

## CLINICAL PRACTICE GUIDELINES

# 2021 CLINICAL PRACTICE GUIDELINES IN THE EVALUATION AND MANAGEMENT OF PEDIATRIC COMMUNITY-ACQUIRED PNEUMONIA

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These guidelines are intended for use by health care providers responsible for the management of immunocompetent infants and children aged 3 months to 18 years with uncomplicated community-acquired pneumonia in both ambulatory and hospital settings.

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

## PREFACE

The Clinical Practice Guidelines (CPG) for the Diagnosis and Management of Pediatric Community-Acquired Pneumonia (PCAP) was initiated by the Philippine Academy of Pediatric Pulmonologists, Inc. (PAPP) and the Pediatric Infectious Disease Society of the Philippines (PIDSP), in cooperation with Philippine Pediatric Society, Inc. (PPS) way back in 2004. Several CPG updates were then undertaken by the PAPP PCAP CPG Task Force from 2008 to 2016. Clinically-relevant research questions were answered with recent and current recommendations based on evidence from local and international data.

The 2021 PCAP CPG initiative was envisioned in March 2018 upon the recommendations of the 2018 PAPP Board for the purpose of updating the evidence in the PCAP CPG 2016 clinical questions. This led to the collaboration of PAPP and PIDSP to develop this CPG. Individual members were identified from each society as content experts to form the Steering Committee along with a clinical epidemiologist and technical writer as review experts. The committee identified the scope and target end user of the CPG as well as additional clinical questions to be included in the 2021 update aside from the questions on the previous CPGs. Selected members from the two societies formed the Technical Working Group (TWG) who did the literature search, appraisal of evidences, and formulation of recommendations. These recommendations were then presented to the stakeholders who became part of the consensus panel. There was no identified conflict of interest among the CPG developers, TWG members and stakeholders. A survey to determine potential competing interests were conducted during the development of this CPG. This initiative was fully funded by the PAPP and PIDSP societies.

The 2021 PCAP CPG significantly differs from the previous CPGs in several aspects. First, the current guideline is a consensus between two pediatric societies. Second, much of the literature review has been centered on meta-analyses or systematic reviews instead of individual studies. Finally, appraisal of published literature was based on Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria. Such methodological differences may provide difficulties in defining evolution of care through the years.

As identified in the previous CPG updates, there is lack of local data hence most of the evidences gathered came from international studies. The applicability of such data to the local setting needs to be critically assessed for its value and relevance. Corollary to this, several gaps in knowledge are identified and these may serve as a guide for future research.

## SUMMARY OF RECOMMENDATIONS

	CLINICAL QUESTIONS	RECOMMENDATIONS
1.	Among infants and children aged 3 months to 18 years, what clinical signs and symptoms will accurately diagnose community-acquired pneumonia?	<p>Pediatric community-acquired pneumonia (PCAP) is considered in a patient who presents with cough or fever, PLUS any of the following positive predictors of radiographically-confirmed pneumonia:  <i>(Conditional recommendation, very low-grade evidence)</i></p> <ol style="list-style-type: none"> <li>(1) Tachypnea            3 months to 12 months old: <math>\geq 50</math> breaths per minute            &gt;1 year old to 5 years old: <math>\geq 40</math> breaths per minute            &gt;5 years to 12 years old: <math>\geq 30</math> breaths per minute            &gt;12 years old: <math>\geq 20</math> breaths per minute</li> <li>(2) Retractions or chest indrawing</li> <li>(3) Nasal flaring</li> <li>(4) O<sub>2</sub> saturation &lt;95% at room air</li> <li>(5) Grunting</li> </ol>
2.	Among infants and children 3 months to 18 years with community-acquired pneumonia, what clinical and ancillary parameters will determine the need for admission?	<p>Patients classified as having severe PCAP or high-risk for pneumonia-related mortality based on the clinical parameters and/or ancillary features are considered for admission.  <i>(Conditional Recommendation, moderate to low-grade evidence)</i></p> <p>See Page 135</p>
3.	Among infants and children aged 3 months to 18 years, what diagnostic aids will confirm the presence of non-severe community-acquired pneumonia in an ambulatory setting?	<p>Routine diagnostic aids are NOT considered for non-severe PCAP in an ambulatory setting.  <i>(Conditional recommendation, Expert opinion)</i></p>
4.	Among infants and children aged 3 months to 18 years, what diagnostic aids will confirm the presence of severe community-acquired pneumonia in a hospital setting?	<ol style="list-style-type: none"> <li>(1) Chest X-ray is strongly recommended as an initial diagnostic aid for patients classified as having severe PCAP.  <i>(Strong recommendation, high-grade evidence)</i></li> <li>(2) Point-of-care chest ultrasonography (POCUS) performed by a skilled expert is strongly recommended as a diagnostic aid for patients classified as having severe PCAP.  <i>(Strong recommendation, high-grade evidence)</i></li> <li>(3) Procalcitonin (PCT) is recommended to be used in conjunction with other factors such as clinical presentation, imaging modalities and other laboratory aids in diagnosing bacterial PCAP.  <i>(Conditional recommendation, moderate-grade evidence)</i></li> <li>(4) Sputum Gram stain and culture are not considered to be done routinely in patients classified as having severe PCAP.  <i>(Conditional recommendation, low-grade evidence)</i></li> <li>(5) Complete blood count, arterial blood gas, serum electrolytes and other diagnostic aids are considered to be used as necessary based on the clinician's evaluation.  <i>(Conditional recommendation, Expert opinion)</i></li> </ol>

	CLINICAL QUESTIONS	RECOMMENDATIONS
5.	Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what clinical and ancillary parameters will determine the need for antibiotic treatment?	<p>Empiric antibiotic therapy is considered to be started in patients with clinical signs and symptoms of PCAP with ANY of the following parameters suggestive of bacterial etiology for both non-severe and severe pneumonia:  <i>(Conditional recommendation, low-grade evidence)</i></p> <ol style="list-style-type: none"> <li>(1) Elevated white blood cell count (WBC)</li> <li>(2) Elevated C-reactive protein (CRP)</li> <li>(3) Elevated procalcitonin (PCT)</li> <li>(4) Imaging findings such as:</li> <li>(5) Alveolar infiltrates in chest radiograph; or</li> <li>(6) Unilateral, solitary lung consolidation and/or air bronchograms and/or pleural effusion in lung ultrasound</li> </ol>
6.	A. Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what empiric treatment is effective if a bacterial etiology is considered?	<ol style="list-style-type: none"> <li>(1) For patients classified as having non-severe PCAP, regardless of immunization status against <i>Streptococcus pneumoniae</i> and/or <i>Haemophilus influenzae type b</i> (Hib), any of the following is considered: <ol style="list-style-type: none"> <li>(1.1) start Amoxicillin trihydrate at 40-50mg/kg/day Q8 for 7 days OR at 80-90mg/kg/day Q12 for 5 to 7days.</li> <li>(1.2) start Amoxicillin-clavulanate at 80-90mg/kg/day Q12 (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) for 5 to 7 days OR Cefuroxime at 20-30mg/kg/day Q12 for 7 days in settings with documented high-level penicillin-resistant pneumococci or beta-lactamase-producing <i>H. influenzae</i> based on local resistance data or hospital antibiogram.  <i>(Conditional recommendation, low-grade evidence)</i></li> </ol> </li> <li>(2) For patients classified as having severe PCAP, regardless of immunization status against <i>Streptococcus pneumoniae</i>, any of the following is considered: <ol style="list-style-type: none"> <li>(2.1) start Penicillin G at 200,000 units/kg/day Q6 if with complete <i>Haemophilus influenzae type b</i> (Hib) vaccination OR Ampicillin at 200mg/kg/day Q6 if with no or incomplete or unknown <i>Haemophilus influenzae type b</i> (Hib) vaccination</li> <li>(2.2) start Cefuroxime at 100-150mg/kg/day Q8 OR Ceftriaxone at 75-100mg/kg/day Q12 to Q24 OR Ampicillin-sulbactam at 200mg/kg/day Q6 (based on ampicillin content) in settings with documented high-level penicillin-resistant pneumococci or beta-lactamase-producing <i>H. influenzae</i> based on local resistance data or hospital antibiogram</li> <li>(2.3) add Clindamycin at 20-40mg/kg/day Q6 to Q8 when <i>Staphylococcal pneumonia</i> is highly suspected based on clinical and chest radiograph features. However, in cases of severe and life-threatening conditions such as sepsis and shock, Vancomycin at 40-60 mg/kg/day Q6 to Q8 is preferred.  <i>(Conditional recommendation, low-grade evidence)</i></li> </ol> </li> </ol>

	CLINICAL QUESTIONS	RECOMMENDATIONS
		<p>(3) For patients with known hypersensitivity to penicillin, classified as</p> <p>(3.1) Non-type 1 hypersensitivity to Penicillin, cephalosporins such as Cefuroxime PO 20-30mg/kg/day Q12 or IV 100-150mg/kg/day Q8 OR Ceftriaxone at 75-100mg/kg/day Q12 to Q24 is considered.</p> <p>(3.2) Type 1 hypersensitivity to Penicillin (immediate, anaphylactic-type), any of the following is considered:</p> <p>(3.2.1) Azithromycin at 10mg/kg/day PO or IV Q24 for 3 days OR 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5</p> <p>(3.2.2) Clarithromycin at 15mg/kg/day Q12 for 7 days</p> <p>(3.2.3) Clindamycin at 10-40mg/kg/day PO or 20-40mg/kg/day IV Q6 to Q8 for 7 days</p> <p><i>(Conditional recommendation, low-grade evidence)</i></p> <p>(4) When an atypical pathogen is highly suspected, starting a macrolide is considered as follows:</p> <p>(4.1) Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, OR 10mg/kg/day Q24 for 3-5 days OR 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5</p> <p>(4.2) Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days</p> <p><i>(Conditional recommendation, low-grade evidence)</i></p> <p>(5) When a specific pathogen is identified, modifying the empiric treatment based on the antibiotic susceptibility pattern and/or the drug of choice is recommended.</p> <p><i>(Strong recommendation, high-grade evidence)</i></p> <p>(6) When treating for uncomplicated bacterial PCAP, 7 to 10 days treatment is considered but a longer duration may be required depending on the patient's clinical response, virulence of the causative organism and eventual development of complications.</p> <p><i>(Conditional recommendation, low-grade evidence)</i></p>
6.	<p>B. Among infants and children aged 3 months to 18 years with bacterial community-acquired pneumonia, will the addition of a macrolide to standard empiric regimen improve treatment outcome?</p>	<p>The addition of a macrolide to standard beta-lactam antibiotic therapy is not considered in the empiric treatment of bacterial PCAP.</p> <p><i>(Conditional recommendation, very low-grade evidence)</i></p>
7.	<p>Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what treatment is effective if a viral etiology is considered?</p>	<p>Oseltamivir is strongly recommended to be started immediately within 36 hours of laboratory-confirmed influenza infection.</p> <p><i>(Strong recommendation, high-grade evidence)</i></p>
8.	<p>Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what clinical and ancillary parameters will determine a good response to current therapeutic management?</p>	<p>(1) For patients classified as having non-severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by improvement of cough or normalization of core body temperature in Celsius in the absence of antipyretics within 24-72 hours after initiation of treatment.</p> <p><i>(Conditional recommendation, very low-grade evidence)</i></p>

	CLINICAL QUESTIONS	RECOMMENDATIONS
		<p>(2) For patients classified as having severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by ANY ONE of the following physiologic and ancillary parameters observed within 24-72 hours after initiation of treatment:</p> <ul style="list-style-type: none"> <li>(2.1) Absence or Resolution of hypoxia</li> <li>(2.2) Absence or Resolution of danger signs</li> <li>(2.3) Absence or Resolution of tachypnea<sup>1</sup></li> <li>(2.4) Absence or Resolution of fever<sup>2</sup></li> <li>(2.5) Absence or Resolution of tachycardia<sup>3</sup></li> <li>(2.6) Resolving or Improving radiologic pneumonia</li> <li>(2.7) Resolving or Absent chest ultrasound findings</li> <li>(2.8) Normal or Decreasing CRP</li> <li>(2.9) Normal or Decreasing PCT</li> </ul> <p><i>(Conditional recommendation, very low-grade evidence)</i></p>
9.	<p>Among infants and children aged 3 months to 18 years with community-acquired pneumonia, what can be done if the patient is not responding to current therapeutic management?</p>	<p>(1) For patients classified as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating therapeutic management, diagnostic evaluation is considered to determine if any of the following is present: <i>(Conditional recommendation, low-grade evidence)</i></p> <ul style="list-style-type: none"> <li>(1.1) Coexisting or other etiologic agents</li> <li>(1.2) Etiologic agent resistant to current antibiotic, if being given</li> <li>(1.3) Other diagnosis <ul style="list-style-type: none"> <li>(1.3.1) Pneumonia-related complication <ul style="list-style-type: none"> <li>(1.3.1.1) Pleural effusion</li> <li>(1.3.1.2) Necrotizing pneumonia</li> <li>(1.3.1.3) Lung abscess</li> </ul> </li> <li>(1.3.2) Asthma</li> <li>(1.3.3) Pulmonary tuberculosis</li> </ul> </li> </ul> <p>(2) For patients as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management,</p> <ul style="list-style-type: none"> <li>(2.1) and started on standard dose Amoxicillin at 40-50mg/kg/day, increasing the dose to 80-90mg/kg/day Q12 OR shifting to Amoxicillin-Clavulanate at 80-90mg/kg/day (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) Q12 OR Cefuroxime at 20-30 mg/kg/day Q12 is considered.</li> <li>(2.2) and started on high-dose Amoxicillin, Amoxicillin-Clavulanate or Cefuroxime, admitting the patient for parenteral antibiotics is considered.</li> <li>(2.3) adding a macrolide is considered when an atypical pathogen is highly suspected: <ul style="list-style-type: none"> <li>(2.3.1) Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, OR 10mg/kg/day Q24 for 3-5 days OR 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5</li> <li>(2.3.2) Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days</li> </ul> </li> </ul> <p><i>(Conditional recommendation, low-grade evidence)</i></p>

<sup>1</sup> Respiratory rate taken at full minute based on the WHO-defined, age-specific values for tachypnea.

<sup>2</sup> Fever is defined as having a core body temperature of 38 degrees Celsius and above

<sup>3</sup> Cardiac rate taken at full minute based on Pediatric Advanced Life Support age-based values for tachycardia

	CLINICAL QUESTIONS	RECOMMENDATIONS
		<p>(3) For patients classified as having severe PCAP and are not improving or clinically worsening, within 24-72 hours after initiating a therapeutic management, diagnostic evaluation is considered to determine if any of the following is present:</p> <ul style="list-style-type: none"> <li>(3.1) Coexisting or other etiologic agents</li> <li>(3.2) Etiologic agent resistant to current antibiotic, if being given</li> <li>(3.3) Other diagnosis               <ul style="list-style-type: none"> <li>(3.3.1) Pneumonia-related complication                   <ul style="list-style-type: none"> <li>(3.3.1.1) Pleural effusion</li> <li>(3.3.1.2) Pneumothorax</li> <li>(3.3.1.3) Necrotizing pneumonia</li> <li>(3.3.1.4) Lung abscess</li> </ul> </li> <li>(3.3.2) Asthma</li> <li>(3.3.3) Pulmonary tuberculosis</li> <li>(3.3.4) Sepsis</li> </ul> </li> </ul> <p><i>(Conditional recommendation, Expert opinion)</i></p> <p>(4) The following diagnostic evaluations are considered in the presence of treatment failure in severe PCAP:</p> <ul style="list-style-type: none"> <li>(4.1) Cultures</li> <li>(4.2) Nucleic acid amplification test (e.g. PCR)</li> <li>(4.3) Serology</li> <li>(4.4) Imaging modalities: (chest radiography, UTZ or CT scan)</li> <li>(4.5) Biomarkers (e.g. CBC, CRP, PCT)</li> </ul> <p><i>(Conditional recommendation, Expert opinion)</i></p> <p>(5) For patients that are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management, a referral to a specialist is considered.</p> <p><i>(Conditional recommendation, Expert opinion)</i></p>
10.	Among infants and children aged 3 months to 18 years, what clinical parameters will determine that switch therapy can be considered in the management of severe community-acquired pneumonia?	<p>Switch therapy is considered among patients with bacterial PCAP when <b>ALL</b> of the following clinical parameters are present:</p> <ul style="list-style-type: none"> <li>(1) Current parenteral antibiotic has been given for at least 24 hours</li> <li>(2) Afebrile for at least 8 hours without the use of any antipyretic drug</li> <li>(3) Able to feed and without vomiting or diarrhoea</li> <li>(4) Presence of clinical improvement as defined by <b>ALL</b> of the following:               <ul style="list-style-type: none"> <li>(4.1) Absence of hypoxia</li> <li>(4.2) Absence of danger signs</li> <li>(4.3) Absence of tachypnoea</li> <li>(4.4) Absence of fever</li> <li>(4.5) Absence of tachycardia</li> </ul> </li> </ul> <p><i>(Conditional recommendation, low-grade evidence)</i></p>
11.	Among infants and children aged 3 months to 18 years, what adjunctive treatment is effective for community-acquired pneumonia?	<ul style="list-style-type: none"> <li>(1) Vitamins A is strongly recommended as adjunctive treatment for measles pneumonia.               <p><i>(Strong recommendation, high-grade evidence)</i></p> </li> <li>(2) Zinc is not considered as adjunctive treatment for severe PCAP as it does not have any effect in shortening recovery time.               <p><i>(Conditional recommendation, low-grade evidence)</i></p> </li> <li>(3) Vitamin D is not considered as adjunctive treatment for severe PCAP as it does not reduce the length of hospital stay.               <p><i>(Conditional recommendation, low-grade evidence)</i></p> </li> </ul>

	CLINICAL QUESTIONS	RECOMMENDATIONS
		<p>(4) Bronchodilators are considered as adjunctive treatment for PCAP in the presence of wheezing. <i>(Conditional recommendation, expert opinion)</i></p> <p>(5) Mucokinetic, secretolytic, and mucolytic agents are not considered as adjunctive treatment for PCAP. <i>(Conditional recommendation, low-grade evidence)</i></p> <p>(6) There is insufficient evidence to recommend the use of the following as adjunctive treatment for PCAP: <i>(Very low-grade evidence)</i></p> <ul style="list-style-type: none"> <li>(6.1) Oral folate</li> <li>(6.2) Probiotics</li> <li>(6.3) Vitamin C</li> <li>(6.4) Virgin coconut oil (VCO)</li> <li>(6.5) Nebulization with saline solution</li> <li>(6.6) Steam inhalation</li> </ul>
12.	Among infants and children aged 3 months to 3 years, what interventions are effective for the prevention of community-acquired pneumonia?	<p>(1) The following strategies are recommended to prevent PCAP:</p> <ul style="list-style-type: none"> <li>(1.1) Vaccination against <i>Streptococcus pneumoniae</i> (pneumococcus), <i>Haemophilus influenzae</i> type b (Hib), <i>Bordetella pertussis</i> (pertussis), Rubeola virus (measles) and Influenza virus <i>(Strong recommendation; high-grade evidence)</i></li> <li>(1.2) Breastfeeding <i>(Strong recommendation; high-grade evidence)</i></li> <li>(1.3) Avoidance of environmental tobacco smoke or indoor biomass fuel exposure <i>(Strong recommendation; high-grade evidence)</i></li> <li>(1.4) Zinc supplementation <i>(Strong recommendation; moderate-grade evidence)</i></li> </ul> <p>(2) There is insufficient evidence to recommend Vitamin A, C or D supplementation for the prevention of PCAP. <i>(Very low-grade evidence)</i></p>

## GUIDELINE DEVELOPMENT

### Lead CPG Developers

The lead CPG developer is formed by key members from the Philippine Academy of Pediatric Pulmonologists and the Pediatric Infectious Disease Society of the Philippines. Together with two evidence review experts, they identified the scope and the target end user of the CPG, coordinated meetings during the development of the CPG, and relevant stakeholders who will be part of the consensus panel.

A Technical Working Group composed of PAPP and PIDSP members is likewise formed to conduct literature search, appraisal of evidence, and formulation of recommendations. This organized PCAP CPG team is identified as the 2021 PAPP/PIDSP Joint Task Force on PCAP in this manuscript.

### Scope, Objectives, and Target Users of the Clinical Practice Guidelines

The 2021 Clinical Practice Guidelines in the Evaluation and Management of Pediatric Community-Acquired Pneumonia (2021 PCAP CPG) is focused on the recognition of clinical features, appropriate and practical diagnostic procedures, effective therapeutic management and preventive measures in an immunocompetent infant and children aged 3 months to 18 years with uncomplicated community-acquired pneumonia. This does not cover topics on coronavirus disease 2019 (COVID-19) pneumonia as well as recurrent, persistent, complicated, aspiration, and health care-associated pneumonia. Moreover, differentiating the three broad categories namely bacterial, viral and atypical pathogens in terms of their peculiar management approaches were not tackled. Treatment options were directed to the most common causative agents for PCAP but are not organism-specific and did not include pathogens such as *Mycobacterium tuberculosis*, fungi, and viruses other than the Influenza virus. These guidelines are intended for use by health care providers responsible for the management of PCAP in both ambulatory and hospital settings. This CPG is envisioned to guide the clinician and should not supersede sound clinical judgement in the overall care of pediatric patients with community-acquired pneumonia.

### Clinical questions pertaining to evaluation, treatment and prevention

The lead CPG developers updated the recommendations to answer the clinical questions formulated in the first Clinical Practice Guideline in the Evaluation and Management of Pediatric Community-acquired Pneumonia (2004) created by the joint efforts of PPS, PIDSP, and PAPP. The clinical questions in 2004 were identified through consensus meetings among the lead CPG developers then and were based on a prospective study on the knowledge, attitude, and practice of pediatricians, family physicians, and general practitioners in the Philippines. The 2008, 2012 and 2016 CPG updates used the same clinical questions.

### Literature search, and inclusion and appraisal of evidence

The literature search, and inclusion and appraisal of evidence was made in line with DOH and PhilHealth's Manual for Clinical Practice Guideline Development (2018). Members of the TWG assigned in each clinical question were tasked to search the literature. Local researches submitted to the Philippine Pediatric Society (PPS) and published on the Abstracts of Philippine Pediatric Researches 2012-2015, Philippine Academy of Pediatric Pulmonologists (PAPP), and Pediatric Infectious Disease Society of the Philippines (PIDSP) Journal, Health Research and Development Information Network (HERDIN); and international publications identified using the systematic literature search of PubMed, Cochrane Library, and Google Scholar databases were searched and limited to the following: [1] Existing CPGs, meta-analyses or systematic reviews (individual studies were considered in the absence of the aforementioned study types); [2] source of data from January 1, 2016 to April 31, 2021; [3] 3 months to 18 years of age; and [4] immunocompetent host. Search terms were structured based on the PICO format of each clinical question. Bibliography search within the initially selected articles was also done to expand literature search.

Based on the Manual for Clinical Practice Guideline Development 2018, existing and published CPGs, systematic reviews and meta-analyses can be used as references to answer the PICO questions. In this case, an existing systematic review is

evaluated to determine if it can be used instead of performing a de novo systematic review. Titles and abstracts were screened and those that met the inclusion criteria for each clinical question were retrieved as full-text.

### Quality Assessment using GRADE Approach

STUDY DESIGN	QUALITY OF EVIDENCE	DOWNGRADE IN PRESENCE OF	UPGRADE IN PRESENCE OF
Randomized trial	High	<b>Risk of bias</b> (-1) Serious (-2) Very serious	<b>Large effect</b> (+1) Large, no plausible confounders, consistent and direct evidence
	Moderate	<b>Inconsistency</b> (-1) Serious (-2) Very serious  <b>Indirectness</b> (-1) Serious (-2) Very serious  <b>Imprecision</b> (-1) Serious (-2) Very serious	(+2) Very large, no major threats to validity and direct evidence  <b>Dose response</b> (+1) Evidence of a gradient
Observational study	Low	<b>Publication bias</b> (-1) Serious (-2) Very serious	<b>All plausible confounding</b> (+1) Would reduce a demonstrated effect
	Very low		(+1) Would suggest a spurious effect when results show no effect

Source: Guyatt G et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. [Adapted Journal of Clinical Epidemiology 64 (2011) 383-394] as cited in the DOH and PhilHealth Manual for CPG Development (2018).

Appraisal of evidence and interpretation of results were done in line with DOH and PhilHealth guidelines. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used in assessing the quality of evidence and strength of recommendations. GRADE was developed by an international panel that considered clinical questions on diagnosis, screening, prevention and therapy, and assessing them based on potential sources of bias.

For existing Clinical Practice Guidelines, the International Appraisal of Guidelines, Research and Evaluation version 2009 (AGREE II) was used. This is also an internationally-recognized assessment tool endorsed by DOH. This tool consists of the following dimensions: Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, Editorial Independence, and Overall Guideline Assessment.

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

The results of studies as reported in the Summary of Evidence are summarized to include study design, clinically important end points, and effect measures.

### Grade recommendation with description of level of evidence

The 2021 PCAP CPG adopted the following recommendation statement as supported by corresponding levels of evidence:

GRADE	Strength of recommendation	Recommendation Statement	Description of evidence
<b>High</b>	Strong	Should [or should not] be recommended OR Strongly [or strongly not] recommended	Evidence based on an existing high-quality CPG, meta-analysis, or systematic review.
<b>Moderate</b>	Can be strong or conditional	Is [or is not] recommended	Evidence based on an existing moderate quality CPG, meta-analysis, systematic review, or individual studies with definite evidence.
<b>Low or Very Low</b>	Conditional	Is [or is not] suggested/considered	Evidence based on an existing low-quality CPG, meta-analysis, systematic review, or individual studies with equivocal evidence.
<b>No evidence</b>	Conditional	Expert opinion	The recommendation was based on a consensus among members of the 2021 PAPP/PCAP Joint Task Force on PCAP.

Development of recommendations also accounted for facilitators and barriers to implementation. These include the presence or lack of training and/or access to resources to follow the recommendation. A limitation, however, in the development of recommendations is the lack of economic evaluation of the health interventions mentioned and so the costs of interventions as potential barrier were not presented.

### Stakeholder's consultation

Results of questionnaire surveys on PCAP among participants of the PAPP Annual Convention from 2016-2019 were reviewed and considered in this 2021 CPG. In addition, a preliminary draft was sent to selected stakeholders for individual evaluation as to clarity, acceptability, and applicability of the CPG. The preliminary draft was also presented to them by the lead CPG developers through an online teleconference where each stakeholder was given the opportunity to ask clarifications and give comments. Potential facilitators and barriers for the CPG pursuit were brought up during the stakeholder's consultation and these were considered when finalizing the CPG. Opinions expressed by the individual stakeholder did not necessarily reflect the medical society or institution he/she is affiliated with.

The following stakeholders were engaged during the development of this CPG:

1. CLEMENCIA BONDOC M.D. - Association of Municipal Health Officers of the Philippines (AMHOP)
2. ZASHKA ALEXIS GOMEZ, M.D. – DOH - Disease Prevention and Control Bureau (DOH-DPCB)
3. RAZEL NIKKA HAO, M.D.- DOH - Disease Prevention and Control Bureau (DOH-DPCB)
4. JAN DEREK JUNIO, M.D.- DOH - Disease Prevention and Control Bureau (DOH-DPCB)
5. MR. PHILIP BUGAYONG – DOH - National Reference Laboratories (DOH-RITM-NRL) for Microbiology and Virology
6. MAYAN LUMANDAS, M.D. – DOH - National Reference Laboratories (DOH-RITM-NRL) for Microbiology and Virology
7. FERDINAND DE GUZMAN, M.D. - Philippine Academy of Family Physicians (PAFP)
8. RACQUEL LOPEZ, M.D. - Philippine Academy of Family Physicians (PAFP)
9. ENDRIK SY, M.D. - Philippine Academy of Family Physicians (PAFP)
10. DORIS LOUISE OBRA, M.D. - Philippine Academy of Pediatric Pulmonologists (PAPP)
11. RITA MARIE LOURDES VERGARA, M.D. - Philippine Academy of Pediatric Pulmonologists (PAPP)
12. RODOLFO PAGCATIPUNAN, JR., M.D. - Philippine College of Chest Physicians (PCCP)
13. RICHARD HENRY SANTOS, M.D. - Philippine College of Emergency Medicine
14. PATRICK JOSEPH TIGLAO, M.D. - Philippine College of Emergency Medicine

15. MS. CHARISSE BANAAG – Philippine Health Insurance Corporation (PhilHealth)
16. MERCY JEANE UY-ARAGON, M.D. - Pediatric Infectious Disease Society of the Philippines (PIDSP)
17. BELLE RANILE, M.D. - Pediatric Infectious Disease Society of the Philippines (PIDSP)
18. MARGARITA LUISA ALFONSO, M.D. - Philippine Pediatric Society (PPS)
19. EDNA SARAH MORADA, M.D. - Philippine Pediatric Society (PPS)
20. MICHELLE ANNE MANGUBAT, M.D. - Philippine Society of Adolescent Medicine Specialists (PSAMS)
21. OLIVIA CAMILLE REYES, M.D. - Philippine Society of Pediatric Emergency Medicine
22. MA. VICTORIA RIBAYA, MD. - Philippine Society of Pediatric Emergency Medicine
23. ROBERTO PADUA, JR. M.D. - Philippine Society of Pathologists (PSP)
24. MIRIAN VITERBO, M.D. - Philippine Society of Pathologists (PSP)
25. NATHAN DAVID CONCEPCION, M.D. - Philippine Society of Pediatric Radiology
26. JOANNA CHOA-GO, M.D. - Philippine Society of Pediatric Radiology
27. LEONILA DANS, M.D. – Professor, University of the Philippines, Manila

### Formulation of the final draft

At least three-fourths of the members of the PAPP and PIDSP lead CPG developers met through teleconferencing and voted to reach consensus for each recommendation. Consensus was defined as more than 75% of the participating members. Stakeholders made up the consensus panel during the finalization of the recommendations and consensus was defined as at least 75% agreement among the members (one organization is equivalent to one participation). As a contingent plan if a consensus is not reached in a clinical question, the members who disagree can present new evidence or perspectives to the lead CPG developers and concur again in a consensus panel meeting through teleconference. A survey will then be done to determine if a consensus can be made. If still a consensus regarding a clinical question is not attained despite the discussions, it will then be declared as undecided. However, for this CPG there was a consensus from the participating members in all the recommendations presented. The final draft was presented to the 2020-2021 PAPP and PIDSP Board Members for approval and official endorsement then forwarded to the stakeholders.

### Dissemination and Monitoring Plan

Copies of the 2021 PCAP CPG will be distributed to PAPP, PIDSP, and PPS training institutions, posted on their official websites, and stakeholders' websites. Survey forms will be disseminated during the annual conventions of the PAPP and PIDSP to assess compliance and applicability of the formulated guidelines. This will be done annually for the next 3 years in time for the next CPG update in 2024. Assessing the knowledge, attitude, and practices of physicians on the 2021 PCAP CPG will also be part of the research agenda of PAPP and PIDSP for the succeeding years.

## EVIDENCE SUMMARIES and RECOMMENDATIONS

### Clinical Question 1

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT CLINICAL SIGNS AND SYMPTOMS WILL ACCURATELY DIAGNOSE COMMUNITY-ACQUIRED PNEUMONIA?

#### KEY RECOMMENDATION

Pediatric community-acquired pneumonia (PCAP) is considered in a patient who presents with cough or fever, PLUS any of the following positive predictors of radiographically-confirmed pneumonia<sup>1</sup>:

*(Conditional recommendation, very low-grade evidence)*

#### Tachypnea<sup>2</sup>

3 months to 12 months old:  $\geq 50$  breaths per minute

>1 year old to 5 years old:  $\geq 40$  breaths per minute

>5 years to 12 years old:  $\geq 30$  breaths per minute

>12 years old:  $\geq 20$  breaths per minute

#### Retractions or chest indrawing<sup>3</sup>

Nasal flaring

O<sub>2</sub> saturation <95% at room air<sup>4</sup>

Grunting

Chest radiograph was the reference standard used in the studies.

<sup>2</sup> The age-specific definition of tachypnea was adopted from the WHO (below 5 years old) and PALS (age 5 years and above). Currently, there is no age-specific criteria of tachypnea in the Filipino population

<sup>3</sup> Chest indrawing was defined by the WHO as *“the inward movement of the lower chest wall when the child breathes in, and is a sign of respiratory distress. It does not refer to the inward movement of the soft tissue between the ribs.”*

<sup>4</sup> The oxygen saturation of <95% cut-off was based on expert opinion. No study was found that recommends a specific cut-off value predictive of pneumonia.

#### SUMMARY OF EVIDENCE

Outcome 1	Sensitivity, Specificity, +LR, -LR of clinical signs and symptoms in diagnosis of CAP in children		Importance: Critical
# of studies (and list of authors)	Study Design/s	Key findings	Grade level of evidence
17 (Schot, 2018)	Systematic Review	<p><i>High prevalence pneumonia (&gt;10%)</i></p> <p>Cough:  <i>Sen = 78.5-88 Sp = 16-30.2</i>            PPV= 36.8-37.2. NPV = 70.6-72.7. LR = 1.3</p> <p>Fever:  <i>Sen = 47-94. Sp = 36-68</i>            PPV= 20-45. NPV = 70-97. LR = 2.9</p>	Very low

<p>23 (Shah 2017)</p>	<p>Meta-analysis of Cohort studies</p>	<p>Cough:  <i>Sen</i>= 88 (80-97)      <i>Sp</i>= 25(08-42)  +LR= 1.2 (0.98-1.4)    -LR= 0.47 (0.24-0.70)</p> <p>Fever: &gt;37.5 °C  <i>Sen</i>= 80-92              <i>Sp</i>= 47-54  +LR= 1.7-1.8            -LR= 0.17-0.37</p> <p>Chest pain:  <i>Sen</i>= 22 (5-62)        <i>Sp</i>= 91 (56-99)  +LR= 1.9 (1.1-3.4)    -LR= 0.82 (0.66-1.0)</p> <p>Oxygen saturation  ≤96%:  <i>Sen</i>= 64 (49-78)        <i>Sp</i>= 77 (73-81)  +LR= 2.8 (2.1 -3.6)    -LR= 0.47 (0.32-0.67)</p> <p>≤95%:  <i>Sen</i>= 16 (11-2)        <i>Sp</i>=96 (93-97)  +LR=3.5(2.0-6.4).    -LR=0.88(0.82-0.94)</p> <p>≤92%:  <i>Sen</i>= 26 (21-32)        <i>Sp</i>= 88 (82-93)  +LR= 2.2 (1.3-3.8)    -LR= 0.84 (0.76-0.94)</p> <p>Grunting:  <i>Sen</i>=13 (5-32)        <i>Sp</i>=95 (83-99)  +LR=2.7 (1.5-5.1)    -LR=0.92 (0.80-0.97)</p> <p>Nasal flaring:  <i>Sen</i>= 36 (17-54)        <i>Sp</i>= 84 (71-97)  +LR= 2.2 (1.3-3.1).    -LR= 0.77 (0.64-0.90)</p> <p>Retractions or indrawing:  <i>Sen</i>= 38 (20-56)        <i>Sp</i>= 80 (70-90)  +LR= 1.9 (1.2-2.5)    -LR= 0.78 (0.61-0.94)</p>	<p>Very low</p>
<p>19 (Rambaud-Althaus 2015)</p>	<p>Meta-analysis of Cohort and Case-control studies</p>	<p>Cough:  <i>Sen</i>=96 (91-98)        <i>Sp</i>=14 (3-46)  +LR=1.12 (0.90-1.39) -LR=0.30 (0.09-0.96)</p> <p>History of fever:  <i>Sen</i>=94 (88-97).        <i>Sp</i>=12 (6-23)  +LR=1.06 (1.0-1.12)    -LR=0.53 (0.41-0.69)</p> <p>Respiratory rate &gt;50:  <i>Sen</i>=53 (30-74)        <i>Sp</i>=72 (58-83)  +LR=1.9 (1.5-2.5)    -LR=0.6 (0.5-0.9)</p> <p>Nasal flaring:  <i>Sen</i>= 47 (28-66)        <i>Sp</i>= 73 (52-87)  +LR= 1.75 (1.20-2.56) -LR= 0.73 (0.59-0.89)</p>	<p>Very low</p>

		<p>Grunting:</p> <p>Sen=24 (10-47)      Sp=87 (65-96)</p> <p>+LR=1.8 (1.1-2.9)      -LR=0.9 (0.8-1.0)</p>	
		<p>Retractions or indrawing:</p> <p>Sen= 48 (16-82)      Sp= 72 (47-89)</p> <p>+LR= 1.8 (0.9-1.2).      -LR= 0.7 (0.4-1.4)</p>	

## CONTEXT AND CONSIDERATIONS

The positive predictors of radiographically-confirmed pneumonia were included based on the positive likelihood ratio of  $\geq 2$  or sensitivity of  $\geq 80\%$ . If the given criteria are not met but pneumonia is highly considered, further diagnostic work-up is suggested. Auscultatory lung findings such as decreased breath sounds, crackles or rales, wheeze and rhonchi were not included due to their low sensitivity ( $<80\%$ ) or positive likelihood ratio ( $<2$ ) for diagnosing pneumonia mainly due to interobserver variability. No single clinical feature was found to predict pneumonia accurately. There was no supporting evidence on the predictive accuracy of a combination of signs and/or symptoms in giving a definitive diagnosis of pneumonia.

The 2021 PAPP/PIDSP Joint Task Force on PCAP retained the position statement of the 2012 PAPP 2<sup>nd</sup> PCAP update that chest radiograph is the reference standard in establishing the presence or absence of pneumonia. The task force similarly acknowledges the limitation of chest radiograph as a diagnostic tool. There is no evidence evaluating the accuracy in comparison with microbiology as the gold standard. In addition, moderate reliability exists due to interobserver variability in radiographic interpretation.

Even in the absence of chest radiograph, pneumonia may be considered using the above clinical predictors. Chest radiograph findings should always be correlated with the patient's clinical findings. A normal chest radiograph does not exclude the presence of pneumonia. Inconsistencies in the chest radiograph and clinical findings warrant re-evaluation or referral to a specialist.

## REFERENCES

1. Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. *The Lancet infectious diseases*. 2015 Apr 1;15(4):439-50. doi:10.1016/S1473-3099(15)70017-4
2. Shah SN, Bachur RG, Simel DL, Neuman MI. Does This Child Have Pneumonia?: The Rational Clinical Examination Systematic Review [published correction appears in *JAMA*. 2017 Oct 3;318(13):1284]. *JAMA*. 2017;318(5):462-471. doi:10.1001/jama.2017.9039
3. Schot MJC, Dekker ARJ, Giorgi WG, et al. Diagnostic value of signs, symptoms and diagnostic tests for diagnosing pneumonia in ambulant children in developed countries: a systematic review. *NPJ Prim Care Respir Med*. 2018;28(1):40. Published 2018 Oct 26. doi:10.1038/s41533-018-0104-8

## Clinical Question 2

### AMONG INFANTS AND CHILDREN 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CLINICAL AND ANCILLARY PARAMETERS WILL DETERMINE THE NEED FOR ADMISSION?

#### KEY RECOMMENDATION

Patients classified as having severe PCAP or high-risk for pneumonia-related mortality based on the following clinical parameters and/or ancillary features are considered for admission: (*Conditional Recommendation, moderate to low-grade evidence*)

PARAMETERS AT SITE-OF-CARE	RISK CLASSIFICATION FOR PNEUMONIA-RELATED MORTALITY			
	Low Risk (Non-Severe PCAP)		High Risk (Severe PCAP)	
Formerly classified as:	PCAP A	PCAP B	PCAP C	PCAP D
<b>Clinical Parameters*</b>				
<b>Respiratory signs</b>				
1.1 Cyanosis/ Hypoxemia	None		Present	
1.2 Head bobbing	None		Present	
1.3 Chest indrawing/Retractions	None		Present	
1.4 Apnea	None		Present	
1.5 Grunting	None		Present	
<b>Central nervous system signs</b>				
2.1 Altered sensorium	None or irritable But consolable		Lethargic/stuporous/comatose/ GCS <13	
2.2 Convulsion	None		Present	
<b>Circulatory signs</b>				
3.1 Poor perfusion	None		Capillary refill >3s or in shock	
3.2 Pallor	None		Present	
<b>General considerations</b>				
4.1 Malnutrition**	None or mild		Moderate to severe	
4.2 Refusal OR inability to drink/ feed/ take oral medications	No		Yes	
4.3 Dehydration	None		With some to severe signs	
4.4 Age <6 months	No		Yes	
<b>Ancillary Parameters</b> (desirable variables but not necessary as determinants for admission at site-of-care)				
1. Chest radiograph or ultrasound findings of consolidation, multi-focal disease, moderate to large effusion, abscess, air leak	None		Present	
2. Sustained oxygen saturation at RA using pulse oximetry for 20-30 minutes	>94%		<93%***	

\*Each of the clinical parameters and radiographic findings is an independent predictor of pneumonia-related mortality. The presence of any of the above predictors classifies the patient into the high-risk category.

\*\*Weight for Height [WFH]<sup>4</sup>: moderate = SD score < -2; severe = SD score < -3 (WHO Management of severe malnutrition: a manual for physicians and other health workers. Geneva. World Health Organization 1999); Weight for Age (based on 2017 WHO IMCI Update on Assessing and managing children at primary healthcare facilities to prevent overweight and obesity in the context of the double burden of malnutrition): moderate = -2 SD (≥ -2 Z score); severe = -3 SD (≥ -3 Z score)

\*\*\*If oxygen saturation is less than 90%, oxygen therapy should be initiated.

<sup>4</sup> Although body mass index (BMI) was not mentioned in the studies/ reviews used in the development of this CPG, it may be used in the assessment of the nutritional status of children and adolescents. However, the same recommendations for malnutrition status as a parameter for admission cannot be applied since no evidence was gathered as to the level associated with mortality among patients with pneumonia.

### SUMMARY OF EVIDENCE

Outcome 1	Severe Pneumonia and Pneumonia-related Mortality		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
56 (Dean & Florin,2018)	Meta-analysis of Cohort and Case-control studies	<p>Sustained SPO<sub>2</sub> of &lt;90% at RA – hypoxemia OR = 11; 95% CI = 6.2 – 19.6</p> <p>Age &lt;6 months associated with treatment failure and mortality OR = 2.2; 95% CI = 1.1 – 4.2</p> <p>Chest indrawing was associated with severe outcomes OR = 2.12; 95% CI = 1.62 – 2.78</p> <p>Head bobbing was associated with mortality RR = 8.3; 95% CI = 2.71 – 12.77 and mechanical ventilation RR = 4.7 95% CI = 1.50 – 6.36</p> <p>Grunting is associated with hypoxemia and suggestive of impending respiratory failure OR = 5.210; 95% CI = 2.287 – 7.482</p> <p>AMS associated with severe outcomes OR = 11.9; 95% CI = 6.41 – 22.23</p> <p>AMS – Glasgow Coma Score &lt;13 was the most associated with mortality in children admitted with pneumonia OR = 324; 95% CI = 131 – 805</p> <p>In children admitted with WHO-defined severe or very severe pneumonia, AMS was associated with mortality RR = 5.44; 95% CI = 1.34–17.56</p> <p>In children admitted with WHO-defined pneumonia in a developing nation, “alteration of general status” based on clinician impression was also associated with mortality OR = 3.23; 95% CI = 1.17–8.94</p> <p>Oxygen saturation &lt;90% at RA OR = 20.9; 95%CI = 5.0–87</p>	Low
5 (Deardorff <i>et al.</i> ,2018)	Systematic review of cohort and case-control studies	<p>Chest indrawing OR = 4.6; 95%CI = 2.2–9.4</p> <p>Wheezing OR = 0.2; 95% CI = 0.05 – 0.6</p> <p>Refusing to feed OR = 1.8; 95% CI = 0.9 – 3.8</p>	Moderate

		<p>Unable to drink/ breastfeed OR = 1.8; 95% CI = 1.2 – 2.8</p> <p>Weight for age: Low (<math>\leq -2</math> Zscore). OR = 2.5; 95% CI = 1.6 – 3.8 Very low (<math>\leq -3</math> Zscore). OR = 6; 95% CI = 2.5 – 14.4</p> <p>Weight for age: Low (<math>\leq -2</math> Zscore) OR = 2.1; 95% CI = 1.3 – 3.2 Very low (<math>\leq -3</math> Zscore) OR = 3.8; 95% CI = 2.7 – 5.4</p> <p>Dehydration OR = 1.9; 95% CI = 1.3 – 2.8</p> <p>Child not conscious at exam (mRISC) OR = 2.3; 95%CI = 1.6 – 3.4</p>	
56 (Dean & Florin,2018)	Systematic review of cohort and case-control studies	<p>Multifocal disease and fluid bronchograms on transthoracic ultrasound are associated with severity (CHEN)</p> <ul style="list-style-type: none"> <li>– multifocal involvement was an independent risk factor for a poor outcome including: <ul style="list-style-type: none"> <li>- ICU admission (OR = 5.38)</li> <li>- longer LOS (&gt;9 days) (OR = 9.75)</li> <li>- tube thoracotomy (OR = 20.12)</li> </ul> </li> <li>– fluid bronchogram was an independent predictor of a longer hospital stay (&gt; 9 days) (OR = 5.00) and tube thoracotomy (OR = 13.33)</li> </ul> <p>Moderate or large effusions were associated with ICU admission (CHEN) OR = 3.2; 95% CI = 1.1–8.9 and mechanical ventilation OR = 14.8; 95% CI = 9.8–22.4</p> <p>Impaired perfusion on lung US – lung necrosis – a longer hospital stay would be expected if moderate-to-massive pleural effusion was observed in addition to impaired perfusion in ultrasonography (LAI) OR = 3.08; 95% CI = 1.15–8.29</p>	Low

### CONTEXT AND CONSIDERATIONS

The PCAP Guideline development from 2004 through 2016 has been utilizing PCAP A, B, C, and D for its pneumonia risk classification nomenclature. The 2021 CPG lead developers recommend the use of Non-Severe PCAP or Low-Risk for pneumonia-related mortality in lieu of PCAP A and B and Severe PCAP or High Risk for pneumonia-related mortality in lieu of PCAP C and D. This change was done to align with existing international guidelines in classifying PCAP.

The Risk Classification for pneumonia-related mortality should be used when assessing a pediatric patient diagnosed to have community-acquired pneumonia for admission. The presence of one (1) parameter, clinical and/or imaging, in the Severe or High Risk for Mortality category is an indication for admission. This classification is not a pneumonia severity classification, rather it is a categorization of the risk of mortality from pediatric pneumonia. It utilizes clinical and diagnostic parameters to assign the patient to a risk level at point-of-care.



The aforementioned clinical parameters and imaging findings are predictors of high-risk for pneumonia-related mortality. To classify to a higher risk category, at least 1 clinical or ancillary parameter should be present. In the absence of an ancillary parameter, a clinical parameter may suffice.

A patient classified as having non-severe PCAP would have a low risk for pneumonia-related mortality and may be treated in an outpatient basis with the recommended management plan. A caveat to this initial disposition would be a return to the facility for admission if there is no clinical improvement OR with signs of deterioration such as hypoxemia, chest indrawing/ retractions, grunting, altered sensorium, pallor within 48 hours; OR if the patient refuses or is unable to feed, drink or take medications. Patients classified as having non-severe PCAP should also be admitted if they have an underlying medical condition that can aggravate the overall clinical status. Other relative indications for admission of non-severe PCAP patients are absence of a reliable caregiver, inability for close follow-up, and no easily accessible medical facility.

A patient classified as having severe PCAP would have a high risk for pneumonia-related mortality and should be admitted for close observation and immediate institution of the recommended management plan. The indications for admission to a critical care unit should also be noted and close monitoring must be performed as these patients are at greater risk for mortality.

## REFERENCES

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### Clinical Question 3

## AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT DIAGNOSTIC AIDS WILL CONFIRM THE PRESENCE OF NON-SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN AN AMBULATORY SETTING?

#### KEY RECOMMENDATION

Routine diagnostic aids are not considered for non-severe PCAP in an ambulatory setting.  
(*Conditional recommendation, Expert opinion*)

#### SUMMARY OF EVIDENCE

No evidence was found regarding the use of diagnostic aids in confirming non-severe PCAP. Diagnostic aids are not routinely recommended in children with mild clinical presentation and managed in an ambulatory setting. It is the discretion of the attending physician to request for diagnostic aids based on his initial clinical assessment.

## Clinical Question 4

# AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT DIAGNOSTIC AIDS WILL CONFIRM THE PRESENCE OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN A HOSPITAL SETTING?

### KEY RECOMMENDATIONS

Chest X-ray is strongly recommended as an initial diagnostic aid for patients classified as having severe PCAP. (*Strong recommendation, high-grade evidence*)

Point-of-care chest ultrasonography (POCUS) performed by a skilled expert is strongly recommended as a diagnostic aid for patients classified as having severe PCAP. (*Strong recommendation, high-grade evidence*)

Procalcitonin (PCT) is recommended to be used in conjunction with other factors such as clinical presentation, imaging modalities and other laboratory aids in diagnosing bacterial PCAP. (*Conditional recommendation, moderate-grade evidence*)

Sputum Gram stain and culture are not considered to be done routinely in patients classified as having severe PCAP. (*Conditional recommendation, low-grade evidence*)

Complete blood count, arterial blood gas, serum electrolytes and other diagnostic aids are considered to be used as necessary based on the clinician's evaluation. (*Conditional recommendation, Expert opinion*)

### SUMMARY OF EVIDENCE

#### 1. Chest radiography

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
12 (Balk <i>et al.</i> , 2017)	Meta-analysis of Cohort and Case-control studies	Chest X-ray is recommended as an initial test Sn: 86.80% Sp: 98.20% LR (+): 48.22. LR (-): 0.13	High

## 2. Chest ultrasonography

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
6 (Wang <i>et al.</i> , 2019)	Meta-analysis of Cohort and Case-control studies	CUS <sup>5</sup> as a diagnostic aid Sn: 86.80% Sp: 98.20% LR (+): 48.22 LR (-): 0.134	High
22 (Najgrodzka <i>et al.</i> , 2019)	Meta-analysis of Cohort and Case-control studies	CUS as a diagnostic aid Sn: 96.70%. Sp: 87.39% LR (+): 7.61. LR (-): 0.04	High
12 (Hua Xin <i>et al.</i> , 2017)	Meta-analysis of Cohort and Case-control studies	CUS as a diagnostic aid Sn: 93.00% Sp: 96.00% LR (+): 23.25. LR (-): 0.07	High
6 (Zar <i>et al.</i> , 2017)	Meta-analysis of Cohort and Case-control studies	CUS as a diagnostic aid Positive: 0.71 Negative: 0.80	Very low

## 3. Procalcitonin

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
25 (Tsou <i>et al.</i> , 2020)	Meta-analysis of Cohort and Case-control studies	PCT for bacterial pneumonia Sn: 64.00% Sp: 72.00% LR (+): 2.29 LR (-): 0.50	Moderate

## 4. Sputum GS/CS

Outcome	Positive diagnosis of pneumonia		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
21 (Ogawa <i>et al.</i> , 2019)	Meta-analysis of Cohort and Case-control studies	Sputum Gram stain, culture, and sensitivity as a diagnostic aid for bacterial CAP <i>S. pneumoniae</i> Sn: 69.00 Sp: 91.00 LR (+): 7.67 LR (-): 0.34 <i>H. influenzae</i> Sn: 76.00 Sp: 97.00 LR (+): 25.33 LR (-): 0.25	Low

<sup>5</sup> CUS – chest ultrasound

## CONTEXT AND CONSIDERATIONS

Chest radiography remains to be the initial diagnostic aid of choice for severe PCAP. Postero-anterior and lateral (PA-L) views are preferred for children who are able to stand upright, otherwise antero-posterior *and lateral* (AP-L) views are acceptable especially for younger infants. Proper patient positioning is vital to obtain a good quality chest radiograph. As best practice, consider having two (2) radiologists to review the X-ray images to eliminate intra-observer variability and encourage clinicians to review the radiographs for better clinical correlation.

In recent years, robust evidences show the value of chest ultrasonography as an initial tool in the diagnosis of PCAP. Zar *et al.* enumerated the advantages of point-of-care ultrasound (POCUS) in their study, namely: [1] it can be performed at point-of-care; [2] it is feasible and less costly than chest radiography; [3] it is less affected by movement or crying than other imaging modalities; [4] it can be done in sleeping children and [4] it is free of ionizing radiation. Operator dependency is one of the limitations often cited with regard to the ultrasound imaging study (Wang *et al.*, 2019), other limitations include: [1] inability to visualize the whole lung at the same time or to identify consolidation deep within the lung parenchyma;(Zar *et al.*, 2017) [2] subscapular or sub-clavicular consolidations that did not reach the pleura are inaccessible to ultrasound imaging and may be missed;(Najgrodzka *et al.*, 2019) [3] the spleen or air in the stomach can be misinterpreted as lung consolidation with air bronchograms (Zar *et al.*, 2017).

The meta-analysis of Hua Xin *et al.* highlighted 4 major abnormalities that are frequently observed on CUS: pulmonary consolidation, positive air bronchogram, abnormal pleural line, and pleural effusion. Among these 4, positive air bronchogram and lung consolidation are the most often detected signs on CUS.

There is some evidence that procalcitonin (PCT) can be used to distinguish between bacterial and viral aetiology of pneumonia. PCT, a precursor of the calcitonin hormone, increases after exposure to bacterial endotoxins and inflammatory cytokines (Dandona *et al.* 1994). It is a favourable characteristic in a biomarker for diagnosis of bacterial infections, determination of disease severity, evaluation of patients' response to treatment, and prevention of antibiotic overuse (Shcuetz, McCluskey *et al.*, 2017). Current evidence on the other biomarkers such as CRP, plasma interferon- $\gamma$  protein-10, chitinase 3-like-1, RNA biosignatures remain conflicting and overlapping (Principi *et al.*, 2017).

Gram stain of expectorated sputum is an inexpensive, non-invasive, readily available test that can promptly identify causative bacteria if performed by an experienced observer in a qualified laboratory on good-quality specimens (Skerrett *et al.*, 1999). A good-quality specimen is defined as one containing  $\geq 25$  leukocytes and  $< 10$  squamous epithelial cells per low power field (Ogawa *et al.*, 2020). One meta-analysis was found advocating sputum GS, culture and sensitivity as a diagnostic aid for bacterial CAP. This study, though with modest limitation in terms of methodology, showed that sputum GS was highly specific to diagnose *S. pneumoniae* and *H. influenzae* infections in patients with CAP with values of 91% and 97% respectively. Sensitivity, on the other hand for the two microorganisms were 69% and 76%. Selecting good-quality specimens could increase this yield, although data supporting this are limited (Ogawa *et al.*, 2020). There is insufficient evidence to support the routine use of culture and sensitivity of blood, tracheal aspirate, and bronchoalveolar lavage for the diagnosis of severe PCAP.

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## Clinical Question 5

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CLINICAL AND ANCILLARY PARAMETERS WILL DETERMINE THE NEED FOR ANTIBIOTIC TREATMENT?

#### KEY RECOMMENDATION

Empiric antibiotic therapy is considered to be started in patients with clinical signs and symptoms of PCAP with ANY of the following parameters suggestive of bacterial etiology for both non-severe and severe pneumonia: (*Conditional recommendation, low-grade evidence*)

Elevated white blood cell count (WBC)<sup>1</sup>

Elevated C-reactive protein (CRP)

Elevated procalcitonin (PCT)

Imaging findings such as:

Alveolar infiltrates in chest radiograph; or

Unilateral, solitary lung consolidation and/or air bronchograms and/or pleural effusion in lung ultrasound

Age	Mean (x10 <sup>3</sup> /ml)	Range (x10 <sup>3</sup> /ml)
1 month	10.8	4.0 – 19.5
6 mos – 2 years	10.6	6.0 – 17
2 – 6 years	8.5	5.0 – 15.5
6 – 12 years	8.1	4.5 – 13.5
12 – 18 years	7.8	4.5 – 13.5

Reference: The Harriet Lane Handbook 22<sup>nd</sup> ed, 2021

#### SUMMARY OF EVIDENCE

Outcome:	Differentiating bacterial from viral pneumonia using CBC, CRP, PCT		Importance: Critical
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
12 (Thomas <i>et al.</i> , 2020)	Meta-analysis of Cohort and Case-control studies	CRP: Sn 63.5 - 75%      Sp 53.8 - 90% PCT: Sn 63.8 - 86%      Sp 38.9 - 80% WBC: Sn 41.6%              Sp 61.3%	Very Low
25 (Po-Yang <i>et al.</i> , 2020)	Meta-analysis of Cohort and Case-control studies	Procalcitonin showed moderate diagnostic accuracy for diagnosis of bacterial pneumonia in children, and may be used in conjunction with clinical presentation and laboratory and imaging findings prior to starting of antibiotics. Pooled Sn: 0.64 (95% CI: 0.53–0.74)	Low

		<p>Pooled Sp: 0.72 (95% CI: 0.64–0.79)</p> <p>Pooled +LR 2.3 (95% CI: 1.8–3.0)</p> <p>Pooled -LR: 0.50 (95% CI: 0.38–0.66)</p>	
Zar, <i>et al.</i> , 2020	CPG	General tests for infection, including acute-phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white cell count (WCC), neutrophil count and procalcitonin (PCT)) do not reliably differentiate bacterial from viral pneumonia and should not be routinely used. CRP concentrations $\geq 40$ mg/L with radiological confirmation of pneumonia suggests bacterial pneumonia.	High
Tapiainen, <i>et al.</i> , 2016	CPG	Elevated C-reactive protein concentrations or leucocyte counts increase the possibility of bacterial pneumonia, but low C-reactive protein concentrations or leucocytes do not exclude bacterial pneumonia.	High

Outcome:	Differentiating bacterial from viral pneumonia using imaging findings		Importance: Critical/ Important
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
Buonsenso <i>et al.</i> , 2021	individual cohort study	<p>Differentiating bacterial from viral pneumonia:</p> <p>Large-sized consolidation: OR 13.62 (95% CI 1.16-159.88)</p> <p>Air bronchogram: OR 6.58 (95% CI 1.67-25.93)</p> <p>Pleural effusion: OR 1.48 (95% CI 0.42 – 5.16)</p> <p>Deep vertical artifacts: OR 0.27 (95% CI 0.07-1.06)</p>	Very low
Malla <i>et al.</i> , 2020	individual cross-sectional analytical study	<p>Sn 91% (95% CI 84-96)</p> <p>Sp 91.3% (95% CI 84-96)</p> <p>PPV 91.9% (95% CI 85-96)</p> <p>NPV 90.3% (95% CI 82-95)</p>	Very low

Berce <i>et al.</i> , 2019	Individual cohort study	<p>Differentiating bacterial from viral pneumonia            Unilateral consolidation:            OR 12.42 (95% CI 4.59-33.62)            PPV 65.7 NPV 85.7            Solitary consolidation:            OR 9.01 (95% CI 3.94-20.60)            PPV 71.3. NPV 78.3</p> <p>Differentiating bacterial from atypical pneumonia:            Unilateral consolidation:            OR 9.41 (95% CI 2.80-31.66)            PPV 65.7. NPV 85.7            Solitary consolidation:            OR 8.86 (95% CI 2.96-26.51)            PPV 71.3. NPV 78.3</p>	Very low
Tapiainen, <i>et al.</i> , 2016	CPG	Alveolar pneumonia is reliably detected in chest radiography, but interstitial changes are not so reliably diagnosed. Alveolar infiltrates suggest bacterial pneumonia.	High

## CONTEXT AND CONSIDERATIONS

There is insufficient evidence to differentiate bacterial from viral pneumonia based on clinical signs and symptoms alone. In the absence of the aforementioned ancillary parameters, the decision to start antibiotics empirically is based on the clinician's assessment and sound judgment. Efforts should be made to obtain evidence of the causative pathogen for PCAP to avoid unnecessary use of antibiotics and to provide optimal pathogen-directed care to patients.

Laboratory tests and chest imaging are not routinely requested prior to starting antibiotic therapy. If these ancillary tests are done, empiric antibiotics may be started in patients with clinical signs and symptoms of PCAP with elevated WBC for age, elevated CRP or elevated procalcitonin. However, a low or normal level of biomarkers does not exclude bacterial pneumonia. Furthermore, no optimal cut-off values for CRP and procalcitonin can be derived from the reviewed literature since different units, cut-off values and laboratory testing systems were used in the clinical setting. In patients with clinical signs and symptoms of PCAP, the presence of alveolar infiltrates, solitary lung consolidation or air bronchogram on chest radiograph and pleural effusion on lung ultrasound are suggestive of a bacterial etiology and warrants antibiotic use.

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## Clinical Question 6A

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT EMPIRIC TREATMENT IS EFFECTIVE IF A BACTERIAL ETIOLOGY IS CONSIDERED?

#### KEY RECOMMENDATIONS

For patients classified as having non-severe PCAP, regardless of immunization status against *Streptococcus pneumoniae* and/or *Haemophilus influenzae type b* (Hib), any of the following is considered:

start Amoxicillin trihydrate at 40-50mg/kg/day Q8 for 7 days **OR** at 80-90mg/kg/day Q12 for 5 to 7 days.

start Amoxicillin-clavulanate at 80-90mg/kg/day Q12 (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) for 5 to 7 days **OR** Cefuroxime at 20-30mg/kg/day Q12 for 7 days in settings with documented high-level penicillin-resistant *pneumococci* or beta-lactamase-producing *H. influenzae* based on local resistance data or hospital antibiogram.

(Conditional recommendation, low-grade evidence)

For patients classified as having severe PCAP, regardless of immunization status against *Streptococcus pneumoniae*, any of the following is considered:

start Penicillin G at 200,000 units/kg/day Q6 if with complete *Haemophilus influenzae type b* (Hib) vaccination **OR** Ampicillin at 200mg/kg/day Q6 if with no or incomplete or unknown *Haemophilus influenzae type b* (Hib) vaccination

start Cefuroxime at 100-150mg/kg/day Q8 **OR** Ceftriaxone at 75-100mg/kg/day Q12 to Q24 **OR** Ampicillin-sulbactam at 200mg/kg/day Q6 (based on ampicillin content) in settings with documented high-level penicillin-resistant *pneumococci* or beta-lactamase-producing *H. influenzae* based on local resistance data or hospital antibiogram

add Clindamycin at 20-40mg/kg/day Q6 to Q8 when *Staphylococcal* pneumonia is highly suspected based on clinical and chest radiograph features. However, in cases of severe and life-threatening conditions such as sepsis and shock, Vancomycin at 40-60 mg/kg/day Q6 to Q8 is preferred.

(Conditional recommendation, low-grade evidence)

For patients with known hypersensitivity to penicillin, classified as

Non-type 1 hypersensitivity to Penicillin, cephalosporins such as Cefuroxime PO 20-30mg/kg/day Q12 or IV 100-150mg/kg/day Q8 **OR** Ceftriaxone at 75-100mg/kg/day Q12 to Q24 is considered.

Type 1 hypersensitivity to Penicillin (immediate, anaphylactic-type), any of the following is considered:

Azithromycin at 10mg/kg/day PO or IV Q24 for 3 days **OR** 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5

Clarithromycin at 15mg/kg/day Q12 for 7 days

Clindamycin at 10-40mg/kg/day PO or 20-40mg/kg/day IV Q6 to Q8 for 7 days

(Conditional recommendation, low-grade evidence)

When an atypical pathogen is highly suspected, starting a macrolide is considered as follows:

Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, **OR** 10mg/kg/day Q24 for 3-5 days **OR** 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5

Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days

(Conditional recommendation, low-grade evidence)

### KEY RECOMMENDATIONS

When a specific pathogen is identified, modifying the empiric treatment based on the antibiotic susceptibility pattern and/or the drug of choice is recommended.

*(Strong recommendation, high-grade evidence)*

When treating for uncomplicated bacterial PCAP, 7 to 10 days treatment is considered but a longer duration may be required depending on the patient's clinical response, virulence of the causative organism and eventual development of complications.

*(Conditional recommendation, low-grade evidence)*

### SUMMARY OF EVIDENCE

#### Antimicrobial Resistance Surveillance Pattern from 2016 to 2020 (<https://arsp.com.ph/>)

<i>Streptococcus pneumoniae</i>	ALL ISOLATES		RESPIRATORY ISOLATES				
	69% resp.	66% resp.	2016	2017	2018	2019	2020
Penicillin (nm)	6.1%	10%	1%	0.8%	1.1%		
Chloramphenicol	3.4%	4.8%	-	-	-		
Cotrimoxazole	18.1%	15.1%	18%	13.8%	22.4%		
Erythromycin	7%	9.8%	15%	11.3%	12%		
Ceftriaxone (nm)	3%	1.2%	3%	0	3.8%		
Levofloxacin	1.1%	0.8%	2%	1.7%	0		
Clindamycin	-	-	-	-	5.1%		

<i>Haemophilus influenzae</i>	ALL ISOLATES		RESPIRATORY ISOLATES				
	94% resp.	95% resp.	2016	2017	2018	2019	2020
Ampicillin	7.8%	14%	10%	10.8%	7.2%		
Amoxicillin-clavulanate	5.8%	-	5%	2.6%	2.2%		
Ampicillin-sulbactam	-	5%	3%	2.7%	3.5%		
Chloramphenicol	5.3%	9%	-	8.2%	-		
Cefuroxime	-	-	7%	1.5%	-		
Ceftriaxone	-	-	1%	2.9%	2%		
Levofloxacin	0	0	0	0.7%	-		
Azithromycin	0	0	0	0	0		

<i>Staphylococcus aureus</i>	ALL ISOLATES				
	resp. 19%	21%	20.5%	21.1%	22.51%
	2016	2017	2018	2019	2020
Oxacillin	61.5%	57%	54.2%	52.1%	47.6%
Cotrimoxazole	24.6%	26%	31.8%	35.5%	34.3%
Clindamycin	11.4%	13%	12.4%	10.4%	10.7%
Vancomycin	0.8%	2%	1%	0.8%	1.2%
Linezolid	1.4%	1%	1%	0.6%	0.7%

<b>SUMMARY OF EVIDENCES</b>			
<b>Outcome</b>	<b>Etiology</b>		<b>Importance: Critical</b>
<b># of studies included in SR/MA and authors</b>	<b>Study Design/s</b>	<b>Key Findings</b>	<b>Grade level of evidence</b>
1 Nathan, <i>et.al.</i> 2020	Cohort	<i>H. influenzae</i> , <i>S. aureus</i> and <i>S. pneumoniae</i> were the most commonly detected bacteria	Very low
48 Ning, <i>et.al.</i> , 2017	Meta-analysis of Cohort studies	The most frequently detected bacterial pathogens were <i>K. pneumoniae</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> and <i>S. aureus</i>	Very low
1 Das, <i>et.al.</i> 2016	Cohort	The most common detected bacterial pathogen obtained through nasopharyngeal swab and BAL were <i>S. pneumoniae</i> and non-type b <i>H. influenzae</i> followed by <i>K. pneumoniae</i> and MSSA	Very low
<b>Outcome</b>	<b>Treatment, Dose and Duration of Therapy</b>		<b>Importance: Critical</b>
South African Thoracic Society Guidelines (Reubenson <i>et al.</i> , 2020)	CPG	<ol style="list-style-type: none"> <li>1. Oral amoxicillin is recommended for children &gt;1 month of age who do not require hospitalization</li> <li>2. For ambulatory treatment of pneumonia, amoxicillin (45 mg/kg/dose 12-hourly) remains the preferred antibiotic for children &gt;1 month old.</li> <li>3. Treatment duration should be 5 days, but longer duration may be needed in children with severe or complicated disease.</li> <li>4. Bacteremic staphylococcal pneumonia should be treated for 14-28 days, dependent on complications and response to treatment while uncomplicated presumed staphylococcal pneumonia (blood culture negative) may be managed with 10-day course of targeted antibiotic therapy, depending on clinical response.</li> <li>5. If cultures are positive, use targeted therapy according to organism's susceptibility pattern.</li> <li>6. Macrolide antibiotics should be used if pertussis, Mycoplasma or Chlamydia is suspected (evidence level IVa) such as Azithromycin 10mkg daily for 5 days, or Clarithromycin 15mkg Q12 for 10days</li> </ol>	High
Chou et al, 2019	CPG	<ol style="list-style-type: none"> <li>1. Empiric therapy for outpatient treatment of CAP in children for presumed atypical pneumonia is macrolides, Azithromycin 10mkg daily for 3-5 days and Clarithromycin 15mkg Q12 for 7-14 days.</li> <li>2. Targeted therapy for treatment of CAP in children with atypical organisms such as Mycoplasma and Chlamydia are Azithromycin and Clarithromycin with 3 to 7 days treatment duration</li> </ol>	High
1 (Mathur <i>et al.</i> , 2017)	Evidence review	2014 revision preferred oral amoxicillin to oral cotrimoxazole for the treatment of fast-breathing pneumonia and was equivalent to injectable penicillin/ampicillin in cases of chest-in-drawing pneumonia.	Low

1 (Messinger <i>et al.</i> 2021)	Evidence review	1. Length of therapy for uncomplicated bacterial CAP should not exceed 7 days 2. similar success rates of 7 days when compared with 10 days and 5 days	Low
1 (Leung, <i>et.al.</i> , 2018)	Evidence review	1. In previously healthy children under the age of 5 years, high dose amoxicillin is the treatment of choice. 2. For those with type 1 hypersensitivity to penicillin, clindamycin, azithromycin, clarithromycin, and levofloxacin are reasonable alternatives. 3. For children with a non-type 1 hypersensitivity to penicillin, cephalosporins should be considered.	Low
1 (Dizon and Rivera, 2019)	RCT	Paediatric community-acquired pneumonia A and B can be treated as efficaciously with either high-dose (80mkg in 2 divided doses for 5 days) or standard-dose (40mkg in 3 divided doses for 7 days) Amoxicillin. No significant difference in the clinical course of the 2 groups by days 3 and 7 and frequency of adverse events were also similar.	Low

## CONTEXT AND CONSIDERATIONS

The causative agents of community acquired pneumonia vary according to age of the child and the setting in which the infection is acquired. Generally, viruses notably Respiratory Syncytial Virus (RSV), are the most common cause of pneumonia in children younger than 5 years. *Streptococcus pneumoniae* is the most common bacteria across all age groups. Other important bacterial causes in children younger than 5 years include *Hemophilus influenzae*, *Streptococcus pyogenes* and *Moraxella catarrhalis*. In children 5 years and older, other important causes include Mycoplasma and Chlamydia.

The advent of universal childhood immunization with pneumococcal and Hib conjugate vaccines have resulted in a shift in bacterial etiology, with non-typeable *H. influenzae* and *Staphylococcus aureus* causing a greater proportion of severe pneumonia in hospitalized children worldwide.

With the global emergence of antimicrobial resistance, judicious use of antibiotics cannot be overemphasized. The choice of empiric antibiotics in PCAP should always be guided by the general principles of rational antibiotic use and the most likely pathogen should be considered. Starting with broad spectrum antibiotics to treat uncomplicated PCAP is highly discouraged and such antibiotics should be reserved for more complicated forms of the disease and for drug-resistant pathogens. Amoxicillin is still the treatment of choice because it is effective against the majority of pathogens causing CAP in this age group. High-dose amoxicillin is recommended for treatment of suspected or confirmed penicillin-resistant *S. pneumoniae*; the resistance of which can be overcome at higher drug concentrations. Practitioners commonly presume that oral cephalosporins are superior to amoxicillin for *S. pneumoniae*; this likely stems from the knowledge that some penicillin-resistant pneumococci isolates are susceptible to ceftriaxone hence, oral cephalosporins are assumed superior to amoxicillin. However, oral cephalosporins have short half-lives, highly protein bound and often have long dosing intervals. This results in serum concentrations that do not provide enough bactericidal time. Because the pharmacokinetics of the oral cephalosporins are far inferior to amoxicillin, their use in CAP should be reserved for patients who are allergic to penicillin or patients with isolates known to be resistant to amoxicillin but susceptible to cephalosporins such as *M. catarrhalis* or beta-lactamase-positive *H. influenzae*. When atypical pathogens are highly suspected especially in a child who is not ill-looking despite having clinical pneumonia (“walking pneumonia”), although clinical presentation may be indistinguishable with viral pneumonia, starting a macrolide may be considered.

Staphylococcal pneumonia may present with high fever or hypothermia, cough, respiratory distress, signs of shock, and or with presence of skin lesions (point of bacterial entry). However, skin lesions may also be absent in other instances. Pulmonary auscultation is often normal; sometimes with dullness indicating pleural effusion. Typical chest radiographic findings may show multi-lobar consolidation with cavitation, pneumatoceles and/or spontaneous pneumothorax. Other bacterial agents, however, may have similar imaging findings.

There is no definite recommendation for an acceptable antimicrobial resistance rate, but some literature state that between 10-20% is tolerable. Allowable resistance rate will also depend on certain factors such as local resistance data and hospital antibiograms as this varies from place to place and over time.

Currently, there is no defined optimal duration of antibiotic therapy in PCAP. Most experts and guidelines recommend that 7 to 10 days antibiotic treatment is appropriate for most uncomplicated PCAP. However, treatment duration should be extended as necessary depending on the patient's clinical response, virulence of the causative organism and eventual development of complications. Recent studies are now looking into shortening the duration of antibiotic therapy especially in non-severe cases of PCAP.

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## Clinical Question 6B

# AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH BACTERIAL COMMUNITY-ACQUIRED PNEUMONIA, WILL THE ADDITION OF A MACROLIDE TO STANDARD EMPIRIC REGIMEN IMPROVE TREATMENT OUTCOME?

### KEY RECOMMENDATION

The addition of a macrolide to standard beta-lactam antibiotic therapy is NOT considered in the empiric treatment of bacterial PCAP. (*Conditional recommendation, very low-grade evidence*)

### SUMMARY OF EVIDENCE

Outcomes of studies which **did not recommend** the use of macrolides

Outcome 1:	Macrolide resistance		Importance: CRITICAL
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
24 (Chen <i>et al.</i> , 2020)	Meta-analysis of Randomized trials	Overall effect of macrolide resistance  Pooled OR 4.42, 95%CI = 2.32-8.41)	High

Outcomes of studies which **recommended** the use of macrolides

Outcome 2:	Length of hospitalization		Importance: NOT CRITICAL
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
8 (Lin <i>et al.</i> , 2018)	Meta-analysis of Cohort and Case-control studies	Length of stay (LOS) for macrolide-treated group -0.051 days, range: -0.377 to 0.274 days, $p = 0.756$ , $I^2 = 76.8\%$	Very Low
1 (Williams <i>et al.</i> , 2017)	Individual cohort study	Time to discharge ( <i>reported in hazard ratio and 95%CI</i> ) HR (Propensity score-matched): 0.92, 95%CI = 0.77-1.08 HR (Propensity score-weighted): 0.92, 95%CI = 0.79-1.07	Low

Outcome 3:	Treatment failure		Importance: <b>NOT CRITICAL</b>
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
1 (Ambroggio <i>et al.</i> , 2016)	Individual cohort study	Treatment failure: 14 Day TF: 1 to <6 years OR 1.34, 95%CI = 0.83-2.18) 6-18 years OR 0.51, 95%CI = 0.28-0.95)  7 Day TF: 1 to <6 years OR 1.33, 95%CI = 0.74-2.39 6-18 years OR 0.33, 95%CI = 0.12-0.91	Very low

### CONTEXT AND CONSIDERATIONS

There is some evidence on the empiric use of macrolides as an add-on therapy to beta-lactams for non-severe PCAP in patients >5 years of age to cover for atypical pathogens when suspected. However, this practice is not routinely recommended, considering that several studies attest that it is difficult to clinically distinguish signs and symptoms definitive to the diagnosis of atypical pneumonia, and that the inadvertent use of macrolides have the potential to induce macrolide resistance.

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## Clinical Question 7

# AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT TREATMENT IS EFFECTIVE IF A VIRAL ETIOLOGY IS CONSIDERED?

### KEY RECOMMENDATION

Oseltamivir is strongly recommended to be started immediately within 36 hours of laboratory-confirmed influenza infection. (*Strong recommendation, high-grade evidence*)

### SUMMARY OF EVIDENCE

Outcome	Reduction in the duration of illness		Importance: CRITICAL
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
5 (Malosh <i>et al.</i> , 2018)	Meta-analysis of Randomized trials	<p>Significant reduction in the duration of illness among those who received timely oseltamivir treatment</p> <p>(RMST difference -17.6 hours, (95% CI, -34.5 to -0.7 hours)</p> <p>Stratified analysis: Observed larger RMST for individual who received early treatment (&lt;24 hours compared to those who received treatment 24 to 48 hours after the onset (-22 hours, (95% CI, -29.4 to 16.2 hours VS -4.4 hours,95%CI, -15.5 to 6.5 hours</p>	High
20 (Jefferson <i>et al.</i> , 2014)	Meta-analysis of Randomized trials	<p>Oseltamivir in healthy children reduced the time to first alleviation of symptoms with mean difference of 29 hours, (95% confidence interval 12 to 72 hours(p=0.001)</p> <p>Hospitalization No significant effect on hospitalization. Risk difference (RD) 0.15%(95% CI -0.78 to 0.9)</p> <p>Pneumonia Oseltamivir significantly reduced self-reported, investigator mediated, unverified pneumonia. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia</p> <p>Harm of treatment In children, induced vomiting (RD 5.34%, 94% CI 1.75 to 10.29)</p>	High

## CONTEXT AND CONSIDERATIONS

Recommendations on the treatment of viral pneumonia are limited by the availability of laboratory confirmation for influenza and the available antiviral treatments accessible to clinicians. As of this writing, only oseltamivir is available locally as treatment for influenza.

Laboratory confirmation for influenza may be costly and is not widely available in all healthcare facilities. These point-of-care tests, when available, are helpful in initiating early therapy and decreasing the use of unnecessary diagnostics and antibiotics. These point of care tests include influenza point of care kits and the multiplex respiratory panel. This respiratory panel uses nasopharyngeal specimens to detect 4 bacteria and 18 respiratory viruses, including SARS-CoV2. It has an overall sensitivity of 97.1% and specificity of 99.3%.

Treatment for suspected or confirmed influenza is recommended in those with severe illness, i.e, those who are admitted in the hospital, have serious complications like myocarditis and encephalitis, or who are clinically deteriorating. While for non-severe illness suspected with viral pneumonia, treatment is indicated in 1) high-risk children such as those less than five years old, especially those under 2 years old, or those with other comorbidities, and 2) children with high-risk contacts to reduce amount of viral shedding and decreasing risk of transmission to high-risk contacts.

Laboratory-confirmed influenza should be treated with oseltamivir. Timing of treatment should be within 48 hours of symptoms. Early antiviral treatment has been shown to provide maximal benefit. Initiating treatment beyond 48 hours of symptom onset may still provide clinical benefit in hospitalized children or those with serious complications or deteriorating disease. Treatment of oseltamivir is given twice a day for 5 days with the following doses: (1) for children younger than 1 year old, 3mg/kg/dose; (2) for 1 year and older, dose varies by child's weight: for 15kg or less, 30mg; for >15 to 23 kg, 45mg; for >23 to 40kg, 60mg; and for >40kg, the dose is 75mg.

Antiviral may be considered in the following circumstances: (1) any previously healthy, symptomatic outpatient not at high-risk for complications in whom influenza is suspected or confirmed if treatment can be given within 48 hours; and (2) children with suspected or confirmed influenza disease whose siblings/household contacts are less than 6 months old or at high risk for influenza complications.

Immunization status for influenza for the year should not influence decision to initiate treatment with oseltamivir if influenza is highly considered.

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## AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CLINICAL AND ANCILLARY PARAMETERS WILL DETERMINE A GOOD RESPONSE TO CURRENT THERAPEUTIC MANAGEMENT?

### KEY RECOMMENDATIONS

For patients classified as having non-severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by improvement of cough or normalization of core body temperature in Celsius in the absence of antipyretics within 24-72 hours after initiation of treatment. (*Conditional recommendation, very low-grade evidence*)

For patients classified as having severe PCAP, good clinical response to current therapeutic management is considered when clinical stability is sustained for the immediate past 24 hours as evidenced by **ANY ONE** of the following physiologic and ancillary parameters observed within 24-72 hours after initiation of treatment:

- Absence or Resolution of hypoxia
- Absence or Resolution of danger signs<sup>2</sup>
- Absence or Resolution of tachypnea<sup>3</sup>
- Absence or Resolution of fever<sup>4</sup>
- Absence or Resolution of tachycardia<sup>5</sup>
- Resolving or Improving radiologic pneumonia
- Resolving or Absent chest ultrasound findings<sup>6</sup>
- Normal or Decreasing CRP
- Normal or Decreasing PCT

(*Conditional recommendation, very low-grade evidence*)

Hypoxia is defined as having peripheral O<sub>2</sub> saturation less than 95% at room air.

<sup>2</sup> Danger signs are nasal flaring, grunting, head bobbing, cyanosis.

<sup>3</sup> Respiratory rate taken at full minute based on the WHO-defined, age-specific values for tachypnea.

<sup>4</sup> Fever is defined as having a core body temperature of 38 degrees Celsius and above

<sup>5</sup> Cardiac rate taken at full minute based on Pediatric Advanced Life Support age-based values for tachycardia

<sup>6</sup> Chest ultrasound findings include fluid bronchogram (presence of fluid in the airways), multifocal involvement, and pleural effusion.

## SUMMARY OF EVIDENCE

Outcome 1	Time to recovery and treatment failure		Importance: Critical/ Important
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
1 (Basnet <i>et al.</i> , 2015)	Individual cohort study	Absence of hypoxia (SpO <sub>2</sub> < 90%) OR 0.52 (1.33, 2.74). p < 0.001 Absence of any danger sign (nasal flaring, grunting, head bobbing, cyanosis) OR 0.61 (1.18, 2.32) p = 0.004 Absence of radiologic pneumonia OR 0.45 (1.49, 3.31) p < 0.001	Moderate

Outcome 2	Disease progression or complicated pneumonia		Importance: Critical/ Important
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
1 (Chen <i>et al.</i> , 2017)	Individual cohort study	Absent multifocal involvement and ICU admission OR 0.19 p = 0.0027 Absent multifocal involvement and LOS > 9 days OR 0.10 p = 0.02 Absent pleural effusion and LOS > 9 days OR 0.17 p = 0.003 Absent fluid bronchogram and LOS > 9 days OR 0.20 p = 0.006 Absent multifocal involvement and tube thoracotomy OR 0.05 p = 0.0262 Absent fluid bronchogram and tube thoracotomy OR 0.08 p = 0.0262	Low
1 (Erdman <i>et al.</i> , 2015)	Individual cohort study	End-point pneumonia vs normal CXR using CRP Sn 80% Sp 78.7% +LR 3.8 -LR 0.25 End-point pneumonia vs normal CXR using PCT Sn 70% Sp 69.2% +LR 2.3 -LR 0.43	Very Low

<p>1 (Wolf <i>et al.</i>, 2015)</p>	<p>Individual observational cohort</p>	<p>Median time of normalization of physiologic parameters (in hours, CI 95%)  <b>Age &lt;2years</b>            Fever: 14.5 (4.5-45.3)            Tachycardia: 4.5 (0.3-18.4)            Tachypnea: 38.6 (18.7-68.9)  <b>Age 2-4 years</b>            Fever: 18.4 (2.8-42.8)            Tachycardia: 21.8 (5.7-51.9)            Tachypnea: 31.6 (9.5-61.9)  <b>Age 5-17 years</b>            Fever: 10.6 (0.8-34)            Tachycardia: 18 (5.8-42.2)            Tachypnea: 24.3 (10.8-59.2)</p>	<p>Low</p>
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### CONTEXT AND CONSIDERATIONS

It is important to define several terms that are used in these recommendations. *Absolute clinical stability* is defined as the resolution of ALL pneumonia-associated signs and symptoms AND recovery to pre-pneumonia health status. *Approaching clinical stability* is defined as resolution of ANY pneumonia-associated sign or symptom OR delayed recovery to pre-pneumonia health status.

It is also important to note that even if absence of radiographic pneumonia on repeat chest X-ray is one of the ancillary parameters that determines good response to therapeutic management, performing a follow-up chest X-ray is not routinely done as long as there is clinical improvement as evidenced by the physiologic parameters mentioned.

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## Clinical Question 9

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS WITH COMMUNITY-ACQUIRED PNEUMONIA, WHAT CAN BE DONE IF THE PATIENT IS NOT RESPONDING TO CURRENT THERAPEUTIC MANAGEMENT?

#### KEY RECOMMENDATIONS

For patients classified as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating therapeutic management, diagnostic evaluation is considered to determine if any of the following is present: *(Conditional recommendation, low-grade evidence)*

Coexisting or other etiologic agents

Etiologic agent resistant to current antibiotic, if being given

Other diagnosis

    Pneumonia-related complication

        Pleural effusion

        Necrotizing pneumonia

        Lung abscess

    Asthma

    Pulmonary tuberculosis

For patients as having non-severe PCAP and are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management,

and started on standard dose Amoxicillin at 40-50mg/kg/day, increasing the dose to 80-90mg/kg/day Q12 **OR** shifting to Amoxicillin-Clavulanate at 80-90mg/kg/day (based on Amoxicillin content using a 14:1 amoxicillin:clavulanate formulation) Q12 **OR** Cefuroxime at 20-30 mg/kg/day Q12 is considered.

and started on high-dose Amoxicillin, Amoxicillin-Clavulanate or Cefuroxime, admitting the patient for parenteral antibiotics is considered.

adding a macrolide is considered when an atypical pathogen is highly suspected:

    Azithromycin at 10mg/kg/day PO or IV Q24 for 5 days, particularly in infants less than 6 months old whom pertussis is entertained, **OR** 10mg/kg/day Q24 for 3-5 days **OR** 10mg/kg/day on day 1 followed by 5 mg/kg/day Q24 for days 2 to 5

    Clarithromycin at 15mg/kg/day Q12 for 7 to 14 days

*(Conditional recommendation, low-grade evidence)*

## KEY RECOMMENDATIONS

For patients classified as having severe PCAP and are not improving or clinically worsening, within 24-72 hours after initiating a therapeutic management, diagnostic evaluation is considered to determine if any of the following is present:

- Coexisting or other etiologic agents
- Etiologic agent resistant to current antibiotic, if being given
- Other diagnosis
  - Pneumonia-related complication
    - Pleural effusion
    - Pneumothorax
    - Necrotizing pneumonia
    - Lung abscess
  - Asthma
  - Pulmonary tuberculosis
  - Sepsis

*(Conditional recommendation, Expert opinion)*

The following diagnostic evaluations are considered in the presence of treatment failure in severe PCAP:

- Cultures
- Nucleic acid amplification test (e.g. PCR)
- Serology
- Imaging modalities: (chest radiography, UTZ or CT scan)
- Biomarkers (e.g. CBC, CRP, PCT)

*(Conditional recommendation, Expert opinion)*

For patients that are not improving or clinically worsening within 24-72 hours after initiating a therapeutic management, a referral to a specialist is considered. *(Conditional recommendation, Expert opinion)*

## CONTEXT AND CONSIDERATIONS

The recommendations as to the clinical approach to take for the different severities of pediatric community-acquired pneumonia are all based on expert opinion and would still warrant validation studies. Each clinical scenario of non-response to treatment may warrant different approaches hence studies designed to individualize the clinical pathways and validate their effectiveness need to be undertaken.

Regarding ancillary work-up, performing a blood culture is not routinely done in pediatric patients with community-acquired pneumonia, especially in non-severe cases, as studies have shown a low positive culture yield of only 0.4% to 2.5% of cases. However, if a patient is classified as having severe pneumonia and is suspected have concomitant septicemia or bacteremia, blood culture and sensitivity is considered. Other appropriate cultures may be included and are not limited to sputum, bronchoalveolar lavage and endotracheal aspirates.



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## Clinical Question 10

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT CLINICAL PARAMETERS WILL DETERMINE THAT SWITCH THERAPY CAN BE CONSIDERED IN THE MANAGEMENT OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA?

#### KEY RECOMMENDATION

Switch therapy is considered among patients with bacterial PCAP when **ALL** of the following clinical parameters are present: (*Conditional recommendation, low-grade evidence*)

Current parenteral antibiotic has been given for at least 24 hours

Afebrile for at least 8 hours without the use of any antipyretic drug

Able to feed and without vomiting or diarrhoea

Presence of clinical improvement as defined by **ALL** of the following:

Absence of hypoxia

Absence of danger signs

Absence of tachypnoea

Absence of fever

Absence of tachycardia

#### SUMMARY OF EVIDENCE

##### RECOMMENDATION:

1. Current parenteral antibiotic has been given for at least 24 hours
2. Afebrile for at least 8 hours without the use of any antipyretic drug
3. Able to feed and without vomiting or diarrhea

Outcome 1	Length of hospital stay and Readmission rate (within 30 days upon discharge)		Importance: CRITICAL
# of studies (and list of authors)	Study Design/s	Key findings	Grade level of evidence
1 (In-iw <i>et al.</i> 2015)	Individual randomized trial	Length of hospital stay: Conventional therapy: 4.77+1.5 days Switch therapy: 3.8+1.6 days P value 0.019  Readmission rate: Conventional therapy: 1 (3.8%) Switch therapy: 2 (6.5%) P value 0.66	MODERATE

<b>RECOMMENDATION:</b>			
Presence of clinical improvement as defined by <u>ALL</u> of the following: Absence of hypoxia, danger sign, tachypnoea, fever, tachycardia			
<b>Outcome 1</b>	<b>Time to recovery and treatment failure</b>		<b>Importance: CRITICAL</b>
<b># of studies (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>	<b>Grade level of evidence</b>
1 (Basnet <i>et al.</i> , 2015)	Cohort	Absence of hypoxia (SpO2 < 90%) OR 0.52 (1.33, 2.74) p <0.001  Absence of any danger sign (nasal flaring, grunting, head bobbing, cyanosis) OR 0.61 (1.18, 2.32) p = 0.004	MODERATE
<b>Outcome 2</b>	<b>Physiologic Parameters and Time to clinical stability</b>		<b>Importance: CRITICAL</b>
<b># of studies included in MA or SR (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>	<b>Grade level of evidence</b>
1 (Wolf <i>et al.</i> , 2015)	Individual observational cohort	Median time of normalization of physiologic parameters (in hours, CI 95%) <b>Age &lt;2years</b> Fever: 14.5 (4.5-45.3) Tachycardia: 4.5 (0.3-18.4) Tachypnea: 38.6 (18.7-68.9)  <b>Age 2-4 years</b> Fever: 18.4 (2.8-42.8) Tachycardia: 21.8 (5.7-51.9) Tachypnea: 31.6 (9.5-61.9)  <b>Age 5-17 years</b> Fever: 10.6 (0.8-34) Tachycardia: 18 (5.8-42.2) Tachypnea: 24.3 (10.8-59.2)	Low

## CONTEXT AND CONSIDERATIONS

Switch therapy is an approach in the management involving discontinuation of intravenous (IV) antibiotics and be shifted to oral antibiotics as soon as the patient's condition allows. The choice of antibiotics from intravenous to oral must take into account the appropriate antibacterial spectrum, the pharmacokinetics and pharmacodynamics, and should have proven clinical efficacy in the condition being treated. There is no new evidence found for this clinical question, hence, the TWG decided to carry over the recommendations in the 2016 CPG update. The first three recommendations are taken from the inclusion criteria of the RCT done by In-iw, *et al.*, comparing the treatment outcomes of switch therapy and conventional therapy in pediatric patients with community-acquired pneumonia who required hospitalization. The clinical outcomes showed that there was statistically significant reduction in length of hospital stay found in the switch therapy group ( $p = 0.019$ ), whereas the readmission rate for both groups was not significantly different ( $p = 0.66$ ). Furthermore, switch therapy can also be considered in the presence of clinical improvement as defined in the studies of Basnet *et al.* and Wolf *et al.* as absence of danger signs and hypoxia and normalization of fever, tachypnea and tachycardia, respectively. The advantages of switch therapy include reduced length of hospital stay which can lead to lesser risk of infections from infected IV lines and hospital pathogens and reduced cost. In an observational study of Sharma, *et al.*, the switch therapy group showed lower number of complications but there was no difference in treatment outcome when compared to the standard treatment group. Restricted and monitored antibiotics should follow the DOH-Antimicrobial Stewardship Manual of Procedures regarding switch therapy.

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## Clinical Question 11

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 18 YEARS, WHAT ADJUNCTIVE TREATMENT IS EFFECTIVE FOR COMMUNITY-ACQUIRED PNEUMONIA?

#### KEY RECOMMENDATIONS

Vitamins A is strongly recommended as adjunctive treatment for measles pneumonia. (*Strong recommendation, high-grade evidence*)

Zinc is not considered as adjunctive treatment for severe PCAP as it does not have any effect in shortening recovery time. (*Conditional recommendation, low-grade evidence*)

Vitamin D is not considered as adjunctive treatment for severe PCAP as it does not reduce the length of hospital stay. (*Conditional recommendation, low-grade evidence*)

Bronchodilators are considered as adjunctive treatment for PCAP in the presence of wheezing. (*Conditional recommendation, expert opinion*)

Mucokinetic, secretolytic, and mucolytic agents are not considered as adjunctive treatment for PCAP. (*Conditional recommendation, low-grade evidence*)

There is insufficient evidence to recommend the use of the following as adjunctive treatment for PCAP: (*Very low-grade evidence*)

Oral folate

Probiotics

Vitamin C

Virgin coconut oil (VCO)

Nebulization with saline solution

Steam inhalation

#### SUMMARY OF EVIDENCE

Outcome	Treatment success		Importance: CRITICAL
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
4 CHANG (2014)	SR	<p>Pediatric - Mucolytics - no significant difference between groups (odds ratio (OR) 0.40, 95% confidence interval (CI) 0.10 to 1.62)</p> <p>In the combined data (adult &amp; pedia) meta-analysis showed no significant difference between groups for the primary outcome of 'not cured or not improved' (OR 0.85, 95% CI 0.40 to 1.80)</p>	LOW

Outcome	Decreased length of stay, treatment failure, time to recovery		Importance: CRITICAL
# of studies included in MA or SR (and list of authors)	Study Design/s	Key findings	Grade level of evidence
11 (Brown <i>et al.</i> , 2020)	SR/MA	There is no evidence that adjunctive zinc treatment improves recovery from pneumonia in children in LMICs.  <u>Treatment failure -</u> For all pxs (OR 0.95 (95% CI 0.80 to 1.14) For severe pneumonia (OR 0.93 (95% CI 0.75 to 1.14)  <u>Time to recovery -</u> HR 1.01 (95% CI 0.89 to 1.14)	Moderate
7 (Das <i>et al.</i> , 2018)	SR/MA	<u>time to resolution of acute illness (hours)</u> (mean difference (MD) -0.95, 95%(CI) -6.14 to 4.24;  <u>mortality rate</u> (risk ratio (RR) 0.97, 95% CI 0.06 to 15.28;  <u>duration of hospitalisation</u> (MD 0.49, 95% CI -8.41 to 9.4  <u>time to resolution of fever</u> (MD 1.66, 95% CI -2.44 to 5.76)	Low
13 (Yang <i>et al.</i> , 2021)	SR/MA	<u>Time to resolution of pneumonia (hours)</u> MD = -1.02; 95% CI, -5.74 to 3.70; P = .67; I <sup>2</sup> = 12%;  <u>Duration of hospitalization (hours).</u> MD = -1.40; 95% CI, -9.53 to 6.73; P = .74; I <sup>2</sup> = 12%  <u>Recovery rate of pneumonia.</u> recovery rate of pneumonia in the vitamin D group (RR = 1.28; 95% CI, 0.94–1.74; I <sup>2</sup> = 13%) compared with that in the placebo group, which was not statistically different (P = .12)	

### CONTEXT AND CONSIDERATIONS

Vitamin A is a necessary substrate for preserving epithelial cell integrity and also plays a role in immune modulation. WHO recommends that all children diagnosed with measles, in communities where vitamin A deficiency is a recognized problem, vitamin A should be administered as follows: 100,000 IU by mouth for infants younger than 12 months of age and 200,000 IU for older children. The dose should be repeated in 24 hours and after 4 weeks in the presence of ophthalmologic signs of vitamin a deficiency such as night blindness, xerophthalmia or Bitot’s spots (grayish white deposits on the bulbar conjunctiva adjacent to the cornea).

Mucokinetic agents like short-acting bronchodilators (SABA) and secretolytic or mucolytic agents such as ambroxol, carbocisteine, acetylcysteine, and bromhexine are not suggested to be used as adjunctive treatment during the course of illness of non-severe pneumonia due to the limited studies and conflicting outcomes that were reported in these studies (Chang *et al.*, 2014). Furthermore, this same study also mentioned that there is insufficient evidence to decide whether OTC medications for cough associated with acute pneumonia are beneficial.

Bronchodilators are drugs that relax the airway smooth muscles. Narrowing or obstruction of the bronchial airways which leads to wheezing may occur during an infection, an episode of allergy and/or hyperreactive airway disease. Hence, bronchodilators are considered in PCAP in the presence of wheezing.

Based on the WHO recommendations, zinc can be added to the management of pediatric community acquired pneumonia, however recent evidences show that zinc does not shorten the recovery time of childhood pneumonia.

As part of standard of care in the management of pediatric community-acquired pneumonia, hydration and oxygenation if indicated must be administered.

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## Clinical Question 12

### AMONG INFANTS AND CHILDREN AGED 3 MONTHS TO 3 YEARS, WHAT INTERVENTIONS ARE EFFECTIVE FOR THE PREVENTION OF COMMUNITY-ACQUIRED PNEUMONIA?

#### KEY RECOMMENDATIONS

The following strategies are recommended to prevent PCAP:

**Vaccination** against *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b (Hib), *Bordetella pertussis* (pertussis), *Rubeola virus* (measles) and *Influenza virus* (Strong recommendation; high-grade evidence)

**Breastfeeding** (Strong recommendation; high-grade evidence)

**Avoidance of environmental tobacco smoke or indoor biomass fuel exposure** (Strong recommendation; high-grade evidence)

**Zinc supplementation** (Strong recommendation; moderate-grade evidence)

There is insufficient evidence to recommend Vitamin A, C or D supplementation for the prevention of PCAP. (Very low-grade evidence)

#### SUMMARY OF EVIDENCE

Outcome 1	Disease prevention and PCV		Importance: Critical
Number of studies (and list of authors)	Study Design/s	Key findings	Grade level of evidence
(Zar et al., 2020)	CPG	In children aged 24–59 months, a reduction of 9% (95%CI: 5–14%, p-value < 0.001) and of 24% (95%CI: 12–33%, p-value < 0.001) in the hospitalization rates for clinically and radiologically confirmed pneumonia, respectively, after the introduction of the novel PCVs.	High
12 (Alicino et al., 2017)	Meta-analysis of Cohort and Case-control studies	In children aged < 24mos, a reduction of 17% (95%CI: 11–22%, p-value < 0.001), and of 31% (95%CI: 26–35%, p-value < 0.001) in the hospitalization rates respectively for clinically and radiologically confirmed pneumonia, respectively, after the introduction of the novel PCVs.	Low

<b>Outcome 2</b>		<b>Disease prevention and breastfeeding</b>		<b>Importance: Critical</b>
<b>Number of studies (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>		<b>Grade level of evidence</b>
(Zar et al., 2020)	CPG	<p>Breastfeeding has been shown to decrease the incidence of pneumonia in young children by up to 32% (Wright et al., 1998)</p> <p>Shorter duration of breastfeeding is associated with pneumonia mortality, particularly among infants 95% confidence interval (CI) 0.67 - 332.74) (Lamberti et al., 2013)</p>		<b>High</b>
<b>Outcome 3</b>		<b>Disease prevention and avoidance of tobacco smoke or indoor biomass fuel exposure</b>		<b>Importance: Important</b>
<b>Number of studies (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>		<b>Grade level of evidence</b>
(Zar et al., 2020)	CPG	<p>Reduction in tobacco smoke or indoor fuel exposure</p> <p>Active and passive exposure to tobacco should be strongly discouraged in women of child-bearing age, particularly among pregnant women, and more generally in the household. Exposure to fumes from indoor cooking fuels should be limited by opening windows and doors when cooking; the chimney should function well; the stove should be cleaned and maintained; and there should be safe child location practices while fires are burning in the house. The practice of carrying children on caregivers' backs while cooking is an independent risk factor for pneumonia morbidity and mortality. Children should sleep in rooms separate from where food is cooked</p>		<b>High</b>
<b>Outcome 4</b>		<b>Disease prevention and zinc supplementation</b>		<b>Importance: Important</b>
<b>Number of studies (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>		<b>Grade level of evidence</b>
6 (ZS et al., 2016)	SR/MA RCTs	<p>Analysis showed that zinc supplementation reduced the incidence of pneumonia by 13% (fixed-effect risk ratio (RR) 0.87; 95% confidence interval (CI) 0.81 to 0.94, six studies, low-quality evidence) and prevalence of pneumonia by 41% (random-effects RR 0.59; 95% CI 0.35 to 0.99, one study, n = 609, low-quality evidence). On subgroup analysis, zinc reduced the incidence of pneumonia defined by specific clinical criteria by 21% (i.e. confirmation by chest examination or chest radiograph) (fixed-effect RR 0.79; 95% CI 0.71 to 0.88, four studies, n = 3261), but had no effect on lower specificity pneumonia case definition (i.e.</p>		<b>Moderate</b>

		age-specific fast breathing with or without lower chest indrawing) (fixed-effect RR 0.95; 95% CI 0.86 to 1.06, four studies, n = 1932)	
<b>Outcome 5</b>	<b>Disease prevention and Vitamin C supplementation</b>		<b>Importance: Important</b>
<b>Number of studies (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>	<b>Grade level of evidence</b>
7 (Padhani et al., 2020)	SR/MA RCTs (5) Quasi-RCT (2)	Due to the small number of included studies and very low quality of the existing evidence, we are uncertain of the effect of vitamin C supplementation for the prevention and treatment of pneumonia	<b>Very Low</b>
<b>Outcome 6</b>	<b>Disease prevention and Vitamin D supplementation</b>		<b>Importance: Important</b>
<b>Number of studies (and list of authors)</b>	<b>Study Design/s</b>	<b>Key findings</b>	<b>Grade level of evidence</b>
4 (MY et al., 2016)	SR/MA RCTs	For pneumonia, episodes of 'radiologically confirmed' first or only episode of pneumonia were little different in the supplemented and un-supplemented group (Rate Ratio: 1.06, 95% confidence interval (CI) 0.89 to 1.26; two trials, 3134 participants, moderate quality evidence), and similarly for children with confirmed or unconfirmed pneumonia (RR 0.95, 95% CI 0.87 to 1.04; one trial, 3046 participants).  In the single large trial from Afghanistan, the trial authors reported that vitamin D supplementation was associated with an increase in repeat episodes of pneumonia confirmed by chest radiograph (RR 1.69, 95% CI 1.28 to 2.21; one trial, 3046 participants), but not reflected in the outcome of confirmed or unconfirmed pneumonia (RR 1.06, 95% CI 1.00 to 1.13; one trial, 3046 participants).	<b>Very Low</b>

## CONTEXT AND CONSIDERATIONS

Advances in the prevention of paediatric pneumonia have led to a reduction in the burden of disease and have lowered the case fatality risk and mortality over the past two decades. The following strategies can prevent community-acquired pneumonia in children:

### Vaccination

Pneumonia can be prevented by immunizing against *Haemophilus influenzae* type b (Hib), pneumococcus, measles and pertussis (whooping cough) (WHO 2015). WHO also recommends the inclusion of PCVs in childhood immunization programs worldwide. The use of pneumococcal vaccine should be complementary to other disease prevention and control measures, such as appropriate case management, promotion of exclusive breastfeeding for the first 6 months of life and reducing known risk factors such as indoor air pollution and tobacco smoke. The 23-valent pneumococcal polysaccharide vaccine is not routinely recommended for immunocompetent children and is only given to children >2 years old, who are

at risk of developing invasive pneumococcal disease, including those with chronic diseases, with primary and secondary immune deficiencies and with functional or anatomical asplenia.

### **Breastfeeding**

Nutrition including breastfeeding for the first six months of life plays a major role by boosting immunity against causative organisms of pneumonia (WHO 2015). Breastfeeding has been shown to decrease the incidence of pneumonia in young children by up to 32%. Shorter duration of breastfeeding is associated with pneumonia mortality, particularly among infants < 5 month of age. Mortality among infants who are not breastfed compared with exclusively breastfed infants through 5 months of age is ~15-fold higher (relative risk (RR) 14.97; 95% confidence interval (CI) 0.67 - 332.74). (Zar, 2020)

### **Avoidance of environmental tobacco smoke or indoor biomass fuel exposure**

Pneumonia remains the leading cause of childhood mortality outside the neonatal period, in low- and middle-income countries. Environmental tobacco smoke (ETS) exposure is strongly associated with an increased risk for pneumonia and of severe disease. ETS exposure often begins in utero with maternal smoking or exposure. Antenatal or early-life ETS exposure, from maternal, household, or community contacts, may impact on the susceptibility of the infant to develop respiratory disease and impair lung development. However, the effects of postnatal tobacco smoke exposure may also be substantial, leading to poorer respiratory health. (Vanker, 2017). ETS exposure is reported as an important risk factor for childhood LRTI in several studies. A systematic review found smoking by either parent (OR 1.22, 95% CI 1.10–1.35), both parents (OR 1.62, 95% CI 1.38–1.89), or a household member (OR 1.54, 95% CI 1.40–1.69) significantly increased the risk of LRTI (Vanker, 2017). Exposure to household air pollution almost doubles the risk for childhood pneumonia and is responsible for 45% of all pneumonia deaths in children less than 5 years old. (WHO, Household Air Pollution and Health, 22 September, 2021)

### **Zinc supplementation**

Zinc plays an important role in cell regeneration, immunity and growth. Zinc deficiency decreases T-lymphocytes and T-helper, impairs macrophage function and reduced killer cells, and adversely impacts innate immunity affecting interferon (IFN) gamma production, interleukin-2 (IL-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )(Lassi, 2016). A local study done by Goyena *et al.* assessed the adequacy of dietary zinc intake and the prevalence and associated factors of serum zinc deficiency among Filipino preschool-age children 6–71 months old. Data from the 8th National Nutrition Survey (NNS) conducted in 2013, involving 2,892 preschool-age children, were analyzed. Almost half (47.2%) of preschool-age children had inadequate zinc intake. The national prevalence of serum zinc deficiency was 17.9%, and it is highest among children 6–23 months old and those from rural, poorest, and food-insecure households relative to other subgroups (Goyena, 2021). Daily supplementation with 10mg of Zinc (as gluconate or sulfate) for at least 4 to 6 months can prevent pneumonia in children aged 2 to 59 months. Zinc supplementation in children increases levels of complement in the blood that modulate the function of T-lymphocytes, T-helper, macrophages and neutrophils and hence improves the ability to fight infection. Zinc supplementation improves circulating levels of T-lymphocytes and other macrophages that enhance ability to fight infection. (Lassi, 2016)

The Technical Working Group did not find robust evidence that supplementation with vitamin A, C or D can prevent pneumonia in children.

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## AREAS FOR FUTURE RESEARCH

The 2021 PAPP/PIDSP Joint Task Force on PCAP has identified several gaps in knowledge in the evaluation and management of pediatric community-acquired pneumonia. There is paucity of data in some of the clinical questions due to limited high quality studies, more particularly in the local setting. Objective outcome measures should be established to understand fully the difference in the clinical course between causative agents, across all pediatric age groups and socio-economic strata. Relevant outcomes to be considered include time to resolution of observed abnormalities in the clinical and ancillary parameters, development of pneumonia-associated complications, and mortality. Other outcomes that can be measured to assess the effectiveness of interventions include the requirement for hospitalization, length of hospital stay, readmission after hospital discharge, persistence of clinical and laboratory signs and symptoms, and costs of care. These outcomes should be measured, standardized and compared to guide clinicians in decision-making and ultimately improve patient care. We, therefore, recommend adequately powered, well-designed and well-conducted clinical trials in the following areas to provide more specific, evidence-based guidance in the future:

- Identification of clinical feature/s or oxygen saturation level to accurately predict PCAP
- Evaluation of the accuracy of scoring systems using clinical features and oxygen saturation level in predicting the likelihood of PCAP
- Standard triage criteria for selection of the initial site of care, whether ambulatory or in-hospital settings, and to identify patients at high or low risk of clinical deterioration, pneumonia-associated complications and mortality
- Epidemiology of PCAP caused by specific bacteria, viruses, atypical bacteria, and presence of co-infection, especially in areas with good vaccine coverage against *Streptococcus pneumoniae* and *Hemophilus influenzae* type b
- Use of less or non-invasive diagnostic tests using blood, induced sputum, or other respiratory tract secretions and lung tissues that will reliably/accurately document clinical disease caused by one or more pathogens
- Use of laboratory tests, such as acute-phase reactants like procalcitonin, that to aid in clinical diagnosis, severity classification and assessment of appropriate treatment response in PCAP.
- Clinical, laboratory and epidemiological risk factors for severe PCAP, respiratory failure and hospitalization in the local setting
- Best imaging techniques that provide will high-quality diagnostic information with minimal radiation exposure
- Development and validation of a standard criteria for interpretation of chest radiographs in the diagnosis of PCAP
- Evaluation of the role of point-of-care chest ultrasonography (POCUS) as a diagnostic aid for PCAP in local setting
- Strengthening of antimicrobial resistance surveillance and reporting in the local and national levels and disseminate these data to guide local and institutional policy-makers of antimicrobial stewardship programs.
- Information on the lowest effective antimicrobial dose and shortest optimal duration of therapy to decrease risk of toxicity and development of resistance
- Role of antimicrobial therapy for atypical bacterial pathogens in PCAP particularly children <5 years of age.
- Assessment of the value of combination antimicrobial therapy for severe pneumonia, especially the addition of a macrolide in the regimen
- Impact of viral testing on patient outcomes and antibiotic prescribing behavior to avoid inappropriate use of antibiotic therapy.
- Use of clinical, laboratory, and oximetry parameters that will reliably assess the outcome of interventions for non-severe and severe PCAP
- Cost-effectiveness analysis of each diagnostic and therapeutic intervention for PCAP
- Standard discharge criteria required for children who continue to need antibiotics administered intravenously, intramuscularly, or orally
- Role of parenteral outpatient therapy for severe pneumonia and use oral antibiotics for severe bacterial PCAP in hospitalized patients



- Outcome of switch therapy in the management of severe PCAP
- Role of vitamin C and D in the treatment and prevention of PCAP
- Assessment of the value of adjunctive treatment (such as oral folate, probiotics, virgin coconut oil, steam inhalation, and nebulization with saline solution) in the management of PCAP
- Identification of non-clinical factors including psychosocial or behavioral concerns, socio-economic issues, likelihood of non-adherence to prescribed therapy, and other barriers medical care
- Analysis of medical costs in the management of PCAP, including non-medical costs such as lost parental income and family stress
- Long-term outcomes of children who had one or more episodes of PCAP