43.5-34.0; *p*=0.88)

Intention-to-treat analysis:

<2 years old: RR 16.0% (95% CI: -7.3-34.2; *p*=0.16)
3-11 months: RR 19.8% (95% CI: -8.8-40.8; *p*=0.15)

b. Study design: Cross sectional [comparative data between pre PCV 7 1996-1999 versus post PCV 7 2001-2007 [Grijalva C,2010]

Endpoint: all-cause pneumonia incidence rate

Intervention: 7-valent PCV

Result: <2 years old decreased by 33% (28%–37%)

c. Study design: Cross sectional [comparative data prePCV 1997 versus post PVC 2006] [Lee GE, 2010]

Endpoint: CAP discharges; any complication

Result: CAP discharges

prePCV 7: 199.1 (198.1–200.1) per 100,000 versus
postPCV 7: 201.2 (200.2–202.2) per 100,000

Any complication

prePCV 7: 11.8 (11.6–12.1) per 100,000 versus
postPCV7: 15.1(14.8–15.3) per 100,000

2.1.2. *Influenza.*

a. Study design: case controlled study [Joshi AY, 2009]

Endpoint: vaccine effectiveness

Result: OR 0.14 (95% CI 0.03-0.71)

b. Study design: meta-analysis [Jefferson T. 2008]

Endpoint: vaccine efficacy and effectiveness

Result: Vaccine efficacy: 59% [95% CI 41-71]
Vaccine effectiveness: 36% [95% CI 24-46]

2.2. Micronutrient.

2.2.1. Zinc.

a. Study design: meta analysis [Lassi ZS, 2010]
Endpoint: reduction of incidence of pneumonia
Intervention: zinc 10 mg x 4-6 months versus placebo for children 2-59 months old
Result: RR 0.87 [95% CI 0.81-0.94]

b. Study design: meta analysis [Yakoob MW 2011]
Endpoint: pneumonia-specific mortality
Intervention: zinc x 3 months versus control for children 4-59 months old
Result: RR 0.81 [95% CI 0.73-0.90]

2.2.2. Vitamin D.

Study design: randomized, double-blind, placebo-controlled trial [Manaseki-Holland S, 2010]
Endpoint: risk reduction of repeat episode of pneumonia within 90 days of supplementation
Intervention: 100,000 units of Vit D (3) (cholecalciferol) given to children 1-36 months diagnosed with non-severe or severe pneumonia
Result: RR 0.78 [95% CI 0.64-0.94]

**3. Intervention of doubtful benefit to prevent pneumonia.**

3.1. Micronutrient.

3.1.1 Vitamin A.

Study design: meta-analysis [Mathew, 2010]
Endpoint: risk of developing pneumonia
Intervention: vitamin A versus placebo among children less than 5 years old
Result: RR 1.01 [95% CI 0.91-1.13]

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## Appendix . Definition of terms

**Absolute risk reduction (ARR)**
The absolute difference in risk between the experimental and control groups in a trial. It is used when the risk in the control group exceeds the risk in the experimental group, and is calculated by subtracting the AR in the experimental group from the AR in the control group.

**Baseline risk**
The risk of the event occurring without the active treatment. It is estimated by the baseline risk in the control group.

**Confidence interval (CI)**
The 95% confidence interval (or 95% confidence limits) includes 95% of results from studies of the same size and design in the same population. This is close but not identical to saying that the true size of the effect (never exactly known) has a 95% chance of falling within the confidence interval. If the 95% confidence interval for a relative risk (RR) or an odds ratio (OR) crosses 1, then this is taken as no evidence of an effect.

**Hazard ratio (HR)**
It is broadly equivalent to relative risk (RR); it useful when the risk is not constant with respect to time. The term is typically used in the context of survival over time. If the HR is 0.5 then the relative risk of dying in one group is half the risk of dying in the other group.

**Likelihood ratio**
The ratio of the probability that an individual with the target condition has a specified test result to the probability that an individual without the target condition has the same specified test result.

**Meta-analysis**
It is a statistical technique that summarises the results of several studies in a single weighted estimate, in which more weight is given to results of studies with more events and sometimes to studies of higher quality.

**Negative likelihood ratio (NLR)**
It is the ratio of the probability that an individual with the target condition has a negative test result to the probability that an individual without the target condition has a negative test result. This is the same as the ratio (1-sensitivity/specificity).

**Odds ratio (OR)**
It is the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to one, the smaller the difference in effect between the experimental intervention and the control intervention. If the OR is greater (or less) than one, then the effects of the treatment are more (or less) than those of the control treatment. Note that the effects being measured may be adverse (e.g. death or disability) or desirable (e.g. survival). When events are rare the OR is analagous to the relative risk (RR), but as event rates increase the OR and RR diverge.

**Positive likelihood ratio (LR+)**
It is the ratio of the probability that an individual with the target condition has a positive test result to the probability that an individual without the target condition has a positive test result. This is the same as the ratio (sensitivity/1-specificity).

**P value**
It is the probability that an observed or greater difference occurred by chance, if it is assumed that there is in fact no real difference between the effects of the interventions. If this probability is less than 1/20 (which is when the P value is less than 0.05), then the result is conventionally regarded as being "statistically significant".

**Relative risk (RR)**
It is the number of times more likely (RR > 1) or less likely (RR < 1) an event is to happen in one group compared with another. It is the ratio of the absolute risk (AR) for each group. It is analogous to the odds ratio (OR) when events are rare. Relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR) which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group. The closer the RR is to one, the smaller the difference in effect between the experimental intervention and the control intervention. If the RR is greater (or less) than one, then the effects of the treatment are more (or less) than those of the control treatment

**Sensitivity**
It is the chance of having a positive test result given that you have a disease.

**Specificity**
It is the chance of having a negative test result given that you do not have a disease.

**Statistically significant**
It means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level (P < 0.05) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases.