Rationale and expectations of the Pneumonia Etiology Research for Child Health (PERCH) study

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The Pneumonia Etiology Research for Child Health (PERCH) project is an ambitious attempt at improving our understanding of the changing etiology of pneumonia given increasing access to effective vaccine utilization against the two major bacterial pathogens of pneumonia in children and recent advances in general child survival strategies [1].

Pneumonia is the leading global killer of children under the age of 5 years, with an estimate of 1.575 million deaths in 2008 [2], accounting for one in five deaths in children under 5 years of age. More than 155 million new episodes of clinical pneumonia occur in children under 5 years of age annually with 97% of these in the developing world [3]. Childhood pneumonia deaths are declining since the last decade [2,4] following intensified global efforts to increase access to effective vaccination and treatment management, but pneumonia is still an important cause of serious pediatric illness and will remain so in the nearest future.

Pneumonia has remained the ‘forgotten killer of children’ for several decades owing to its apparent lack of attention and funding [5]. Reducing the burden of pneumonia mortality is essential to reaching the Millennium Development Goals (MDGs), and the Bill & Melinda Gates Foundation is pursuing a number of initiatives aimed at reducing childhood mortality and morbidity due to pneumonia, from diagnostics to vaccines and epidemiology to economics, and evaluation of innovative antimicrobial treatment options.

Pneumonia is a syndrome but it is yet unclear what pathogens are responsible for a large fraction of pneumonia deaths, which creates an important knowledge gap. The leading risk factors contributing to pneumonia incidence are lack of exclusive breastfeeding, undernutrition, exposure to indoor air pollution, low birth weight, crowding and absence of immunization. In countries with weak health systems and limited access to care, far too many of the cases of severe pneumonia progress to death. In order to achieve the MDG 4 child health target of reducing pneumonia mortality by two-thirds between 1990 and 2015, it will be essential to scale-up the use of the available tools for prevention and treatment, as directed by the 2010 World Health Assembly resolution calling for more concerted efforts toward protecting children from pneumonia [6].

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Early etiology studies identified Streptococcus pneumoniae and Haemophilus influenzae type B (Hib) as the main bacterial pathogens associated with severe and/or fatal childhood pneumonia [7,8]. A more representative epidemiology study covering Asia, Africa and Latin America...
initiated by the Board of Science and Technology for International Development (BOSTID) at the US National Academy of Sciences in the early 1980s also identified pneumococcus and Hib as major bacterial causes of childhood deaths due to pneumonia [9]. These studies made important contributions to the development and implementation of prophylactic vaccines and treatment strategies for these agents. Despite their success, there were certain limitations to the BOSTID studies, including the lack of standardization of case definitions, insensitive diagnostics and the challenges with ascertaining pneumonia causality.

The result is the need to establish an etiologic diagnosis by considering multiple possible etiologies (exposures) as the cause of the pneumonia episode.

PERCH is a large, multicenter, case–control study to determine the etiology of pneumonia among children of less than 5 years of age. It is a 5-year study covering seven countries – five in Africa and two in Asia – that is designed to address some of the major limitations of past studies and to anticipate the prevailing epidemiologic patterns of the future. Seven research sites have been selected based on technical capacity, local epidemiology, demographics and status of Hib and pneumococcal conjugate vaccine immunization.

The PERCH project is sponsored by a grant from the Bill & Melinda Gates Foundation to the International Vaccine Access Center at the Johns Hopkins Bloomberg School of Public Health. The study will be carried out using standardized methods, collecting novel or uncommon specimens (e.g., induced sputum and post-mortem lung tissue) and applying advanced diagnostic techniques to address the potential for multiple possible etiologies. PERCH is primarily a hospital-based study because of the need to focus on severe and potentially fatal pneumonia and because this is the setting in which the most important diagnostic procedures can be performed and specimens can be collected (e.g., blood, lung aspirates, induced sputum and post-mortem tissue). Five sites will also link cases with population denominators, providing pathogen-specific pneumonia incidence estimates as well.

The clinical protocol and study methods for PERCH study have been finalized, based on expert input and results from two pilot sites and are available to the research community on the internet at [101]. Multiplex PCR assays were systematically evaluated in the laboratory and ultimately a final platform from FastTrack Diagnostics (Luxembourg) was selected based on a careful evaluation of costs, logistics and provision of service support. Enrollment in PERCH began in August 2011 and participants are expected to be enrolled for 2 full years.

PERCH will provide etiology data that can be overlaid with incidence figures to produce an estimate of the incidence, by etiology, of pneumonia for each country, and permit the estimation of mortality rates by pathogen. These estimates will be valuable to a wide range of public health stakeholders. They will provide a firm evidence base for developing countries to take decisions on program priorities, for donors to focus investments in health, for developers of vaccines, drugs and diagnostics to target their efforts on new products, and for clinicians to reform protocols and best practice recommendations on empiric therapy regimens.

While PERCH is undoubtedly the largest multicountry pneumonia etiology study in two decades, it cannot be assumed that the diversity from various epidemiologic settings will be covered in studies undertaken in only seven countries. It is crucial to complement PERCH with results from other ongoing pneumonia studies or from those that have been recently concluded in several other developed and developing country settings. The challenges with this effort will include the use of a variety of clinical and

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“Reducing the burden of pneumonia mortality is essential to reaching the Millennium Development Goals...”

Several important changes have also occurred since those studies. Hib and pneumococcal conjugate vaccines, which can protect against pneumonia caused by these pathogens, have been developed and are showing promising effects [10,11]. With funding from the GAVI Alliance, access to these new vaccines is being accelerated for resource-poor countries and this is expected to lead to dramatic reductions in Hib and pneumococcal pneumonia, consequently changing the etiology of pneumonia [12,13]. HIV-infection has become widespread and this increases the frequency of pneumonia and modifies the distribution of pneumonia pathogens [14]. Moreover, substantial changes in nutrition, living conditions (e.g., urbanization) and access to care are likely to modify transmission of agents and the natural history of infection.

On the diagnostic side, there are new molecular platforms with increased sensitivity of pathogen detection [55] that can now be deployed. It is crucial that the advances in molecular tools are explored to monitor the evolving etiology of pneumonia and improve our efforts to develop new approaches and algorithms for preventing, diagnosing and treating childhood pneumonia.

Studying pneumonia etiology is complicated by various epidemiologic and microbiologic factors:

- Pneumonia, an infection of the lung tissue, ranges in severity and outcome;
- The pathogens causing pneumonia and the distribution of those pathogens vary according to severity of the episode. The distribution of pathogens causing mild cases of pneumonia is not the same as that causing cases resulting in death;
- Obtaining biologic samples for etiologic testing from the site of infection, the lung, is generally not possible;
- Many pathogens causing pneumonia are commonly identified in humans who do not have pneumonia;
- Cases of pneumonia are commonly associated with infection by more than one infectious agent.

Thus, identification of a pathogen in a case of pneumonia does not necessarily mean that it is the cause of the illness and, conversely, failure to identify a pathogen does not mean it is absent.
laboratory methods, thus making comparability of results from these studies difficult for drawing more generalizable conclusions. Ultimately, the entire research community benefits when pneumonia etiology studies have acceptable and understandable levels of comparability in their methods. Thus, further efforts to harmonize the methods used in pneumonia etiology studies is an important next step and one that the whole community needs to participate in undertaking.

**References**


**Website**

101. PERCH: pneumonia etiology research for child health. www.jhsph.edu/ivac/perch.html