SUPPLEMENT ARTICLE

# Identification and Selection of Cases and Controls in the Pneumonia Etiology Research for Child Health Project

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**Methods for the identification and selection of patients (cases) with severe or very severe pneumonia and controls for the Pneumonia Etiology Research for Child Health (PERCH) project were needed. Issues considered include eligibility criteria and sampling strategies, whether to enroll hospital or community controls, whether to exclude controls with upper respiratory tract infection (URTI) or nonsevere pneumonia, and matching criteria, among others. PERCH ultimately decided to enroll community controls and an additional human immunodeficiency virus (HIV)–infected control group at high HIV-prevalence sites matched on age and enrollment date of cases; controls with symptoms of URTI or nonsevere pneumonia will not be excluded. Systematic sampling of cases (when necessary) and random sampling of controls will be implemented. For each issue, we present the options that were considered, the advantages and disadvantages of each, the rationale for the methods selected for PERCH, and remaining implications and limitations.**

The Pneumonia Etiology Research for Child Health (PERCH) study aims to be the largest study of the etiology of severe pneumonia in children in >20 years [1]. Unlike many pneumonia etiology studies, PERCH was designed as a case-control study, with controls providing essential data for the interpretation and extrapolation of findings from patients (cases). Specifically, controls will help improve interpretation of test results from nasopharyngeal samples, determine the specificity of certain diagnostic blood tests that are calibrated using normal values from the general population (eg, *Mycoplasma pneumoniae* immunoglobulin M serology), and identify risk factors (and estimate the magnitude of association as an odds ratio) for severe pneumonia and for etiologic-specific pneumonia. Additionally, the use of controls allows us to estimate population-attributable risks and compare communities in which the study is done, and guides the interpretation of any differences in the etiologic distribution of pneumonia cases between sites.

An essential component of PERCH is the case and control selection process, which must be standardized across the study sites located in 7 countries: Dhaka and Matlab, Bangladesh; Basse, The Gambia; Kilifi, Kenya; Bamako, Mali; Soweto, South Africa; Nakhon Phanom and Sa Kaeo, Thailand; and Lusaka, Zambia. Epidemiologic challenges addressed in the design of PERCH included eligibility criteria for case and control enrollment, matching criteria, the sampling strategy for both cases and controls, where to identify controls, and whether to enroll controls with upper respiratory tract infection (URTI) or nonsevere pneumonia. The methods chosen needed to (1) ensure study objectives

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could be met, (2) ensure adequate sample size, (3) minimize selection bias, and (4) anticipate the need to control for confounding in analyses.

The PERCH Core Team presented options for each issue, usually identifying 1 preferred option, to the Pneumonia Methods Working Group (PMWG) [1] for consideration and recommendation. The PERCH Core Team and the site investigators adapted the final recommendations of the PMWG to the study's protocol [2].

This manuscript summarizes decisions made by the PMWG and PERCH Core Team about the principles of case and control selection. It describes the case and control identification and selection methods that were ultimately decided for PERCH, and the options considered along the decision pathway, the implications and tradeoffs for each, and rationale for the final decisions.

## METHODS

### Case Identification and Selection

#### *Case Eligibility Criteria*

We will limit case enrollment to children hospitalized with World Health Organization–defined severe or very severe pneumonia [3]. Sites will enroll cases throughout the year to obtain seasonal distribution of cases and throughout the week and day, including weekends and evenings/nights, to enroll cases representative of the distribution of disease severity. Enrollment rates will be proportional to case detection rates, meaning a greater number of cases will be enrolled during peak hours and during peak seasons (Figure 1).

#### *Defining the Reference Population and Catchment Area*

Risk factors and circulating pathogens are expected to vary within the study populations. To avoid bias, cases and controls must be selected from the same reference population. We therefore need to define the reference population from which cases, detected at study hospitals, are drawn and select controls from the same geographic area. We considered several factors in defining the reference population. In settings with a single referral hospital, cases may originate from great distances because the hospital attracts severely ill children. Patients may come from varied settings, such as urban and rural areas. In large, densely populated cities with several hospitals and highly mobile populations, it may be difficult to define the areas from which cases come because hospital quality and cost may take precedence over distance in determining the choice of facility.

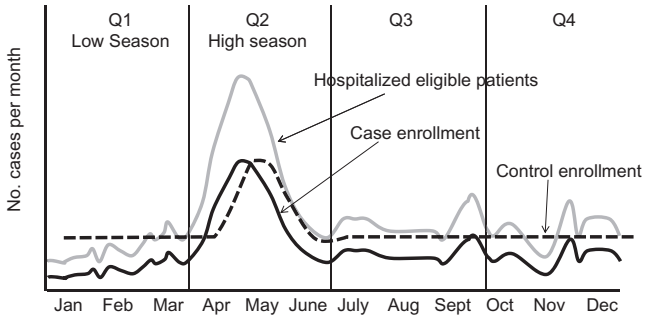


**Figure 1.** An illustration of case and control sampling proportional to the case detection rates. A small time lag is anticipated for controls frequency-matched to the month of enrollment of cases, due to the expected interval from observed cases to the communication of this target number to the field workers who recruit controls.

The catchment area is the study-defined geographic area where eligible study participants (both cases and controls; a subset of the reference population) must live. The catchment area will be defined using residence of cases obtained from hospital logs the previous year. Sites will define the catchment area based on where most cases came from the previous year to avoid having to enroll controls over a too expansive an area. This also has the benefit of not overrepresenting controls from very distant areas that rarely use the study hospital, and of not overrepresenting cases that are not representative of the study site population (ie, from great distances or only visiting the study area). However, excluding the farthest cases may risk excluding the most severe cases resulting from delay in presenting for medical care due to travelling farther distances when seeking hospital care.

#### *Need to Limit the Number of Cases Enrolled*

Power calculations suggested that approximately 6300 cases (and 7000 controls) would be sufficient to evaluate all primary and secondary objectives of PERCH. However, projections from the 7 PERCH sites indicate that nearly twice as many eligible cases (approximately 12 500) might be expected to present at the enrollment hospitals over the course of 2 years. Therefore, several options were considered to limit the number of cases enrolled (see Supplementary Table 1). Options 1–3 were rejected because they potentially biased the representativeness of the study population. Option 4 (testing only a proportion of specimens) would reduce costs, but the effort to enroll all cases at very large hospitals would be burdensome. However, from an ethical standpoint it would not be acceptable to collect specimens that are not tested or enroll cases that would not be included in analyses. Although case sampling (option 5) introduced complexity into the study design, it did not suffer from the previously noted disadvantages and was the preferred option. Thus, a system for selecting the cases to be enrolled among all those eligible was needed.

#### *Case Sampling*

Any form of sampling increases study complexity and potentially introduces bias, but some forms more so than others. We considered random, systematic (eg, enroll every other case or

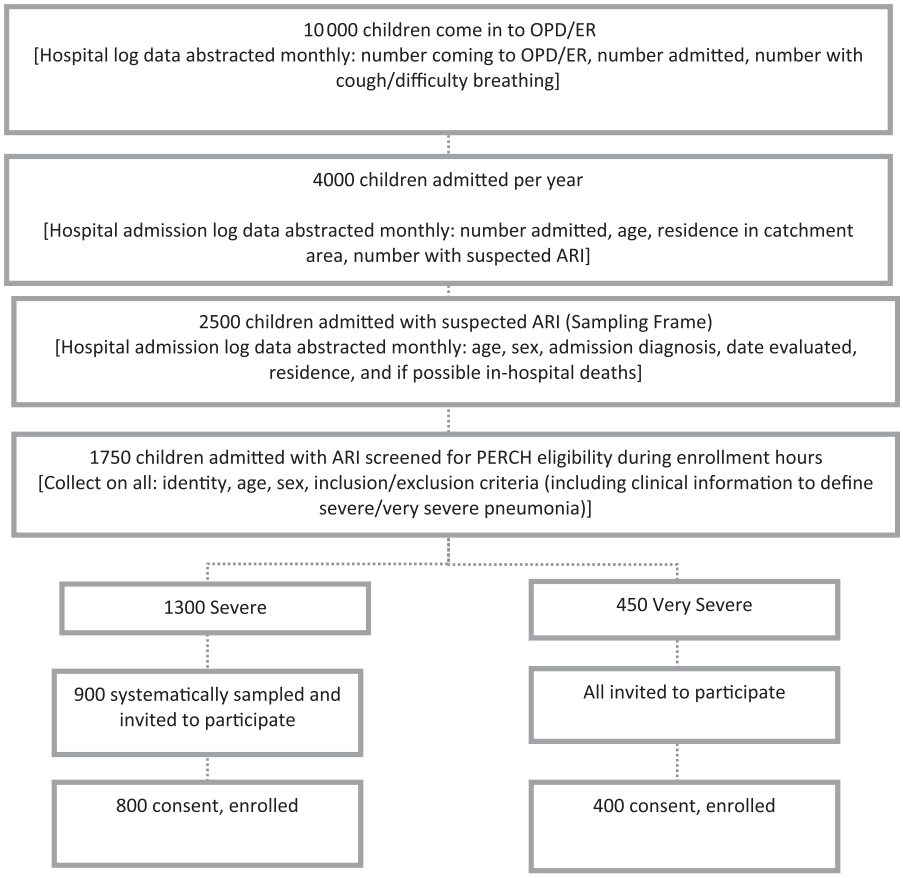


**Figure 2.** An illustration of the patient flowchart. Abbreviations: OPD, outpatient department; ER, emergency room; ARI, acute respiratory infection; PERCH, Pneumonia Etiology Research for Child Health Study.

every other day), convenience (eg, enrollment only between 9 AM and 5 PM on weekdays), and quota (eg, stop when prespecified sample size for that week or month is reached) sampling methods. Whereas random selection was thought to be too logistically complicated to realistically implement, the remaining methods with preselected days or times for enrollment were thought to be subject to selection bias resulting from families bringing their children during ''study'' times. The best option was determined to be systematic sampling with rotating enrollment (ie, alternating which days or hours to enroll).

A benefit of sampling is that it affords an opportunity to control the enrollment ratio of severe to very severe pneumonia cases, which are expected to be fewer. Because PERCH's focus is on identifying pathogens responsible for fatal pneumonia, we sought to increase enrollment of very severe cases. As a result, systematic sampling may be applied only to (or more frequently to) the severe cases; at many sites, all very severe cases will be invited to participate. This is a form of selection bias, albeit one we chose and can control for in the analysis. To optimize analyses stratified by severity, we will aim to balance the ratio. Some sites (Kenya and The Gambia) with projected excess cases will enroll all cases during the first year and sample only during the second year, if necessary. At least 1 site (Thailand) anticipates enrolling all eligible cases and will not apply any sampling criteria.

To minimize selection bias, a dedicated study team (rather than regular hospital staff) will manage the detection, selection, and enrollment of cases at most sites. Key data collected on all admissions, such as age, residence in catchment area, and admission diagnosis from existing hospital sources (eg, admission registers), will help assess the representativeness of the enrolled cases (Figure 2). Children who are screened will be compared with those not screened, and children who are enrolled will be compared with those not enrolled, to assess the representativeness of the PERCH participants. We will identify those who would potentially be eligible but were not screened for enrollment using a set of predefined diagnoses (eg, pneumonia, acute lower respiratory infection, bronchiolitis) on admission registers.

### *Case Representativeness*

The previously noted methodological decisions will result in many cases of severe pneumonia that will not be captured by PERCH. An inherent limitation of the focus on hospitalized cases is that we will miss cases who never come to hospital or who die at presentation before they can be enrolled. At the Kenya site, approximately two-thirds of children who die do so in the community [4], and only half of hospitalized children with severe or very severe pneumonia who died during their hospital stay participated in an etiology study [5]; thus, missed cases may represent those of greatest interest. This is an inherent paradox in hospital-based pneumonia etiology studies that must be accepted; however, to mitigate the consequences, we aim to collect postmortem specimens at 6 sites that may provide insights into the etiology of those who die at or near the time of presentation to hospital [6]. We will also miss the cases who seek care at nonstudy facilities or are not selected for enrollment because of sampling strategies. Although we cannot control the former situation, we will try to minimize the bias in the latter through sampling and analytic methods. The diversity of sites and the large sample size of PERCH will help ensure that we enroll a variety of cases, for which, using subgroup analyses, results can be generalized within these communities and to other similar communities.

## Control Identification and Selection

### *Community Versus Hospital Controls*

We aim to enroll controls that are representative of the population from which cases are drawn. Limited funds restricted us to only 1 control group, either from the community or from the study hospital. These 2 alternative groups have advantages and disadvantages in enabling us to understand the roles of risk factors and detection biases (Supplementary Table 2). Selecting hospital controls would best minimize selection bias due to access to care because both cases and controls have taken the same route to care. However, we were concerned that an insufficient number of eligible controls would be found at the hospital. Another concern was that they would be distorted by pneumonia-causing pathogens that can cause other inpatient syndromes such as sepsis, febrile convulsions, and diarrheal disease. They also would likely overrepresent the community prevalence of risk factors needed to calculate population-attributable risks and complicate the interpretation of findings from nasopharyngeal specimen testing.

Therefore, we decided that a community control group would best meet the analytic objectives of the study. They may be more representative of the catchment population than hospitalized children who might have underlying conditions (eg, malnutrition, human immunodeficiency virus [HIV] infection) that are not representative of the general population and that we would want to evaluate as risk factors for pneumonia. They would also not be skewed with respect to circulating pneumonia-causing pathogens, which hospital controls may have been.

Despite their advantages, using community controls does have some disadvantages. There are greater logistical challenges, such as identifying and locating eligible children who are scattered throughout a relatively large geographic area, selecting among them in an unbiased way, and the need for mobile, trained teams to collect their data. However, 3 sites already have extensive, successful experience enrolling controls from the community. In The Gambia, community awareness raised through radio programs helped successfully enroll controls in similar proportions to cases (S. Howie, written personal communication, 2009). In Dhaka, Bangladesh, community control enrollment was >95% in previous studies [7–9]. Mali has extensive experience enrolling healthy community controls that includes in-field random selection techniques and matching up to 3 controls per case by age, sex, neighborhood, and case-enrollment date [10].

There may also be residual uncertainty about differences in healthcare-seeking behavior and other health-related behaviors between community controls and cases. Healthcare-seeking tendencies may confound both etiology and risk-factor analyses, because cases who seek care may differ from cases who do not seek care regarding characteristics associated with etiology. Such characteristics include vaccination against pneumonia-causing pathogens, residence (because circulating pathogens differ by community), socioeconomic status and ability to afford care, access to early effective treatment that will shift etiology to antibiotic-resistant organisms and viruses, nutrition, crowding, and HIV status, among other risk factors. We are collecting information on all these factors in cases and controls, to control for them in the analysis.

A greater challenge with community controls might be the collection of specimens, particularly blood samples. Collecting blood is often a sensitive issue, the more so among well children. Taking the time to inform the community and each control child's parents and explaining carefully what we are doing and why is likely to overcome most of the resistance to blood sampling. As a potential benefit for participation, many sites will provide blood test results (HIV, thalassemia, sickle cell disease, or anemia) to the parents, and refer them for care if results are positive.

### *Community Control Selection Strategy*

Community controls will be randomly selected from lists of previously enumerated children residing in Demographic Surveillance System areas (Kenya, The Gambia, Bangladesh), where birth registries exist (South Africa), or from lists of households in areas with existing registries of households (Thailand). In the remaining 2 sites, they will be selected using the Expanded Program on Immunization cluster-sampling method [11]. Other sampling methods we considered included creating geographic

"quotas" of controls that ensured equal representativeness of all areas, and selecting controls from among children presenting to community health centers for routine visits. However, these methods were thought to bias controls toward those with good access to care, those who are unwell, or children of vaccine-eligible age.

To minimize bias in the selection of controls, field workers will revisit selected households ≤3 times if eligible children are not at home on the first visit. When possible, to optimize recruitment of the random sample, field workers will visit the household in the early morning or evening hours or make appointments by partnering with village health volunteers. Widespread community dissemination of information about the study may also help reduce refusals.

***Matching and Number of Controls per Case***

Because in most sites the incidence of pneumonia is highly seasonal and the pathogens that cause pneumonia are also seasonal, we debated whether to match controls to the dates of enrollment of cases or to recruit controls at a constant rate throughout the year. The advantage of matching would be to increase the power of season-stratified analyses, whereas constant recruitment would assure adequate measurement of background prevalence of risk factors and etiology in all seasons. To achieve both benefits, we decided on a combination of the 2 approaches, resulting in slightly >1 control enrolled per case. PERCH sites will recruit a minimum of 25 controls per month, and in months with >25 cases enrolled, sites will enroll additional controls for a 1:1 ratio for that month (Figure 1). Controls will also be frequency matched on age to the cases based on previous years' data and adjusted if needed in the following groups: 28 days to <6 months, 6 to <12 months, 12 to <24 months, and 24–59 months.

***Healthy Versus Sick Controls***

We considered whether children with nonsevere pneumonia or URTI characterized by coryza, cough, sneezing, and sore throat should be excluded or enrolled and analyzed as separate control groups. Our understanding of the pathogenesis of pneumonia suggests that most pathogens that infect the lung begin by first infecting the upper respiratory tract and that many of these infections cause URTI symptoms. The concern, therefore, is that URTIs and nonsevere pneumonia could be the early stages of severe pneumonia. However, because the control group should represent the population from which the cases are drawn, because not all URTIs are on the causal pathway to pneumonia, and because some pathogens cause both URTIs and severe pneumonia, an unbiased control population should include children in any state of health, including those with URTI or nonsevere pneumonia, provided that they do not have case-defining severe or very severe pneumonia at the time of enrollment. This decision has 3 significant advantages: (1) It permits an unbiased estimate of the prevalence of exposure variables in the community; (2) it prevents a form of selection bias that could overestimate the role of viral pathogens as the cause of severe pneumonia (otherwise we would have to apply the same rule of excluding URTI patients to cases); (3) it broadens the scope for exploratory analyses regarding the spectrum of illness; and (4) it estimates the prevalence of URTIs and nonsevere pneumonia in the community.

For PERCH, we will exclude as controls children with case-defining severe or very severe pneumonia [3] but not those with symptoms of URTI or nonsevere pneumonia. Including controls with respiratory illness will give us an opportunity to explore the role of nasopharyngeal infection in the pathogenesis of pneumonia through subgroup analyses. Exploratory questions that can be examined with a URTI subgroup include: (1) Is the URTI in the causal pathway (a gradient of infection)? (2) Which pathogens commonly cause URTI but rarely pneumonia? and (3) Is a virus a facilitating cofactor in pneumonia caused by a bacterial pathogen? If a sufficient number of controls with nonsevere pneumonia are enrolled, we can test the relationship between etiology and intermediary stages on the causal pathway to severe pneumonia. Specifically, we can assess whether the etiologic spectrum of nonsevere pneumonia is more similar to URTI, severe pneumonia, or somewhere in between. Although defining distinct respiratory syndromes that can occur along the continuum of respiratory infections will be challenging because symptoms of each syndrome will overlap, use of standardized definitions and training will help limit misclassification.

***HIV-Infected Controls***

Because we expect the etiologic spectrum of pneumonia to differ markedly by HIV status [12, 13], stratifying etiologic analyses by HIV status is necessary. We anticipate 25%–50% of cases to be HIV-infected at sites with high HIV prevalence (ie, Zambia and South Africa). However, because the community prevalence of HIV infection will likely be <5% even in sites of high HIV prevalence, an additional HIV-infected control group is needed to achieve sufficient numbers for HIV-stratified etiologic analyses. A separate HIV control group is not needed for risk factor analyses.

We considered selecting HIV controls from admitted patients at the hospital (see Supplementary Table 3), but the 2–3-day lag time to diagnose HIV infection among inpatients may alter the naso-oropharyngeal flora with nosocomial pathogens. In addition, HIV-infected infants admitted with nonpneumonia diagnoses have been difficult to find in South Africa because of improved prevention of mother-to-child transmission and lower prevalence of HIV infection among newborns. Therefore, controls will be selected from HIV treatment clinics serving the hospital catchment population.

HIV-infected controls will be enrolled in a 1:1 ratio to HIV-infected cases, frequency-matched by age and month of

enrollment; there will be no monthly minimum. Enrollment will be stratified on the duration of antiretroviral treatment (<3 months vs ≥3 months) to adjust for the level of immunosuppression that can influence the presence of pathogens in the naso-oropharynx. Eligibility criteria are the same as for community controls, plus the HIV-infected controls must be confirmed HIV infected and should not have been admitted to a hospital with an acute illness within the preceding 30 days. The latter criterion was added because acute illness can alter the CD4 count, which we will adjust for as an indicator of stage of HIV disease severity.

***Multiple Enrollments in PERCH***

We decided that a case may be reenrolled as a case if the patient is admitted >30 days after the date of hospital discharge from the previous case episode. This is to ensure that the same pneumonia episode is not enrolled twice.

If a control develops severe or very severe pneumonia within 48 hours of their control enrollment date, this control enrollment will be excluded, but the child would be eligible to be a case. This is because any URTI that the child had at the time of control enrollment might have been the early stage of the pneumonia and is considered the same episode as case-defining pneumonia.

To be consistent in the treatment of cases and controls, a child who was previously a case may be enrolled as a control if the control enrollment date is >30 days after the date of hospital discharge from the previous case episode. There is no time period of exclusion between control enrollments, and a community control may be enrolled again as a control if reselected through the random selection process. However, HIV-infected controls may be selected only once because the smaller pool of eligible children is likely to result in many repeat invitations to participate in some age groups.

## CONCLUSIONS

Despite their limitations, case-control studies of pneumonia etiology can provide valuable information on the likely causes of severe and fatal pneumonia in children. Although more expensive, complicated, and time-consuming than a study of hospitalized patients only, the case-control study provides valuable information that is often missing from more-limited studies. For example, a control group clarifies the usefulness and interpretation of some results from upper respiratory specimens, which are otherwise complicated and potentially misleading [5, 13–15].

Pneumonia etiology information is most helpful when it is collected from representative cases and controls. However, hospital-based studies of cases and selection of representative controls from the population are complicated and potentially open to biases that can alter the conclusions. The PERCH project has gone to great efforts to attenuate these limitations. By employing sampling strategies to reduce bias among cases and controls, taking steps to minimize participant refusal, gathering data on potential confounders to use in the analysis, and enrolling controls along the continuum of respiratory illness, PERCH aims to address concerns about bias by minimizing it, assessing where it may occur, and mitigating it by collection of overlapping information and specimens. The description of these methods and their rationale in this manuscript is designed to help with the interpretation of PERCH results when they are available and with the design of other pneumonia etiology research studies.

## 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 author 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 author.

## Notes

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