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SUPPLEMENT ARTICLE

A Literature Review and Survey of Childhood Pneumonia Etiology Studies: 2000–2010

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The Pneumonia Etiology Research for Child Health (PERCH) project is the largest multicountry etiology study of childhood pneumonia since the Board on Science and Technology in International Development studies of the 1980s. However, it is not the only recent or ongoing pneumonia etiology study, and even with seven sites, it cannot capture all epidemiologic settings in the developing world. Funding providers, researchers and policymakers rely on the best available evidence to strategically plan programs, new research directions and interventions. We aimed to describe the current landscape of recent pneumonia etiology studies in children under 5 years of age in the developed and developing world, as ascertained by a literature review of relevant studies with data since the year 2000 and a survey of researchers in the field of childhood pneumonia. We collected information on the study population, study design, case definitions, laboratory samples and methods and identified pathogens. A literature review identified 88 studies with child pneumonia etiology results. As of June 2010, our survey of researchers identified an additional 65 ongoing and recently completed child pneumonia etiology studies. This demonstrates the broad existing context into which the PERCH study must be placed. However, the landscape analysis also reveals a multiplicity of case definitions, levels of clinician involvement, facility types, specimen collection, and laboratory techniques. It reinforces the need for the standardization of methods and analyses for present and future pneumonia etiology studies in order to optimize their cumulative potential to accurately describe the microbial causes of childhood pneumonia.

Each year, approximately 1.6 million children die from pneumonia [1]. The Pneumonia Etiology Research for Child Health (PERCH) study is the largest multisite study of childhood pneumonia since the Board of Science and Technology for International Development (BOSTID) studies were done in the 1980s [2]. The goal of PERCH is to identify the expected etiologies of pneumonia in 2015, a time when the burden of the major causes of bacterial pneumonia in the developing world, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), will likely be significantly reduced by widespread introduction and use of conjugate vaccines. Moreover, PERCH capitalizes upon new molecular diagnostic techniques that were not available 2 decades ago when the BOSTID studies were carried out. Another salient difference between PERCH and the BOSTID studies is that the 7 sites participating in PERCH will follow a highly standardized protocol, which includes standardization of enrollment criteria, specimen collection, and laboratory testing.

Although PERCH is the largest multicountry, childhood pneumonia etiology study in developing countries that has been conducted in the past 2 decades, it is not the only contemporary pneumonia etiology study, and cannot capture the entire complexity of all epidemiologic settings. In recent years, many developed and developing country sites have initiated pneumonia studies that provide etiology data. These studies will

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provide useful complementary data to the PERCH study that will more fully define and characterize the causes of childhood pneumonia throughout the world. Yet, because the clinical, laboratory and statistical analysis approaches of these studies vary significantly, collating the results of multiple etiology studies will likely prove challenging. Differences in observed etiology can arise not only from epidemiologic differences in the sites and populations studied, which are biologic and epidemiologic attributes relevant to public health decision making, but also from variability in study design. Consideration of how study design can affect the results of etiologic studies is crucial to interpreting such studies in the context of PERCH.

In this paper, we describe the global landscape of sites that are currently studying pneumonia etiology or have recently studied it in the developed and developing world as ascertained by a literature review of studies with data since the year 2000 and a survey of pneumonia researchers. We did not aim to conduct a systematic review of the literature or a meta-analysis of study results. Furthermore, we did not undertake a critical evaluation of the methods or results from the studies we identified. The purpose of this project is limited to a landscape analysis to better describe the breadth of available data on child pneumonia etiology.

METHODS

Literature Review

We conducted a literature review to identify studies with pneumonia etiology data. All searches were conducted in June 2010 using the PubMed database and entering search terms that were key words, MeSH terms, synonyms or truncations. Eight separate search strategies were conducted. Titles and abstracts were screened to identify potential studies with pneumonia etiology data in children under five years old. Eligible studies were abstracted by two trained abstractors (ZG, YDK). Information abstracted included study population, study design, case definitions, body fluid samples, laboratory methods and identified pathogens. The studies were grouped by category, and summary statistics were described using Stata version 10 (College Station, TX); no statistical testing was undertaken on the data.

The inclusion criteria for studies were as follows:

- Study of acute community-acquired pneumonia or acute lower respiratory tract infection (ALRI).
- Consistent testing for at least one specific etiology in enrolled patients.
- Enrollment of children <5 years old (can also include older persons).
- Published between June 2005 and June 2010.
- Data collection from the year 2000 onwards.
- ≥ 10 pneumonia/ALRI cases.
- ≥ 1 calendar year of surveillance.
- English language.

The exclusion criteria were as follows:

- Exclusive enrollment of bronchiolitis patients.
- Exclusive enrollment of patients with a specific complication or sequelae of pneumonia (eg, empyema or parapneumonic effusions).
- Inability to distinguish the etiology of pneumonia cases from other syndromes (eg, pneumonia cases within a study of invasive pneumococcal disease).
- Etiology inferred from the upper airway carriage alone.
- Focus only on antibiotic resistance among pneumococcal isolates.
- Exclusive enrollment of hospital-acquired pneumonia patients.

Our aim was to identify sites and studies, not publications. When more than one publication was identified from the same study, we designated the publication with the most comprehensive etiology results or methodology details, longest surveillance period, or the oldest reference, as the ''main publication.'' Results from additional publications supplemented data when possible. When publications referred to a particular surveillance network that included sites in multiple countries, we included a result for the entire surveillance network and individual results for each country if they were published separately.

When studies encompassed other disease syndromes other than pneumonia, such as meningitis and sepsis, we limited results to pneumonia-specific information when possible. Clinical trials were only included if they described methods for etiological diagnoses.

Survey of Pneumonia Researchers

A Web-based survey of researchers who may have conducted pneumonia etiology research was created to capture information regarding unpublished ongoing and recently completed pneumonia etiology studies among children less than five years old (Survey Monkey, Palo Alto, California). This survey was circulated by email on 12 April 2010 to approximately 5000 pneumonia community members that belonged to the email address list of PneumoFOCUS [3], a monthly bulletin providing news about pneumonia, pneumococcal disease, and pneumococcal vaccines that is written and produced by our team at Johns Hopkins School of Public Health. We also contacted researchers who had submitted letters of intent in response to the PERCH Request for Proposals (RFP) for sites, researchers at sites selected to be part of the PERCH study, other known pneumonia surveillance researchers (eg, US Centers for Disease Control and Prevention's International Emerging Infection Program sites) and researchers identified through word of mouth. We individually contacted researchers to clarify and confirm certain responses. We followed up by email with known

pneumonia researchers if they did not respond to our initial survey request.

The survey included questions about the study population, study design, case definitions, body fluid samples, laboratory methods, and identified pathogens. Separate surveys were filled out for each study if more than one study took place in a given geographic site. The studies were grouped by category and summary statistics were described; no statistical testing was undertaken on the data.

RESULTS

Literature Review

Of 2511 titles and abstracts reviewed, 2311 were excluded because they did not meet eligibility criteria. The full text of 200 publications was reviewed, and 88 studies with child pneumonia etiology results were included [4–10] [11–18] [19–25] [26–30] [31–38] [39–43] [44–51] [52–61] [62–71] [72–80] [81–91]. Studies ranged in size from 10 to 21 239 pneumonia patients (median 260 patients). We identified studies in 52 countries (Supplementary Figure 1). Multiple studies were done in 26 countries. Of these, 8 studies were identified in the United States; 7 in each of Bangladesh and India; 6 in Thailand; 5 in South Africa; 4 in each of Brazil, Philippines and Taiwan; 3 in each of China, Hong Kong, Kenya, Korea, Japan, Nepal, Nigeria, and Vietnam; and 2 in each of Argentina, Ethiopia, Finland, Guatemala, Italy, Mexico, Mozambique, Pakistan, Yemen and Zambia. Three studies (3%) in 5 countries (Brazil, Costa Rica, El Salvador, United States and Zambia) reported collecting postmortem specimens [29, 31, 69], and 5 (6%) in 10 counties (Bangladesh, Ecuador, the Gambia, India, Malawi, Mexico, Nigeria, Pakistan, South Africa and Yemen) reported collecting lung aspirates [11, 26, 35, 51, 63]. Seven studies used asymptomatic controls [6, 17, 19, 30, 79, 83, 89]. Additional study characteristics are summarized in Supplementary Table 1.

Survey

We received 81 responses to the survey. A total of 65 studies were identified once we removed responses that did not meet our study criteria. Of the 16 studies excluded from analysis, the reasons for exclusion were the following: the study was not a pneumonia etiology study, the study did not include children less than five years of age or multiple responses were received describing the same study. Studies ranged in size from 12 to 27 778 pneumonia patients (median 780 patients). Among the 65 pneumonia etiology studies, 41 countries were represented (Supplementary Figure 1). There were 16 countries that reported multiple studies. Of these, 6 studies were being conducted in Bangladesh; 5 in each of Brazil, India and Nepal; 4 in Indonesia; 3 in each of Kenya, Mozambique, South Africa, the United States, Australia, Thailand and Spain; and 2 in each of Jordan, Guatemala, China and Israel. Two studies reported that they obtained approval to collect postmortem specimens in their protocols, but neither site had collected any postmortem specimens as of March 2011. Additional study characteristics are reported in Supplementary Table 1.

DISCUSSION

The results of the literature review and survey reveal that many child pneumonia etiology studies have been and are taking place throughout the world since the year 2000, which enable an understanding of PERCH data in the context of a global landscape of ongoing pneumonia research. The large quantity and great depth of the available data highlight the challenges in interpreting various pneumonia etiology studies, particularly when comparing or combining results. Different studies employ different case definitions, levels of clinician involvement, facility types, specimens collected and laboratory tests. The use of a common protocol in a multisite study with broad geographic and epidemiologic representation will enable inferences to be drawn about the similarities and differences from other studies.

Our landscape analysis identified several gaps in the availability of data regarding childhood pneumonia etiology. First, there were few studies identified in Latin America (outside of Brazil, Chile and Argentina), in west and particularly central Africa, and in the Middle East. No studies were identified from Russia or China. This gap may be due in part to our English language inclusion criterion. It is important to have data from places where child pneumonia mortality is the highest [92]. South Asia and parts of Africa, which are regions of the world with the greatest burden of childhood pneumonia deaths, are well-represented in pneumonia etiology studies. Nonetheless, the 5 countries with the highest burden of child pneumonia deaths—India, Nigeria, Pakistan, the Democratic Republic of Congo (DRC) and Afghanistan [1]—are not proportionally represented in our literature review. Our literature review identified only 7 studies conducted in India, 3 in Nigeria, 2 in Pakistan and none in the DRC or Afghanistan. Second, there needs to be more pneumonia etiology studies in countries that have or are currently introducing both the Hib and pneumococcal conjugate vaccines. Such studies will help define the new distribution of pneumonia-causing etiologies in these settings, which will likely have important implications for diagnosis and empiric treatment algorithms. Third, there are few studies that report postmortem results. It is important to understand the spectrum of etiologies for the most severe cases of pneumonia, which will be critical in reducing the still high burden of childhood pneumonia mortality in the world [93]. Although

technically and culturally challenging, postmortem studies reveal a different and complementary picture of etiology that is otherwise underestimated or forgotten. This applies particularly to tuberculosis, HIV-associated conditions (eg, lymphocytic interstitial pneumonia, *Pneumocystis jiroveci (carinii)* pneumonia and cytomegalovirus disease), and to other pathogenic processes that produce a clinical syndrome that mimics pneumonia (eg, severe anemia with heart failure or interstitial lung disease).

Variation in the methods employed by different pneumonia etiology studies can lead to differences in the identified etiologies. For example, the case definition used can influence the distribution of microbial etiologies. Case definitions based on radiologic (eg, alveolar consolidation) and laboratory definitions (eg, left-shift of polymorphonuclear neutrophils) are likely to identify more bacterial than viral pneumonia cases. Alternatively, a simple clinical case definition based on tachypnea (eg, nonsevere pneumonia defined by the Integrated Management of Childhood Illness) or a definition that included wheeze might lead to the identification of relatively more viral infections. Given the association between clinical severity and etiology, the target population and facility type can also determine the spectrum of etiologies. Thus, studies in community-based settings, health centers or outpatient wards may find different ranges of etiologies than studies in referral hospitals. Age is an influential variable and studies that exclude older children and focus on infants are likely to identify more RSV infection, which predominates in infancy. Neonates, in particular, have a distinct set of pneumonia pathogens [92, 94].

Other factors that varied across studies were the type of body fluid specimens collected and the type of laboratory testing done. Detection of bacterial pneumonia is dependent to a large extent on blood culture. While a majority of studies performed blood culture, it is likely that there was considerable variation in the sensitivity of the tests, particularly for *Streptococcus pneumoniae*, which is a fastidious organism requiring optimal collection and laboratory conditions. There are other factors that may result in an over-representation of viral causes of pneumonia. It was notable that the use of PCR as a diagnostic tool was higher in the studies reported on the survey (68%) than in those already published in the literature (46%). As molecular diagnostics become more widely used, it will be important to disaggregate temporal trends in the epidemiology of viral pneumonia from trends in laboratory practice. The findings of PCR testing of nasopharyngeal and oropharyngeal swabs will need to be interpreted judiciously. The presence of viral nucleic acids in the pharynx does not necessarily mean that the virus is acutely causing pneumonia in the lungs [79, 95]. As PCR use increases, strategies must be used to help interpret these findings. One such strategy is to include control children (ie, those without pneumonia) in whom similar body fluids are collected and tested, which will allow for improved ability to interpret the PCR results [95].

Our landscape analysis had several limitations. In spite of employing multiple search strategies, we likely missed identifying some studies. Of note, we only searched the English language literature and only utilized one literature database (PubMed). This likely biased our findings by excluding studies from certain geographic regions such as China, Spanish-speaking Latin America, Russia and the Middle East where there may be a substantial body of evidence in local language publications. We did not search Embase and thus did not include conference abstracts unless researchers directed us to specific abstracts. Second, some published studies lacked sufficient detail to provide information on particular aspects of the study design that were of interest. Notable missing data were case definitions, facility types, and eligibility determination. Our survey likely suffered from similar limitations as far as incompleteness of data that was provided for some studies. Similarly, we only reached out to researchers who were already identified in the field, which might have led to gaps in those contacted. Third, not all identified studies were intended to be pneumonia etiology studies. Several had other primary objectives, such as to study invasive pneumococcal disease or influenzalike illness, and in that process identified children with pneumonia. As such, these studies are by design not comparable to studies that identify multiple pneumonia pathogens in that their case definitions and patient mix would likely differ. Finally, we were unable to verify survey responses.

In conclusion, the review of the literature and the survey of studies illustrate the context within which the PERCH study will be interpreted. Pneumonia etiologies are likely to continue to evolve as more countries introduce Hib and pneumococcal conjugate vaccines. Vaccines for other major causes of childhood pneumonia such as influenza will likely become more widely used across the globe or may be successfully developed (eg, RSV) over the next decade, and therefore, will further influence the pneumonia burden and remaining etiologies. Improvement in global socioeconomic conditions will also influence the pneumonia etiologic spectrum in the future. One of the goals of PERCH is to create a reference standard for the design, conduct and analysis of pneumonia etiology studies. This will provide a framework within which valid between-site comparisons can be drawn and integrated models can be extended geographically. PERCH will also contribute to a refinement of the case definition of pneumonia and provide evidence for the utility of certain body fluid specimens and laboratory tests. We hope that the definition of a standard, and the publication of the validation processes that were undertaken to create that standard, will encourage investigators to analyze existing studies and design future

studies with reference to this standard in order to optimize the epidemiological value of the results.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the authors that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the authors.

Notes

Disclaimer. The findings and conclusions are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

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