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Introduction to the Epidemiologic Considerations, Analytic Methods, and Foundational Results From the Pneumonia Etiology Research for Child Health Study

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PNEUMONIA MORTALITY REDUCTIONS OF PAST 3 DECADES

Over the last 20–30 years, enormous reductions have occurred in the absolute and relative burden of pneumonia mortality in young children around the world. Only 20 years ago, when the population of young children was approximately 625 million, approximately 1.7 million young children died from pneumonia before their 5th birthday (Figure 1) [1–4]. Mortality from pneumonia among children aged <5 years fell to 921 000 in 2015, whereas the population of young children rose to >670 million [1, 2, 5]. This remarkable improvement in child survival and health has resulted from advances in social conditions and economic development [6] but has also been influenced by at least 4 pivotal innovations: (1) the development of a global vaccination program, the World Health Organization's Expanded Program on Immunizations (begun in 1974), which created the architecture around which country investments, donor funding, program strategies, and outcome measurements could be envisioned and implemented; (2) the global consensus to focus funding, programs, and momentum on 6 development targets articulated by the United Nations General Assembly through the Millennium Development Goals (MDGs, agreed upon in 2000)

with MDG4 targeting child survival; (3) the advent of large, health-focused nongovernmental organizations; and (4) the founding of the Global Alliance for Vaccines and Immunization (the Gavi Alliance, formally launched at the World Economic Forum in January 2000), a multilateral funding organization that has allowed for an unprecedented pace of introduction and expanded use of life-saving vaccines in low-income countries. In part, as a result of this multidimensional, multisectoral consensus approach enacted through critical large-scale investments in prevention, protection, and treatment, pneumonia mortality has fallen substantially in many parts of the world because the most fatal of the pathogens and the underlying conditions that put children at risk are being targeted.

NEW EVIDENCE BASE NEEDED TO REDUCE PNEUMONIA BURDEN FURTHER

Over the past 3 decades, much effort has been placed on developing, licensing, introducing, and optimizing coverage with new vaccines and on developing and implementing evidence-based case management strategies for childhood pneumonia. More recently, the focus has extended to reducing the underlying conditions that put children at risk of pneumonia mortality, including reducing human immunodeficiency virus (HIV) infection through prevention of mother-to-child transmission, preventing and treating malnutrition and undernutrition, reducing household and outdoor air pollution exposure, and ensuring that prevention and treatment services are accessible when and where they are needed. The reduction in pneumonia burden over the last decades has not been equal
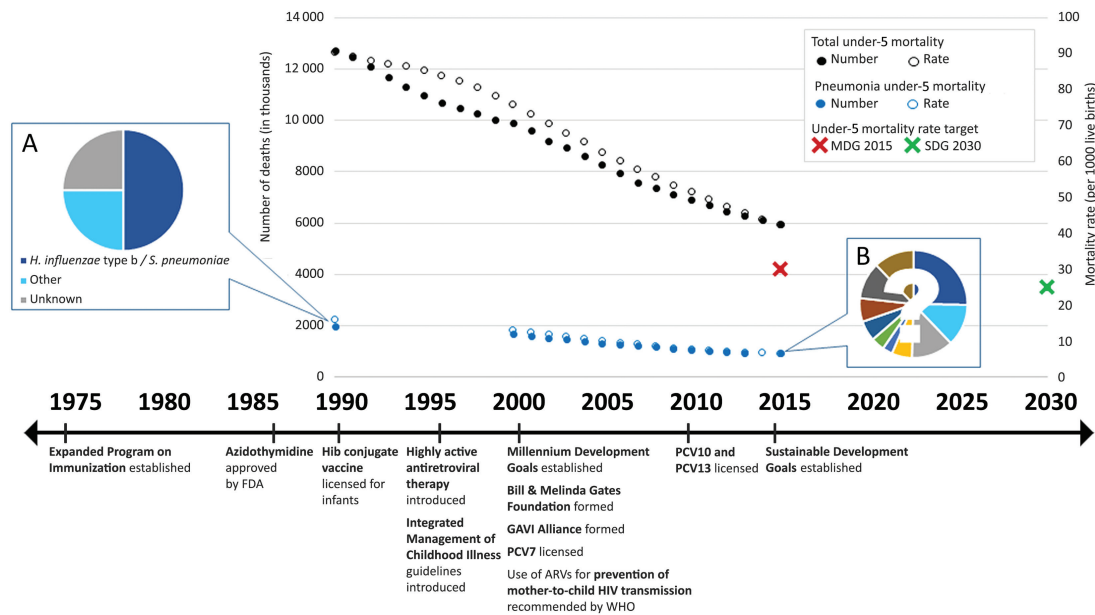
Figure 1. Annual under-5 all-cause and pneumonia mortality rates with global targets and pivotal health interventions, by time. *A*, The conceptual pneumonia mortality etiology distribution from the preconjugate vaccine era and *B*, the unknown etiologic distribution of the present and future. Abbreviations: ARVs, antiretrovirals; FDA, US Food and Drug Administration; Hib, *Haemophilus influenzae* type b; MDG, Millenium Development Goal; PCV, pneumococcal conjugate vaccine; SDG, Sustainable Development Goal; *S. pneumoniae, Streptococcus pneumoniae*; WHO, World Health Organization.

across all pathogens, countries, populations, or communities within countries. Selected pathogens have been targeted by vaccines (eg, *Haemophilus influenzae* type b [Hib], pneumococcus, measles, pertussis), and childhood disease burden from these pathogens has therefore been reduced disproportionately compared with other pathogens. Consequently the current etiologic distribution of pneumonia-causing pathogens is not just a smaller replica of the etiologic distribution from 20–30 years ago. With pneumonia still the leading cause of childhood deaths, the importance of quantifying and characterizing the contribution of pathogens causing those deaths is key (Figure 1).

Furthur advancing the reduction of pneumonia burden among young children means moving beyond the "low-hanging fruit" interventions. Innovation is needed not only to maintain the pace of pneumonia mortality reduction of the past decade but also to accelerate that pace, with the aim of achieving global targets for health [7]. With 48% of pneumonia deaths occurring in 5 countries in Asia and Africa (India, Nigeria, Pakistan, Democratic Republic of Congo, and China), which together account for only 41% of the world's population aged <5 years [1, 2], an understanding of geographic variability in pneumonia is also important.

Motivated by this global vision for accelerating the pace of change, and recognizing that to achieve that vision advances would be needed in pneumonia prevention and control, a simple question was posed to the technical community by the Bill & Melinda Gates Foundation several years ago. In a world where existing tools to reduce pneumonia mortality have been deployed,

including the introduction and widespread use of available vaccines, what will be the remaining causes of pneumonia and targets for prevention and treatment? The answer to this question will inform investments in tools needed to create an accelerated downward inflection in the pneumonia and child mortality rates and achieve the goals set by the world for child survival.

ETIOLOGY OF PNEUMONIA MORTALITY IN A NEW ERA

An expert consultation on pneumonia, convened by the Bill & Melinda Gates Foundation in 2007, recommended that a large-scale study of pneumonia etiology be conducted, focusing on severe pneumonia as the closest proxy for pneumonia mortality. The Pneumonia Etiology Research for Child Health (PERCH) study was commissioned to address this recommendation; its goal is to characterize the etiology of serious pneumonia in young children in geographic settings that would provide a robust evidence base for strategies to accelerate reductions in pneumonia morbidity and mortality, particularly for children in sub–Saharan Africa and south Asia. PERCH enrolled >4000 cases and >5000 controls in 7 countries (Figure 2) and is likely the most comprehensive study of the causes of pneumonia in young children yet undertaken. The study has brought together the expertise and advice of dozens of investigators from around the world. The epidemiologic basis, strategic decisions, and study methods for the PERCH case–control study were published as a supplement in 2012 [8].
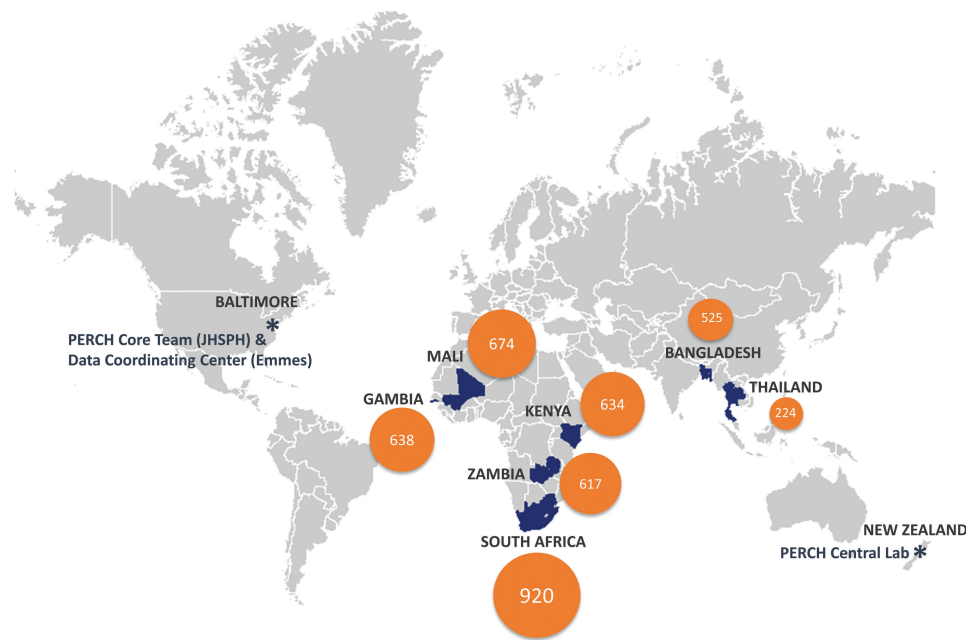
Figure 2. Countries where Pneumonia Etiology Research for Child Health (PERCH) study sites are located, and case enrollment numbers. Abbreviations: Emmes, The Emmes Corporation; JHSPH, Johns Hopkins Bloomberg School of Public Health.

The fundamental and vexing problem in pneumonia etiology work is that we cannot usually sample the tissue where the disease occurs: the lung. This contrasts sharply with the other global public health targets, including diarrhea, measles, malaria, and HIV. For pneumonia, we are stuck collecting and testing samples from multiple body fluids that are contiguous with, but distant from, the site of infection or from body fluids that are a proxy for the site of infection. Pneumonia etiology studies require analytic approaches that can integrate data from multiple sources through sound epidemiologic and statistical methods, which produce valid insights into etiology. In addition to the challenges of specimen collection, there is also imperfect understanding of the likelihood of single-pathogen versus multi-pathogen infections in the pathophysiology of pneumonia, making the validity of assumptions necessary for the analysis of pneumonia etiology data uncertain. Beyond the inability to collect specimens from the site of infection, pneumonia studies lack a clinical case definition that is both highly sensitive and specific, meaning that pneumonia studies will either miss substantial groups of children with pneumonia or will include substantial numbers of children who do not have pneumonia.

This study differs qualitatively and quantitatively from previous pneumonia etiology studies. The efforts to standardize and integrate the clinical, laboratory, epidemiologic, and analytic approaches and data management have been a cornerstone commitment of the project. That is not to say that this study is without limitations because no amount of analysis can fully overcome the challenges inherent in pneumonia research.

CONTEXT, METHODS, AND PREPARATORY RESULTS FROM PERCH

With the articles in this supplement, we begin reporting the findings from PERCH. These articles fall into 3 categories: context, methods, and preparatory results. We provide results from specimens and tests that had not been part of standard pneumonia etiology assessments before (eg, polymerase chain reaction [PCR] density of detected pathogens in the nasopharynx, induced sputum results, C-reactive protein) to assess their inferential value. These articles also aim to provide transparency on the critical quantitative decisions we have made along the path toward the primary etiologic analysis. Several of the articles describe efforts to navigate the fundamental problem of being unable to sample the lung directly.

Context Articles

These articles offer insights into the pneumonia etiology field leading up to the PERCH study and therefore the context within which the methods and results should be considered. The history of pneumonia etiology article [9] walks through the advances and, on occasion, the retreats made in etiology studies over the past century. Our reflections and analysis contextualize why the PERCH study was designed as it was and the vexing limitations that we aimed to overcome through its design. Over the past 100 years of pneumonia etiology work, several analytic approaches have been used, each with their own benefits and limitations, which we organize and interrogate to provide a context for the analytic approaches needed for PERCH [10]. The specific issue of determining the appropriate control group for

the primary analysis was also carefully considered, especially the biases that would be introduced with the inclusion or exclusion of control subjects with respiratory symptoms [11].

Methods Descriptions

Next we provide methods articles, which describe the implementation of the study protocol and analytic approaches that were essential for the use of the pneumonia etiology data. PERCH was committed to conducting all analyses in a fully standardized way across all 7 countries, using the same protocols, methods, equipment, and reagents so that etiology differences across geographies cannot be explained by heterogeneity in methods. Laboratory testing procedures and assessment of the clinical data were measured in as standardized a way as possible across all sites, which included extensive on-site training and monitoring [12, 13]. The chest radiographs formed a key element of the case definition for the case–control analysis. Standardized reading processes are described, along with their degree of concordance in reading [14]. The lessons and methods used in a large, observational, multicountry, multi-investigator study can help future studies adopt and further advance best practices, so in the data management article we provide a full description of the approaches we took to assure the quality of the PERCH data, including reductions in misclassifications, errors, and missing data [15]. To address the limitations of existing analytic methods, we developed a new partial latent class, Bayesian analytic approach that allows for the integration of microbiologic results from multiple body fluids and multiple tests for a single pathogen and incorporates adjustments for sensitivity and specificity. The model has been described in the statistical computational literature [16, 17], and here we provide a description of the approach from an epidemiologic perspective [10] and an analysis of the advantages conferred by the new approach [18].

Preparatory Results

Finally we provide articles that report results from PERCH cases and controls on issues that are relevant to pneumonia etiology studies generally but also inform decisions that were needed for the PERCH main etiology analysis. These results are not unique to the study settings involved but are generalizable and applicable beyond PERCH to other pneumonia diagnostics efforts. For example, induced sputum analysis, including for tuberculosis [19–23], and pathogen density measurement [24–26] are 2 strategies that aspired to approximate more closely testing for the pathogen infecting the lung. Because blood culture for bacterial pneumonia detection is poorly sensitive, we aimed to understand the impact of pretreatment with antibiotics and specimen volume on sensitivity, which is critical for analytic adjustments [27]. To increase the sensitivity of these bacteremic detections, we assessed the value of whole-blood molecular testing on cases and also on controls to quantify the limitations of this new diagnostic test in determining etiology

[28, 29]. In addition, biomarkers like C-reactive protein may help distinguish bacterial from nonbacterial causes of pneumonia [30]. Chest radiograph findings are critical for characterizing the enrolled cases across the different sites and for identifying the cases confirmed to have pneumonia syndrome. The results of the chest radiograph reading process designed to minimize misclassification and the descriptive findings among the cases, by site and case severity, are therefore key to the interpretation of the results from the main etiology analysis [31].

CONCLUSION

The PERCH study has faced a series of critical decisions about how to handle numerous data elements, and we have been committed to basing those decisions on evidence rather than on dogma or anecdote. By clearly showing, through these articles, the evidence and rationale for the decisions we made, we hope to minimize the potential pitfalls of arbitrariness or bias in deriving overall etiologic results in our study and for others. We also aimed through these preparatory analyses to remove the "black box" that can obscure the approach to and analysis of complex data.

By publishing these articles on the context, methods, and preparatory results from PERCH, we hope to provide the pneumonia community a seat at the analytic table. We aim to provide transparency in our lines of thinking, in our interrogation of the data to inform the decisions necessary for a comprehensive analysis of pneumonia etiology, and in our inferences about what these data teach us about a complex biologic condition.

on the core team to collect the data, test the specimens, and analyze the results with scrupulous attention to detail ensure the integrity of the new knowledge from this study.

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