The Definition of Pneumonia, the Assessment of Severity, and Clinical Standardization in the Pneumonia Etiology Research for Child Health Study

J. Anthony G. Scott,[1,2] Chizoba Wonodi,[3] Jennifer C. Moïsi,[1,2,3] Maria Deloria-Knoll,[3] Andrea N. DeLuca,[3] Ruth A. Karron,[4] Niranjan Bhat,[3] David R. Murdoch,[5,6] Jane Crawley,[2] Orin S. Levine,[3] Katherine L. O'Brien,[3] Daniel R. Feikin,[3,7] and the Pneumonia Methods Working Group[a]

[1]KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya; [2]Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom; [3]International Vaccine Access Center, and [4]Center for Immunization Research, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [5]Department of Pathology, University of Otago, and [6]Canterbury Health Laboratories, Christchurch, New Zealand; and [7]Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

To develop a case definition for the Pneumonia Etiology Research for Child Health (PERCH) project, we sought a widely acceptable classification that was linked to existing pneumonia research and focused on very severe cases. We began with the World Health Organization's classification of severe/very severe pneumonia and refined it through literature reviews and a 2-stage process of expert consultation. PERCH will study hospitalized children, aged 1–59 months, with pneumonia who present with cough or difficulty breathing and have either severe pneumonia (lower chest wall indrawing) or very severe pneumonia (central cyanosis, difficulty breastfeeding/drinking, vomiting everything, convulsions, lethargy, unconsciousness, or head nodding). It will exclude patients with recent hospitalization and children with wheeze whose indrawing resolves after bronchodilator therapy. The PERCH investigators agreed upon standard interpretations of the symptoms and signs. These will be maintained by a clinical standardization monitor who conducts repeated instruction at each site and by recurrent local training and testing.

Despite the fact that pneumonia is the most common cause of serious illness and death in young children worldwide, our ability, as clinicians, to infer an infectious pathological process in the lung from specific features of the history and examination is poor. Many common conditions of childhood, including malaria, bacterial sepsis, and severe anemia, produce a spectrum of clinical symptoms and signs that overlaps significantly with pneumonia, and differentiating between these conditions is challenging [1–4]. In adults, the definition of pneumonia relies heavily on characteristic changes on the chest radiograph. However, many children who have suggestive clinical signs of pneumonia and who respond to appropriate antibiotics do not have any abnormalities on the chest radiograph taken at the onset of the illness; furthermore, radiological facilities are not always available in developing countries. In short, there is no single definition of pneumonia in childhood that is sensitive, specific, and can be widely implemented.

This article describes the clinical features and classifications available to define pneumonia in children and reports the rationale for the definition adopted by the Pneumonia Etiology Research for Child Health

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(PERCH) study and the process by which that definition was developed and is being standardized across the 7 PERCH sites.

CLINICAL CASE DEFINITION

At the outset, we identified 5 criteria that would guide the development of a clinical case definition for PERCH: (1) It should be acceptable to and understandable by the majority of healthcare personnel throughout the developing world; (2) it should capture the essence of the global public health problem of pneumonia, which leads to 1.6 million deaths worldwide each year [5]; (3) it should focus on children with severe pneumonia, to target a reduction in child mortality; (4) it should permit the findings of PERCH to bridge to published studies on pneumonia prevention and management over the last 30 years [6], and integrate with analyses of the global burden of pneumonia planned by the Child Health Epidemiology Research Group (CHERG) [7]; and (5) it should be reproducible within and between observers and within and between study sites.

Hospitalized Pneumonia

A key decision that needed to be made at the outset was how broadly to target pneumonia cases throughout the healthcare system. There is a compelling reason to begin by studying children in the community; the majority of pneumonia episodes are nonsevere and are managed in the community by healthcare workers (HCWs) at primary healthcare facilities. However, if the illness worsens, the child may progress through the hierarchy of the healthcare system from primary to secondary or tertiary care. At the same time, the etiology of pneumonia may also evolve, for example, from a viral upper respiratory tract infection to a viral lower respiratory tract infection and develop into a severe illness through superinfection of the lung by opportunistic colonizing bacteria. Studying children at all grades of severity would provide valuable insights into pneumonia pathogenesis.

However, the resources required to undertake a comprehensive etiology study at primary healthcare facilities, rather than referral hospitals, would be very considerable. The procedures used to define etiology, such as sputum induction, percutaneous lung aspiration, pleural aspiration, and gastric lavage, are not practicable without the support of an inpatient facility. The focus of the study is on severe and potentially fatal pneumonia, and the most efficient way to capture such patients is via hospital admissions.

World Health Organization Clinical Case Definition of Pneumonia

During the 1980s, pediatricians and public health physicians recognized that it was necessary to define, in terms easily memorable to primary HCWs, the clinical features that justified antibiotic use in children with potential pneumonia. A series of studies was undertaken in developing countries to examine the sensitivity and specificity of clinical symptoms and signs of pneumonia: these included a history of cough or breathlessness, inability to feed, raised respiratory rate, lower chest wall indrawing, fever, and tachycardia [8–12] (Table 1). In 1990, the World Health Organization (WHO) reviewed the available evidence and produced a guideline that has been the foundation of pneumonia detection in developing countries ever since (Supplementary Figure 1) [13, 14].

The WHO algorithm is applied to children who present with cough or difficulty breathing (Supplementary Figure 1). These were introduced as "signs" [13], suggesting that they are observed by HCWs, although in practice they are elicited more commonly as part of the clinical history from the parent. Fever was considered as a screening sign, but it lacked both sensitivity and specificity for pneumonia [13]. Once captured by the entry definition, the rest of the algorithm is based around 3 management decisions: (1) Children with pneumonia are treated with antibiotics, (2) those with severe pneumonia are referred to the hospital, and (3) those with very severe pneumonia are treated with oxygen therapy.

Integrated Management of Childhood Illnesses

With time, this definition was incorporated into the Integrated Management of Childhood Illnesses (IMCI) strategy [15], which provides triage and management guidelines at the primary healthcare level, and into the WHO guidelines for the management of children in hospital [16, 17]. It is therefore known and accepted throughout the developing world. Because it was incorporated into IMCI, the definition of very severe pneumonia was influenced by the "danger" signs of "very severe disease," an important concept for triage regardless of the underlying syndrome, and the features "lethargy, convulsions or impaired consciousness" were added, as was "vomiting everything." In addition, the original definition of pneumonia did not acknowledge the variation of clinical presentation with age, so head nodding, a mark of respiratory distress in young infants, was included and "unable to drink" was extended to include "unable to breastfeed."

The primary objective of the WHO clinical case definition was to capture the majority of cases of pneumonia for rapid treatment with antibiotics and supportive therapy to reduce childhood mortality. The assumption was that most severe pneumonia was bacterial in origin and that making antibiotics available to such children would save lives. Subsequently, a meta-analysis of 9 community-based trials using the WHO clinical case definition of nonsevere pneumonia confirmed that antibiotics reduced all-cause mortality by 24% among children <5 years [18]. This pragmatic perspective has led to a set of definitions that emphasizes sensitivity over specificity to achieve substantial public health gains.

Table 1. Studies of Childhood Pneumonia Contributing to the Formulation of the World Health Organization Clinical Case Definition

Study	Site	Sample Size	Gold Standard Pneumonia Definition	Clinical Signs/Symptoms Investigated	Conclusions Regarding Definition
Shann et al [8]	Goroka, Papua New Guinea	350	Crepitations on auscultation	Age, RR, lower chest wall indrawing, cyanosis, wheeze, pulse rate, palpable liver, temperature >37.5°C, feeds poorly	RR >50/minute was the most accurate way to differentiate pneumonia from nonpneumonia
Cherian et al [9]	Vellore, Tamil Nadu, India	682	Crepitations, wheeze, bronchial breathing, or radiological abnormalities	RR, parental report of rapid breathing, intercostal retraction	Refined the value of RR by age stratification to >50 for infants and >40 for children >12 months
Campbell et al [10]	Banjul, The Gambia	222 (episodes of illness in a cohort study)	Radiological signs (lobar consolidation)	Vomiting, rapid breathing, refusing to feed, chest indrawing, RR, nasal flaring, temperature, heart rate, crepitations, bronchial breathing or reduced air entry, rhonchi, grunting	Temperature >38.5°C, refusing to feed, and vomiting were the most useful predictors of severe pneumonia in infants, whereas temperature >38.5°C and RR > 60/minute were the most useful among children aged 1–4 years.
Mulholland et al [11]	Philippines, Swaziland	730	Complete history, physical examination by pediatrician, and CXR	Cough, difficult breathing, chest wall indrawing, RR. Cases with wheeze were excluded.	Sensitivity and specificity for RR >40/minute or for lower chest wall indrawing were between 0.77 and 0.81 in 2 different settings, but specificity was lower when judged by a healthcare worker.
Simoes and McGrath [12]	Mbabane, Swaziland	362	Pediatrician's assessment on WHO criteria	Cough, difficult breathing, ability to drink/feed well, convulsions, abnormal sleepiness, stridor, severe undernutrition, fever, wheeze, lower chest wall indrawing, tachypnea, fever	Using RR and lower chest well indrawing, nurses and nursing assistants detected 71%–83% of pneumonia cases with a specificity of 84%–85%.

Abbreviations: CXR, chest radiograph; RR, respiratory rate; WHO, World Health Organization.

WHO Radiologically Confirmed Pneumonia

It was obvious that each level of the hierarchy of the WHO clinical case definition had a low specificity and negative predictive value: a raised respiratory rate is observed in children with anxiety, anemia, sepsis, and reactive airway disease; lower chest wall indrawing may be observed in any condition that leads to tachypnea; and the danger signs incorporated in the very severe pneumonia definition apply to the "final common pathway" of a wide variety of pathogenic processes. In clinical practice, the disadvantage of a low negative predictive value was simply overtreatment. However, when it came to assessing the impact on pneumonia of new conjugate vaccines against *Haemophilus influenzae* type b (Hib) and pneumococcus, the low specificity of the WHO clinical case definition would have diluted the measured impact considerably. In response to this, the WHO undertook a parallel review to produce a case definition that was specific for pneumonia caused by these 2 principal bacteria. The definition selected was based on a common interpretation of chest radiographs [19]. In a trial in The Gambia, the measured efficacy of pneumococcal conjugate vaccine against WHO radiologically confirmed pneumonia was 37%, arguing that the specificity of the case definition was very high, particularly because the efficacy against all invasive pneumococcal disease was only 50% [20]. Although high specificity is desirable in any epidemiological inquiry, the WHO radiological definition was deliberately biased to capture bacterial pneumonia and would not serve well in an investigation of pneumonia etiology in general.

Refining the WHO Clinical Case Definition for Perch

The WHO clinical case definition is highly sensitive but lacks specificity. The WHO radiological definition is specific for Hib and pneumococcus but lacks sensitivity for other etiologies. Unfortunately, there are no clinicopathological data available to develop a case definition that lies more practically between these 2 extremes. Therefore, at the outset of the PERCH project, we selected the sensitive WHO clinical case definition. This would allow us to capture the full spectrum of pneumonia etiologies. It would also allow us to project our etiologic distribution to other studies (eg, CHERG) that have estimated the burden of childhood pneumonia using the same definition. The poor specificity of the definition means that some children without an infectious etiology (eg, paraffin ingestion, congenital heart disease) would be enrolled in the study and subsequently found not to have pneumonia. However, using the WHO clinical case definition would not only provide wide comparability to other studies and wide clinical experience, it may allow us to suggest refinements to improve its specificity.

The next step was to review the details of this definition against the purpose of an etiology study. The PERCH case definition was refined through an iterative process of presentation, criticism, and response during in-person meetings and teleconferences, first with a globally representative group of pneumonia experts, the Pneumonia Methods Working Group (PMWG) [21], and later with the investigators from the 7 sites. The final resolution of the case definition is shown in Supplementary Figure 2. The key areas of adaptation are summarized below.

CLINICAL SIGNS IN YOUNG INFANTS

Although the basic structure of the WHO clinical case definition has been fixed since 1990, there have been amendments and refinements that are reflected by subsequent WHO documents. For example, nasal flaring and grunting (in infants) are not consistently identified as part of the WHO definition of severe pneumonia [16, 17]. Within a multicenter study, we needed a constant reference definition; in the interests of parsimony and persuaded by the argument that children with these 2 signs would almost certainly be included on the basis of lower chest wall indrawing or yet more severe signs, we did not include them in the PERCH case definition.

The WHO clinical case definition applies to children aged 2–59 months, but the PERCH study aims to investigate children from 28 days of age. Children aged <2 months with pneumonia present with a broader spectrum of clinical symptoms and signs than older children [22, 23]. For the purposes of PERCH, we extrapolated the WHO case definition, including the requirement for cough or difficulty breathing, to children aged 29–59 days. Lethargy is difficult to define and assess in children in the second month of life so we adopted the following definition for this age group: "an infant who does not wake up on stimulation or, on waking, subsequently moves only on stimulation or does not move at all" [24].

Convulsions

The WHO classification defines children who present with cough or difficulty breathing and have convulsions as "very severe pneumonia." The PERCH site investigators argued that this would incorporate a significant number of children who presented with simple febrile seizures but had no underlying pneumonia. A febrile illness can lead to both difficulty breathing and a simple febrile convulsion. A febrile convulsion is a single seizure in a 24-hour period lasting <15 minutes in a child with a history of fever [25]. Within the WHO clinical case definition of very severe pneumonia, we refined the interpretation of "convulsions" to encompass 2 precisely defined events: (1) a single convulsion lasting for ≥15 minutes or (2) at least 2 convulsions within a 24-hour period during the current illness.

Wheeze

Lower chest wall indrawing may be caused by wheeze, which is common among young children in some regions and is itself

due to asthma, bronchiolitis, or occasionally bacterial pneumonia. The PERCH project is focused on pneumonia, not bronchiolitis or asthma; therefore, to optimize the proportion of children admitted to the study who have pneumonia as their underlying pathology, we introduced a filter based on the assessment strategy for wheeze recommended by WHO [17]. Children <2 years of age with lower chest wall indrawing and wheeze will be given at least 1 dose of a rapid-acting bronchodilator by inhaler, and children aged ≥2 years will be given 3 doses. Children whose lower chest wall indrawing resolves with this therapy, regardless of its effect on wheeze, will be excluded from the pool of severe pneumonia patients. In this definition, "wheeze" refers to a characteristic whistling sound on expiration that may be heard either on auscultation or on general examination of the child. Children who meet the criteria for very severe pneumonia will be included in PERCH, regardless of the presence or absence of wheeze.

The filter for wheeze is likely to remove children with reactive airways disease but will exclude only a minority of patients with bronchiolitis. The clinical presentation of bronchiolitis overlaps substantially with that of pneumonia and, because children with bronchiolitis can develop a complicating bacterial pneumonia, the treatment of bronchiolitis is similar to that of pneumonia; therefore, it is reasonable to include them within the scope of the project. They may be separated at the analysis stage on the basis of clinical characteristics (eg, wheeze, hyperinflation, and fine crackles on auscultation) and young age.

HOSPITAL-ASSOCIATED PNEUMONIA

In developed countries, the concept of hospital-associated pneumonia is well established. In developing countries, although data are extremely sparse [26], there is no reason to suppose that hospital-associated infections are any less common. The pattern of pathogens causing hospital-associated pneumonia is characteristically different from that causing community-acquired pneumonia, with greater representation of gram-negative bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and greater prevalence of multiple antibiotic resistance [27, 28]. The objective of the PERCH study is to provide etiologic information to guide prevention and treatment of community-acquired pneumonia, and we therefore modified the case definition to exclude children who have been admitted overnight to any hospital within the last 14 days.

A related problem is the development of pneumonia among children who have already been admitted to hospital. If this occurs 48 hours after admission, it is normally considered hospital-associated. However, some children who present at the early stages of an episode of pneumonia do not manifest all of the clinical signs necessary to diagnose the condition but develop them over the next 24–48 hours. This is a relatively infrequent occurrence and it would require considerably more resources to ascertain than a study targeted on the admission assessment. Furthermore, the project seeks to guide the *admission* management of community-acquired pneumonia, and these cases cannot contribute to that guidance. Therefore, we did not include them in PERCH.

CHRONIC PNEUMONIA

Children with chronic respiratory symptoms are likely to have a different spectrum of pathological processes. However, if their disease is sufficiently severe to warrant admission and to meet the definition of severe or very severe pneumonia, then acute pneumonia may be a component of their illness. The underlying etiology of this group may be different, and such differences will be drawn out in the analysis on the basis of length of history, but there are no exclusion criteria in PERCH based on the duration of symptoms.

EVALUATING THE SEVERITY OF PNEUMONIA

In a multisite study of etiology, geography is a key variable of interest. After accounting for variation in major risk factors, such as human immunodeficiency virus infection or sickle cell anemia, are there region-specific differences in etiological agents that provide additional clues about the epidemiology of the disease? One of the strongest confounders for this analysis is disease severity on admission, which may vary as a function of either hospital practice or health-seeking behavior. If one study site recruits less severe cases of pneumonia and another recruits only those in extremis, then the etiologic differences are likely to be due to the admission policy rather than to geographic location. To control for this, we aimed to define an index of clinical severity. The WHO clinical case definition provides only 2 grades—severe pneumonia and very severe pneumonia—and although these are associated with clinical outcome [29, 30], they provide a relatively coarse classification to control for a potential confounder. We considered several approaches to provide a finer grading.

The most efficient approach is to use an existing standard such as the British Thoracic Society guidelines, which classify children as having mild or severe pneumonia but also provide criteria for admission to hospital and for transfer to the intensive care unit [31]. Most of the features used to differentiate the strata are shared with the WHO clinical case classification. A finer differentiation would require considerably more clinical and laboratory data, but the published literature does not provide guidance on the optimal utility of such data.

A second approach is to focus on a single relevant parameter of clinical physiology, the oxygen saturation of the blood. Pulse

oximeters are readily available and widely used in developing countries. Hypoxemia has been extensively studied and is associated with a 2- to 5-fold increase in mortality [32–35]. However, a pulse oximeter may underestimate arterial oxygen saturation if it is incorrectly placed or if the patient has poor peripheral perfusion. In addition, whereas mortality in many cases of pneumonia is driven by poor oxygen exchange, it is not the only mechanism that can lead to death. Oxygen saturation will not accurately capture the degree of mortality risk among pneumonia cases that are threatened by, for example, septic shock, renal failure, or severe anemia.

The third approach we considered, and the one endorsed by the PMWG, was to collect all of the relevant clinical data available at each study site and use these data retrospectively to define a severity index by comparison against a gold standard such as fatal outcome. Such a modeling approach could also be extended to explore whether individual clinical features, or groups of features, are predictive of specific etiological causes, after accounting for severity. The PERCH study protocol included >50 clinical and laboratory variables, refined by PMWG review, which will be obtained on admission from every child. In addition, dynamic measures of severity, including pyrexia, respiratory rate, oxygen saturation, and oxygen requirement, will be obtained 24 hours and 48 hours after first assessment.

STANDARDIZING THE CLINICAL ASSESSMENT OF PNEUMONIA

A clinical case definition is of little value unless its component clinical features are elicited and interpreted with consistency, both between individuals and within individuals over time. In children in developing countries, the assessment of respiratory signs shows marked variation between different pairs of clinicians working in the same pediatric service [36], and the ability of HCWs to elicit "soft" signs (eg, lethargy) consistently is limited [12]. More pertinent, the κ score for interobserver variation among investigators in Tanzania for the key sign of lower chest wall indrawing was <0.4 [37]. Therefore, we considered it vital to adopt an active approach to the standardization of clinical assessment in PERCH.

First, we recruited a senior clinician with long experience of pediatrics in a developing country to design and lead the program as a clinical standardization coordinator. She began with a set of written and visual materials, focusing on the clinical symptoms and signs in the PERCH clinical case definition and on key severity markers (eg, measurement of oxygen saturation). The interpretation of clinical signs was then debated, amended, and finally endorsed by the site investigators. The coordinator visited each site immediately before initiation of the study and used a standard set of materials (with particular emphasis on video and sound recordings) to train all staff involved in clinical assessment or clinical specimen sampling. Lectures were supplemented by clinical case scenarios and practical ward-based sessions. Every participant was tested for competency at the end of the training. Each site appointed 1 or more local clinical standardization monitor(s), who participated actively in the startup training and established a local program of monthly refresher training. The original standardized teaching materials, available to all staff on a clinical standardization Web site, accessed through the PERCH sharepoint, were used for both refresher training and the training of new clinical staff. Every 3 months the coordinator posts an evaluation on the Web site, comprising multiple choice questions and new video recordings of key clinical signs for interpretation, which permits comparison of the performance of clinical staff at each site, as well as cross-site comparisons. Results of evaluations are also used to guide the content of subsequent refresher training and to identify individuals or sites in need of increased support. Through monitoring of case record forms, the relative frequency with which clinicians at the same site diagnose severe or very severe pneumonia is used to alert the coordinator to possible discrepancies in the local clinical standardization process. The initial standards will be reinforced by a second training visit by the coordinator during the first year of the study.

CONCLUSIONS

PERCH uses a constellation of clinical symptoms and signs to define the syndrome of severe or very severe pneumonia in hospitalized children aged 1–59 months. Any syndromic focus inevitably simplifies the complex interaction of acute disease and underlying risk factors that influence morbidity and mortality in the developing world. Pneumonia occurs against a background of nonpulmonary risk factors or chronic lung disease; it varies in severity and duration; and the unique nature of its clinical characteristics is shaped by the epidemiology of other diseases (especially malaria) and by the patterns of health-seeking behavior, which vary markedly by region. We recognize that the PERCH case definition excludes important parts of the spectrum of childhood pneumonia, such as nonsevere pneumonia, nonhospitalized pneumonia, pneumonia in older children and neonates, and hospital-associated pneumonia. However, by anchoring the study in a widely recognizable clinical case definition, formulated and refined by WHO over 2 decades, and by focusing on an age group (1–59 months) that bears the brunt of pneumonia mortality, PERCH will yield comparable results from a wide spectrum of epidemiological settings that can be linked to the broad existing literature on childhood pneumonia and to current models of the global burden of childhood diseases.

Supplementary Data

Notes

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