SUPPLEMENT ARTICLE

Evaluation of Risk Factors for Severe Pneumonia in Children: The Pneumonia Etiology Research for Child Health Study

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As a case-control study of etiology, the Pneumonia Etiology Research for Child Health (PERCH) project also provides an opportunity to assess the risk factors for severe pneumonia in hospitalized children at 7 sites. We identified relevant risk factors by literature review and iterative expert consultation. Decisions for inclusion in PERCH were based on comparability to published data, analytic plans, data collection costs and logistic feasibility, including interviewer time and subject fatigue. We aimed to standardize questions at all sites, but significant variation in the economic, cultural, and geographic characteristics of sites made it difficult to obtain this objective. Despite these challenges, the depth of the evaluation of multiple risk factors across the breadth of the PERCH sites should furnish new and valuable information about the major risk factors for childhood severe and very severe pneumonia, including risk factors for pneumonia caused by specific etiologies, in developing countries.

The Pneumonia Etiology Research for Child Health (PERCH) study is a prospective multisite, case-control study to describe the etiologic distribution of pathogens among 5000–7000 children hospitalized with severe or very severe pneumonia in settings characterized by the introduction of conjugate vaccines against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* [1]. In order to provide generalizable results, sites were selected to represent a variety of epidemiological factors that might affect pneumonia etiology, including geographic location, urban versus rural character, malaria endemicity, and human immunodeficiency virus (HIV) prevalence [2, 3]. A case-control design was adopted to enable the attribution of causality based on diagnostic tests that could be conducted in settings where the transmission of potential pathogens among the healthy population is commonplace. The case-control design, together with the large sample size and wide generalizability of the results, provides ideal conditions for an evaluation of the risk factors for pneumonia, as well as risk factors for pneumonia severity and for pneumonia caused by specific etiologic agents.

Evidence exists in the published literature for a large number of pneumonia risk factors, including indoor air pollution [4, 5], malnutrition [6, 7], lack of breastfeeding [8, 9], low maternal education [6, 10, 11], low socioeconomic status (SES), poor access to care, and concomitant illnesses [11]. It is impracticable to collect data on all possible risk factors, and among parents already distracted by a child's severe illness, the quality of responses at interview may decrease as the number

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of questions increases. Here, we describe the process undertaken to identify and prioritize risk factors for pneumonia in the PERCH study.

RISK FACTOR IDENTIFICATION AND PRIORITIZATION

To obtain a final list of risk factors and corresponding questions, we generated a comprehensive starting list. From this list, we selected key factors, translated the selected factors into questions for the case report forms and finally reduced the list of questions to a manageable length.

Generation of List of Potential Risk Factors

First, we began with the risk factors prioritized by the Child Health Epidemiology Reference Group (CHERG), an academic review group constituted by the World Health Organization, which examined >2000 studies on childhood pneumonia published between 1961 and 2001 [12]. CHERG proposed guidelines for the appropriate conduct of pneumonia etiology studies and specified the minimum data that such studies should collect to allow for valid comparisons and meta-analyses of estimates across studies. These data included a description of the study setting (eg, rural vs urban), geographical features (eg, annual rainfall, altitude), sociodemographic factors (eg, SES, crowding, indoor air pollution), concomitant health problems (eg, malnutrition, HIV infection), and healthcare factors (eg, immunization, access to healthcare). We took this list, and whenever possible, adapted the specified factors for ascertainment at an individual, not community, level to make them compatible with a case-control study design.

Second, we augmented the adapted list of CHERG factors with variables identified by a literature review and additional variables suggested by PERCH investigators (Table 1). In August 2009, we searched PubMed and Web of Science using combinations of the following terms: "pneumonia," "pneumonia etiology," "methodology," "risk factors," "children," and "childhood." Titles of articles identified by this search were screened, and studies evaluating risk factors for pneumonia or severity of pneumonia were selected for abstract review. We then conducted a full text review of studies with relevant abstracts to identify additional established or putative risk factors. Given the overlap in material, most of the risk factors derived from our review had already been identified by CHERG; however, a few additional risk factors emerged, such as prematurity [13], vitamin D deficiency [14], and hypothermia [15]. The literature review also expanded the scope of several risks already classified. For example, from an initial list of 3 comorbidities (diarrhea, AIDS, and malaria), we identified 7 additional comorbid conditions of interest (HIV infection, sickle cell disease, known tuberculosis, anemia, febrile illness, previous pneumonia, and history of respiratory illness such as wheezing and influenza) [16–18]. Following the review, the number of risk factors increased from 22 to 50.

Risk Factor Selection Process

Third, to prioritize the risk factors for inclusion in PERCH, we selected those with the highest population-attributable fractions or with the strongest effects, while balancing pragmatic concerns, such as feasibility, cost of data collection, analytic plans, and comparability with existing data from countries not represented in the PERCH study. An external advisory group of pneumonia experts (the Pneumonia Methods Working Group) [1] that was convened by the study team assisted with further prioritization and suggested new risk factors to assess.

At this stage, we gave particular consideration to newly recognized potential risk factors. Vitamin D deficiency is a good example. A case-control study in Ethiopia [19] suggested a strong association (13-fold greater odds) between nutritional rickets (caused by vitamin D deficiency) and pneumonia. Likewise, an Indian study that measured serum 25(OH)D (25-hydroxyvitamin D) concentrations suggested that subclinical vitamin D deficiency is associated with pneumonia [14]. However, 2 more recent Canadian studies, both published in 2009, failed to find an association between serum 25(OH)D and pneumonia [20, 21]. Although the role of vitamin D in pneumonia risk remains unclear, vitamin D deficiency was not identified as a priority by the Pneumonia Methods Working Group. Due to the competing demand for serum needed to assay vitamin D deficiency, it was not considered practicable to evaluate the role of this vitamin in pneumonia.

Fourth, we defined the variables for the case report forms, balancing questionnaire length against the need to be comprehensive and to minimize the burden on study participants and staff. Specific pragmatic and methodological considerations that guided the variable selection and definition process are highlighted in the sections that follow.

Poor Reliability of Responses

Several questions were dropped because the responses were thought likely to be unreliable. For example, although knowing a family's income level would be useful to assess SES, self-reported data on household cash income was dropped in all but 1 site (South Africa) because the local investigators argued that it was unreliable in these study settings. We instead relied on physical assets, such as household possessions and agricultural assets, to determine long-term wealth.

Standardization of Risk Factor Variables

In a multisite study, it is essential to standardize the ascertainment of exposure (risk factor) variables to ensure comparability across sites during the interpretation of results. However, in

Table 1. Individual Risk Factors/Variables Considered, Source, and Final Status for Inclusion in the Pneumonia Etiology Research for Child Health Study

Risk Factor Category	Risk Factor Variable	Source[a]	Included in PERCH
Demographic			
	Age	1	Yes
	Sex	2	Yes
Birth milestones			
	Place of birth	4	Some sites
	Mode of delivery	4	Some sites
	Birth weight	1	Yes
	Gestational age	4	Some sites
	Prematurity	2	Yes
Birth order		1	No
	Mother's live deliveries (no.)	4	Some sites
	Mother's live births that died (no.)	4	Some sites
Nutrition			
	Breastfeeding[b]	1	Yes
	Malnutrition[c]	1	Yes
	Vitamin A supplementation	2	Yes
	Zinc supplementation	2	No
Past morbidities or comorbidities			
	Malaria parasitemia	1	Some sites
	HIV/AIDS	1	Yes
	Known tuberculosis	2	Yes
	Previous pneumonia hospitalization	2	Yes
	Paraffin ingestion in the past 48 h	4	Yes
	Measles	4	Yes
	History of wheezing or asthma	3	Yes
	Thalassemia	4	Some sites
	Sickle cell disease	2	Some sites
	Anemia	2	Yes
	Diarrhea	1	Yes
Child's vaccination history			
	EPI vaccines[d]	1	Yes
	Influenza, current season	1	Yes
	PCV	1	Yes
	Rotavirus	4	Yes
	Japanese encephalitis	4	Yes
	Measles, mumps, rubella	4	Yes
Mother's vaccination history			
	Influenza, DTaP, PCV, 23-valent pneumococcal polysaccharide	4	Yes
Treatments/interventions			
	Asthma and steroid treatment	3	Yes
	Tuberculosis treatment	2	Yes
	Co-trimoxazole therapy	3	Yes
	Antiretroviral treatment	2	Yes
	Antibiotic use	2	Yes
	Bed-net use	2	Some sites
Childcare experience		1	
	Out-of-home care	3	Yes
Maternal characteristics			
	Mother's ethnic group	4	Yes
	Mother still living	4	Yes
	Maternal age	1	Yes
	Maternal education[e]	2	Yes
	Mother's membership in a social group	4	Some sites

Table 1 continued.

Risk Factor Category	Risk Factor Variable	Source[a]	Included in PERCH
Father's characteristics			
	Father's ethnic group	4	Yes
	Father still living	4	Yes
	Father's education[e]	4	Some sites
	Number of father's wives and mother's order among wives	4	Some sites
Family environment			
	Crowding level[f]	1	Yes
	Smoking exposure at home	1	Yes
	Indoor air pollution[g]	1	Yes
	Exposure to tuberculosis/tuberculosis contact in household	3	Yes
Socioeconomic status		1	
	Home construction material[h]	2	No
	Household possessions (26 items)[i]	4	Yes
	Household ownership of furniture items[j]	4	Some sites
	Household ownership of agricultural land	4	Some sites
	Household ownership of livestock[k]	4	Some sites
	Income[l]	4	Some sites
	Occupation[m]	4	Some sites
Water source			
	Main source of drinking water[n]	4	Yes
	Main source of water to wash hands	4	Yes
	Distance to water source, use of soap, use of shared standing water basin, frequency of running out of water, concern about the cost of water	4	Some sites
Sanitation			
	Type of toilet	4	Yes
Access to care			
	Distance, cost and time to nearest hospital, study facility, and nearest health clinic	1	Yes
	Cost of hospital admission	4	Yes

Abbreviations: DTaP, Diphtheria, Tetanus, and Acellular Pertussis Vaccine, ; EPI, Expanded Programme on Immunization; HIV, human immunodeficiency virus; PCV, pneumococcal conjugate vaccine; PERCH, Pneumonia Etiology Research for Child Health study.

[a] Sources for developing the risk factors list: 1 = Child Health Epidemiology Reference Group list published by Lanata et al [12]; 2 = literature review; 3 = Pneumonia Methods Working Group; 4 = site investigators.

[b] Breastfeeding questions include duration (in mo) and type of breastfeeding (ie, exclusive, mixed, or none).

[c] Malnutrition measured as *z* scores for weight-for-height and weight-for-age.

[d] EPI vaccines include BCG, diphtheria-pertussis-tetanus, and measles in all countries and *Haemophilus influenzae* and hepatitis B in some countries.

[e] Includes no. of years of school completed and type of school (ie, formal, religious, college).

[f] Crowding assessed with the following questions: no. of children living in the same household; no. of people sleeping in the same room.

[g] Ventilation in the main living area; location where cooking is done; type of stove; type of cooking fuel; no. of windows in the cooking area; presence of a hood or chimney; typical location of the child during cooking; method of lighting home; method of heating home (some sites).

[h] Type of floor (some sites), type of wall, type of roof.

[i] Household possessions: electricity in house, generator, air conditioner, electric fan, computer, refrigerator, animal-drawn cart, clock, DVD/video player, television, satellite television, radio, mobile phone, nonmobile telephone, electric iron, watch, grinder, camera, car/truck, motorcycle/scooter, bicycle/rickshaw, boat with a motor, canoe, sewing machine, water heater, washing machine.

[j] Household ownership of at least 5 of the following 6 furniture items: table, chair, sofa, bed, armoire, cabinet.

[k] Household ownership of any livestock (7 items): cattle, sheep, goats, horses, donkeys, pigs, chickens.

[l] Mother's income, weekly cash income (South Africa only), child's receipt of ''child grant.''

[m] Head of household's occupation, father's occupation, mother's occupation.

[n] List of 17 water source options, such as piped into house, well, borehole, river, etc.

working with the investigators, it became clear that there were site-specific constraints that precluded absolute standardization. Some risk factor questions were simply not relevant at some sites; for example, HIV infection was considered irrelevant in Bangladesh because the prevalence is very low (<1%) [22]. Likewise, collecting data on sickle cell disease was thought to be unnecessary for the Asian sites. Moreover, some sites had a particular interest in asking about certain risk factors regardless of whether they would be adopted by the study as a whole. Therefore, we developed 2 sets of risk factor variables—those asked at all sites and, in addition, those asked at some sites. For example, questions about heating the home, cost of water purchased, and possession of assets, such as a clock, electric iron, and sewing machine, were only considered important at a minority of sites.

Historical Consistency

Several of the PERCH sites were already engaged in longitudinal studies of pneumonia and were therefore keen to maintain consistency in their questionnaires over time. These studies generally had a broader target population than PERCH, including children with nonsevere pneumonia or cases from a wider age distribution. Therefore, consistency between PERCH and the existing studies would enable a comparative analysis of risk factors against a wider spectrum of pneumonia cases in those sites, this led to tensions in our efforts to achieve standardization, as the precise wording of the site-specific questions appeared incompatible with the aims of PERCH at the other 6 sites. For example, investigators in The Gambia were obtaining information on children's feeding patterns with 12 variables including breastfeeding, formula feeding, and other liquids and solids; for the PERCH study as a whole, however, only a 4-field breastfeeding assessment was required. After it was established that we could integrate essential data on breastfeeding from either approach, the sites were able to choose the level of detail desired.

Operationalizing Composite Risk Factors

It was difficult to obtain robust measures of some variables, particularly latent constructs such as SES and access to health, with a single question. These types of risk factors require multiple questions on observable attributes and detailed response categories. Likewise, exposure to environmental risk factors such as indoor cooking smoke are best measured physically, but this can be expensive and logistically complex. Given the limited tolerance of participants and limited financial resources of the study, it was not practicable to ascertain all the desirable qualities of risk. The following examples of composite risk factors in PERCH illustrate how the tension between the comprehensive and the practical was resolved through compromise.

Socioeconomic Status

Demographers commonly use directly observable individual-level characteristics such as income level, educational attainment, or type of occupation as proxies for SES. A common assessment of SES, particularly in developed countries, utilizes a composite of these 3 characteristics [23]. However, in developing country settings, where a large part of the population is engaged in subsistence agriculture or informal work, the type of occupation is seldom discriminating therefore, objective and reliable measures of income can be difficult to obtain [24]. In part to address these challenges, the Demographic and Health Surveys developed a wealth index to assess economic status. This index is constructed from questions on household possessions, service access, and dwelling construction. Using principal component analysis, a summary index is used to classify households into wealth quintiles at the country level. This index has been validated and was shown to perform better than the major alternative, a consumption expenditure index [25].

We considered adopting the Demographic and Health Surveys wealth index to determine SES in PERCH, but a careful review suggested that this was impractical. First, the module is long, containing approximately 25 questions, which may take >30 minutes to ascertain. Second, not all of the questions were relevant to every site, as there is significant variation in the macroeconomics of the different countries. Third, an item could be positively correlated with wealth in one setting but negatively correlated in another; for example, motorcycle ownership may represent a relatively wealthy individual in rural communities of The Gambia, but lower SES in a higher-income country like Thailand. Furthermore, as noted previously, some sites had preexisting SES questions (eg, The Gambia, Mali) while others needed to develop a new SES index (eg, Kenya).

We were unable to define a practical instrument for determining SES that could be applied to 7 specific societies and yet be incorporated into a single analysis. Instead, we elected to allow a degree of site-specific choice regarding the questions that would be used to define a composite measure of SES separately at each site. We will then stratify this measure into quintiles and combine the analysis across sites by using the quintile as a common measure of relative wealth within sites. Each has chosen to ascertain data on at least 10 socioeconomic variables, distributed among the categories of income level, educational attainment, type of occupation, household possession, agricultural assets, and home construction material (Table 2).

Access to Care

Access to care can be measured by physical access, such as geographic proximity to a health facility, behavioral factors such as decisions on when to seek care for an illness, and economic factors such as affordability [26]. Physical access is the easiest to assess objectively; however, this can be measured as a distance, a cost, or a means of travel. Ascertaining all 3 would be onerous. Economic

Table 2. Socioeconomic Variables Included by Study Site

Variable	South Africa	Zambia	Kenya	Mali	The Gambia	Thailand	Bangladesh
Occupation of head of household	☒			☒		☒	
Father's occupation							☒
Mother's/primary caregiver's occupation							☒
Cash income of the household	☒						
Mother/primary caregiver regularly earns incomes	☒	☒		☒	☒		
Is child receiving a ''child grant''?	☒						
Ownership of any of the following in working order							
Electricity	☒	☒	☒	☒	☒		☒
Generator				☒	☒		☒
Air conditioner				☒	☒	☒	☒
Electric fan	☒	☒		☒		☒	☒
Computer	☒	☒		☒	☒	☒	☒
Refrigerator	☒	☒		☒	☒	☒	☒
Animal-drawn cart					☒		
Clock		☒					
DVD/video player	☒				☒	☒	
Television	☒	☒		☒	☒	☒	☒
Satellite television		☒		☒	☒	☒	☒
Radio	☒	☒	☒	☒	☒		☒
Mobile phone	☒	☒	☒				☒
Nonmobile telephone							
Electric iron				☒	☒		
Watch	☒				☒		☒
Grinder							
Camera	☒						
Car/truck	☒	☒		☒	☒	☒	
Motorcycle/scooter				☒	☒	☒	☒
Bicycle/rickshaw	☒	☒	☒		☒		☒
Boat with a motor							☒
Canoe							☒
Sewing machine		☒			☒		☒
Water heater						☒	
Washing machine	☒					☒	
Household ownership of livestock[a]		☒	☒		☒	☒	☒
Household ownership of furniture items[b]			☒		☒		☒
Ownership of agricultural land		☒			☒		☒
If yes, number of hectares					☒		

[a] Household ownership of any livestock (7 items): cattle, sheep, goats, horses, donkeys, pigs, chickens.

[b] Household ownership of at least 5 of the following 6 furniture items: table, chair, sofa, bed, armoire, cabinet.

and behavioral barriers to access are of greater interest but are much more difficult to assess. For example, questions such as "Did you seek care in the past month for an illness?" are fraught with contingencies, such as the type of care that was sought (eg, Western vs traditional medicine), and whether seeking care indicates better health-seeking practices or a sicker child. We therefore decided to limit our inquiries to travel time and distance.

Crowding

Living in crowded conditions promotes the transmission of airborne pathogens. Thus, crowding, commonly measured as the number of persons per room in a dwelling unit, is an important risk factor to assess in PERCH [27]. Because the definition of crowding begins with defining the living space, we intended to define the household unit in a standard way to ensure cross-site comparability of the crowding variable, but the considerable differences in living arrangements across the sites made this difficult. For example, our initial definition of a household as a "compound" or "homestead" was rooted in a rural concept of communal living and this had little meaning in the urban African sites of Lusaka, Zambia, and Soweto, South

Africa. Ultimately, we agreed on a household definition using the more universal concept of a group of people "who share a cooking pot." This seemed to fit well in both rural and urban sites of Asia and Africa. We used 3 variables to define household crowding: number of people living with the child, number of children 0–10 years of age living with the child, and number of people sleeping in the same room as the child.

Another example of crowding is daycare attendance, which has been associated with a higher risk of pneumonia [28]. Few children at PERCH sites are enrolled in formal daycare, but informal care by family or neighbors in the company of other children is common and can mimic the daycare environment. We used the term "out of home care" to capture daycare, preschool, family care, or crèche attendance and defined this as being in the company of at least 2 other children for at least 4 hours per day, 3 days a week.

Indoor Air Pollution

Indoor air pollution from biomass fuels has been determined to elevate the risk of pneumonia in children by approximately 80% [4]. Multiple approaches have been used to measure indoor air pollution, ranging from the direct assessment of indoor concentrations of particulate matter or carbon monoxide, to indirect reports of fuel and stove use and household cigarette smoking. Because exposure levels are both dynamic and cumulative, it is necessary to conduct prospective measurements over weeks and months prior to the development of pneumonia to precisely ascertain indoor air pollution. Furthermore, the logistics and instruments required to capture physical measures, even in a case-control design, were beyond the resources available to the PERCH study. For these reasons, for the main PERCH study, we will evaluate exposure to indoor air pollution using reported physical and behavioral markers of exposure, including the type of fuel and stove used, duration of exposure, level of ventilation in the cooking area, presence of the child during cooking, and reported cigarette smoking among household residents.

Particular Considerations for HIV Testing

HIV infection is an established risk factor for pneumonia in general and for pneumonia caused by specific pathogens such as *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, pneumococcus, and Hib [29]. HIV infection status is therefore an important variable to assess as a potential confounder of other risk factors. Despite efforts to introduce routine HIV testing in developing countries, it remains a sensitive issue and many mothers and children remain untested in high-HIV prevalence areas. Furthermore, in areas with very low HIV prevalence, the value of identifying perhaps one child in a thousand who is infected may be outweighed by the disadvantage of negative community reaction to such a survey. After considerable debate, we reached a consensus position that all PERCH subjects would be tested for HIV antibodies but that controls would be tested only at sites where the prevalence was $\geq$5% in the general population, a level sufficiently high to affect the analyses. Sites such as Bangladesh, rural Thailand, and The Gambia, where HIV prevalence is low, would not test controls for HIV.

SUMMARY

As a case-control study, PERCH provides an opportunity to assess risk factors for severe pneumonia in children in 7 developing countries. Identifying risk factors and quantifying the strength of their association with disease can guide strategies to reduce the incidence of pneumonia in high-risk populations, for example, by targeting vaccinations, reducing exposure to indoor air pollution, and promoting schemes for better healthcare utilization. We used existing public health work and a broad literature review to capture all relevant risks, and through a process of iterative review, first with an expert body and later with the investigators at each of the 7 sites, we included a core of essential questions in the PERCH case-control study that were practical and would not result in participant fatigue. Some risk factors are best defined by physical measurements, which were beyond the resources of the project; we will attempt to capture these exposures through surrogate questions. Finally, although we strove to standardize questions across all sites, the varying economic, cultural, and geographic characteristics of the sites required some flexibility in the ascertainment of the same risks in different locations. Despite these challenges, the depth of the evaluation of multiple risk factors across the breadth of the PERCH sites should furnish valuable and new information about the major risk factors for childhood pneumonia in developing countries.

Notes

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