

**Critical Pertussis in U.S. Children: Severe
Morbidity, Sequelae, and Mortality: A
Prospective Cohort Study**

CPCCRN Protocol Number 001

*Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute of Child Health
and Human Development (NICHD)*

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This protocol is CPCCRN Protocol Number 001. The Federal Principal Investigators for this project are Carol Nicholson, M.D. and Fátima Coronado, M.D., M.P.H. from Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the Centers for Disease Control and Prevention (CDC), respectively. Funding for the project is provided by National Vaccine Program Office (NVPO) Unmet Needs Funding. NVPO is in the Department of Health and Human Services (DHHS), Office of the Secretary (OS).

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated.

I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

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Abstract

Background: Despite high coverage for childhood vaccination, pertussis causes substantial morbidity and mortality in U.S. children, especially among young infants. In 2004, 19,902 cases of pertussis were reported to the Centers for Disease Control and Prevention (CDC) in children and adolescents aged <18 years (CDC, unpublished data, 2005). From 1990-2004, 174 US pertussis-related deaths in infants aged <4 months were reported. Among hospitalized infants, data suggest non-fatal pertussis associated with a pediatric intensive care unit (PICU) admission may be approximately 50 times more common than fatal pertussis. Although pertussis is a well known precipitant of critical illness, especially in infants, several gaps in knowledge about critical pertussis (pertussis associated with a PICU admission) exist. In the United States, no national studies have assessed the acute course of critical pertussis. Worldwide, no published studies have comprehensively assessed sequelae of critical pertussis among survivors. The U.S. Advisory Committee on Immunization Practices recently recommended pertussis vaccination for adolescents and adults, known to play an important role in pertussis transmission to young infants. Understanding the morbidity of severe pertussis, will inform national prevention strategies as adequate U.S. data do not exist, generate hypotheses, and help prioritize research.

Aims: Among children <18 years of age with pertussis who require hospitalization in the PICU, the aims of this multicenter study are to 1) characterize the acute course during the PICU admission; 2) assess reported health status and family impact following PICU discharge; 3) assess developmental sequelae and quality of life among infants who were less than 12 months of gestational age at time of PICU admission 12-months following PICU discharge; and 4) assess risk factors associated with developmental sequelae in infants.

Study Design. A prospective cohort of children with critical pertussis will be identified through the National Institute for Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN) and other PICU sites utilizing existing national research infrastructure. With enhanced PICU surveillance, about 200 critical pertussis case-children will be enrolled. Eligible pertussis cases will be defined using study case definitions. Demographic and clinical information will be collected through chart abstraction and parental interview. Six months after hospital discharge, health status will be assessed through parental survey. Among infants <12 months of gestational age at the time of PICU admission, developmental sequelae survivor outcomes will be evaluated with the validated Mullen Scales of Early learning and potential risk factors for sequelae assessed through

univariate and multivariable analyses 12 months after discharge from the PICU.

1 Background and Significance

Pertussis is an acute respiratory illness caused by *Bordetella pertussis*. In the pre-vaccine era, pertussis was a major cause of pediatric mortality. Despite routine childhood vaccination with diphtheria and tetanus toxoids and acellular/whole cell pertussis vaccine (DTaP / DTP) for more than half a century, and high childhood coverage levels, pertussis remains a source of substantial morbidity and mortality in U.S. children.¹⁻⁵ Among the diseases for which universal childhood vaccination has been recommended, pertussis is the least well controlled reportable bacterial disease in the United States.² In 2004, 19,902 cases of pertussis were reported to the Centers for Disease Control and Prevention (CDC) in children and adolescents aged <18 years (CDC, unpublished data, 2005).

Infants aged <12 months with pertussis are more likely than older age-groups to have complications or be hospitalized during their illness.⁶ During 2000-2004, an average of 2,488 cases of pertussis was reported annually among US infants. Of these infants, 63% were hospitalized, and 0.8% died (CDC, unpublished data, 2005). Two to three doses of DTaP (recommended at ages 2, 4 and 6 months) provide protection against severe pertussis.⁶⁻⁸ Of the 203 pertussis-related deaths from 1990-2004, 174 (86%) were among infants aged < 4 months but deaths were reported in all pediatric age-groups (Table 1 on the facing page) (Vitek et al⁷ and CDC unpublished data, 2006). One French study of children admitted to pediatric intensive care units (PICUs) showed that *Bordetella pertussis* was the most common community-acquired bacterial pathogen associated with death in previously healthy infants (aged 10 days to 2 months).⁹ Worldwide, an estimated 400,000 children die from pertussis annually.¹⁰

In spring 2005, two tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) products were licensed for use in the United States in adolescents (and, for one product, use in adults) (FDA, ADACEL[®] and BOOSTRIX[®] package inserts). In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended a single dose of Tdap for adolescents and adults aged 11 to 64 years.^{11,12} The primary goal of these recommendations is to reduce disease in adequately vaccinated populations. In addition, because adolescents and adults are a source of pertussis to young infants, it is hoped that vaccinating individuals beyond childhood with Tdap

Table 1: Reported pertussis-related deaths by age-groups, United States, 1990-2004

Age Group	1990 – 1999	2002 – 2004
0 - 1 month	68	76
2 - 3 months	16	14
4 - 5 months	5	2
6 - 11 months	4	0
1 - 10 years	8	3
11 - 17 years	0	2
≥ 18 years	2	3
Total (all ages)	103	100

will reduce transmission of pertussis to the high-risk population of infants.

As the U.S. enters a new era of pertussis vaccination, understanding the health and impact of severe pertussis in children is crucial to the continued development, implementation, and assessment of national prevention strategies. Adequate analytic burden studies of severe non-fatal pertussis do not exist. Data about severe pertussis increase the acceptance of the new vaccination strategy. In order to address this public health priority, this protocol was formulated as a collaborative effort of the NIH/NICHD CPCCRN, the CDC, and the National Vaccine Program Office (NVPO), across the Department of Health and Human Services.

Passive surveillance data have been used to assess the burden of pertussis in U.S. children.^{6,7} These data are helpful in evaluating trends, but have limitations. Pertussis is under-recognized as a precipitant of critical illness in infancy and diagnostic tests can be unreliable (insensitive and nonspecific). Case reporting is incomplete, and most reported data is not validated against medical records; as well, the occurrence of critical illness, and long-term sequelae have not been assessed in comprehensive studies.^{6,7,13}

Hospital-based active surveillance for pertussis is not done in the United States. Other countries have evaluated the severity of pertussis among hospitalized children, using active, hospital-based surveillance networks. Because non-medical factors, such as young age itself, can influence the decision to hospitalize a young child with pertussis, admission to the PICU is a better indicator for severe pertussis (critical pertussis) than admission to the hospital.

Data suggest that non-fatal critical pertussis may be up to 52 times

more common than fatal pertussis among infants hospitalized with pertussis.¹⁴ One US study assessed the number of pertussis-related hospitalizations using ICD-9 codes from state-wide hospital databases in 4 states, CA, FL, WA, and MA. Of the 2,266 infants identified with pertussis, 317 (14%) required intensive care, for a mean duration of 8 days and 6 patients died. A Canadian study capturing > 85% of tertiary pediatric hospital beds, of 1082 pertussis-related hospital admissions among young children (1991-1997), reported that 19% of infants aged < 6 months and 5% of children aged 6-23 months required PICU admission; the mean duration in the PICU was 10 days in the young infants.⁸ In an Australian study (2001), of 140 infants aged < 12 months hospitalized with pertussis, 18% were admitted to the PICU; the median PICU duration was 6 days and 56% were mechanically ventilated.¹⁵ Kowalzik and colleagues conducted a prospective study in 7 countries outside the United States. They assessed the rate of pertussis among infants presenting to the PICU with certain cardiorespiratory symptoms associated with pertussis (e.g., apnea) and the source of pertussis infection. In this study, 99 (12%) of 842 enrolled infants had pertussis. The mean age of case-infants was 2.2 months and half had not received the first dose of DTP/DTaP. The median duration of hospitalization was 8 days and 2 (2%) of the 99 infants died. At least one household contact was identified as the source of infection in 27% of case-infants and mothers were the most frequently identified source.¹⁶

The literature suggests that pediatric long-term neurological, developmental and respiratory sequelae in critical pertussis survivors are not uncommon; no U.S. studies have comprehensively evaluated sequelae among critical pertussis survivors.¹⁷⁻¹⁹ Sequelae might be triggered by *B. pertussis* infection and/or untoward effects of therapeutic interventions. For example, extracorporeal membrane oxygenation (ECMO), invasive vascular access and monitoring, right heart catheterization, and pressor agents for hemodynamic support increase morbidity risk in survivors of childhood critical illness. Overall, children admitted to the PICU are at risk for adverse outcomes following hospital discharge. One study among 1032 persons (aged 0-29 years, median age 19 months), admitted to an Australian PICU for any reason, reported that an additional 7% of survivors died following hospital discharge, and that 10% of these survivors were likely to require dependent care.²⁰

Bordetella pertussis toxin is a complex of several physiologically active agents, with diverse properties. At least 400,000 children die from pertussis annually; the actual incidence of critical pertussis globally remains unknown. The number is probably an understatement, as polymerase chain-reaction

(PCR) testing has suggested.^{13,21} Most cases of critical pertussis, and most fatalities, occur in very young infants (1-10 weeks of age).¹⁰ These children are immunologically immature, and have long presented unique diagnostic and therapeutic challenges in sepsis and organ failure.²² Critical pertussis is associated with leukocytosis and a relative lymphocytosis, with a prominence of small lymphocytes with cleaved nuclei. The most definitive work in characterizing this response suggests that L-selectin activity is lost across several immunologic cell lines. While the relevance for critical organ failure of this relative loss of L-selectin activity remains incompletely understood, it is possible that there is an immunoparalysis induced by *B. pertussis*, perhaps more pronounced in an immunologically immature host; this may explain the course of critical pertussis in this age group.^{23,24} Some reports have indicated that the lymphocytosis is uniform across B and T cells,²⁵ but extensive functional immunophenotyping studies have not been a prominent feature of recent pertussis literature. In acute pertussis infection, the Th-1 phenotype appears to be preferentially increased.²⁵ As yet, the significance of the downregulation of L-selectin activity, and induction of critical organ failure remains understudied, despite recent more definitive descriptions of pertussis pathogenesis.^{26,27} These reports include complex regulation of Type III secretion systems and caspase -independent induction of cell death *in vitro* in *Bordetella* laboratories.²⁶ These incompletely understood mechanisms represent important scientific opportunities for understanding the mechanism of critical organ failure.

One of the well known effects of *B. pertussis* toxin is that on adenylyl cyclase. Via an ADP-ribosylating effect, G proteins such as G_i , G_t , and G_0 are inactivated. As this represents fundamental dismantling of cellular stress responses, there are diverse biological effects attributed to this phenomenon: enhancement of insulin secretion, inactivation of Ca^{2+} dependent channels, acceleration of cyclic (cGMP) dependent phosphodiesterase activity, inhibition of adenylyl cyclase, and paradoxical immunosuppressive and immunostimulatory effects.²⁶ At least one author has suggested that one or more of these downstream, diverse tissue effects may singly or in cohort represent a “point of no return” irreversibility in critical organ failure.²⁸ As well, there are suggestions in the contemporary literature that G-protein uncoupling may be a common pathway of organ-failure induction utilized by diverse agents, especially in view of recent work implicating siRNA in pathogenesis.^{29,30} Thus, it is likely that this descriptive study of a relatively homogeneous cohort of infants represents the scientific opportunity to develop translational hypotheses that will inform further scientific efforts, and enhance the development of the rationale underlying pediatric critical

care practice.

Vaccine-preventable diseases (VPDs) continue to cause severe morbidity and mortality in children worldwide. Remarkably, despite high immunization coverage, morbidity and mortality in developed countries persists. Recent data show markedly increased rates of survival among children with critical illness and highlight the importance of understanding long-term outcomes in survivors.³¹ Moreover, since survival to discharge has become much more common than mortality, quantification of morbidity and acute course characteristics has become urgent. This study in children with a VPD-related critical illness will provide important information used to evaluate vaccination programs. Establishing federal interagency / academic collaboration and the use of existing NIH/NICHD pediatric critical care research infrastructure will provide value beyond the immediate scientific purposes of this study.

2 Specific Aims

The overall purpose of this multicenter prospective cohort study is to describe the societal burden of severe pertussis in the US pediatric population from clinical and health outcome perspectives. Children < 18 years of age with pertussis who require hospitalization in the pediatric intensive care unit (PICU) during their illness will be studied (critical pertussis). The specific aims of this study are:

Specific Aim 1. Characterize children's presentation and acute course of critical pertussis during the PICU admission. Assess severity of illness (Pediatric Risk of Mortality (PRISM III)) at the time of PICU admission, provision of selected modalities of therapy, lengths of ventilatory support, duration of PICU stay, and disposition, including neurologic status, at the time of discharge.

Specific Aim 2. Assess reported health status and family impact in children following discharge from the PICU.

Specific Aim 3. Assess developmental sequelae and quality of life 12 months after discharge from the PICU, for infants who were admitted to the PICU at < 12 months of gestational age, using standardized tools.

Specific Aim 4. Assess risk factors associated with developmental sequelae in children who were admitted to the PICU at < 12 months of gestational age.

3 Eligibility and Enrollment

3.1 Sample Size

This study will collect in-hospital information from eligible pediatric patients admitted to the PICU with confirmed or probable pertussis at participating institutions. These participating hospitals will include the 7 clinical sites in the Collaborative Pediatric Critical Care Research Network (CPCCRN), and 15 to 25 participating centers outside of the CPCCRN; many will be members of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. It is estimated that 200 eligible patients will be identified over the course of the study.

3.2 Study Eligibility

Eligible subjects for this study are those who meet one of the enrollment case definitions for pertussis (age-specific definitions in Table 2 on the next page), are < 18 years of age, and require hospitalization in a pediatric intensive care unit (PICU) during their pertussis illness. Subjects must have:

- Spent ≥ 24 consecutive hours in PICU; OR
- Spent any time in the PICU and died in the unit.

Cases that meet any of definitions 1 to 4 in Table 2 on the following page will be considered confirmed cases. Cases that meet definition 5 in the Table will be considered probable cases.

3.3 Sources of Study Patients

Eligible patients will be admitted to the pediatric intensive care unit (PICU). Subjects at all participating sites will be identified through passive and enhanced surveillance methods.

3.4 Case Finding Strategies for Subject Identification

3.4.1 Role of the Site Principal Investigator

The pediatric intensivist who is the site principal investigator for the study (site PI) is responsible for ensuring he/she (or a delegate such as the research coordinator) can usually be alerted by the next business day whenever a suspected pertussis patient is identified. This site PI is responsible for educating pediatric intensive care unit staff and departments about the study

Table 2: Pertussis Case Definition for Enrollment

	Pertussis Lab Result	Clinical Chronological Age Group	
		A.<6 months	B.≥6 months
1	Culture positive (any specimen)	High index of suspicion for pertussis ^a	High index of suspicion for pertussis ^a
2	PCR positive (any specimen); culture negative, pending, or not done	Same as 1-A	High index of suspicion for pertussis, ^a AND Any cough, any duration
3	Culture and PCR negative, pending, or not done, BUT epidemiologic link to close contact with lab-confirmed pertussis case ^b	Same as 1-A	Same as 2-B
4	Culture and PCR negative, pending, or not done, BUT post-mortem evidence of pertussis ^c	Same as 1-A	Same as 2-B
5	Culture and PCR negative or not done (“Clinical” case)	At least one respiratory symptom, for ≥ 1 week: cough, rhinorrhea, sneeze, respiratory distress, wheeze; or any apnea , AND high index of suspicion for pertussis, ^a AND no other likely etiology	Cough for ≥ 1 week AND at least one classic pertussis symptom (paroxysms, post-tussive emesis, whoop) AND high index of suspicion for pertussis, ^a and no other likely etiology

^aIndex of suspicion must be high enough to inform parent and attending of record that the child likely has pertussis and report case to hospital infection control or health department in accordance with institution, local and state guidelines. Subject inclusion is subject to final adjudication by NIH/CDC Federal PI.

^bThe contact to whom the study subject is epidemiologically linked must meet the CDC/CSSTE definition for lab-confirmed pertussis; the study subject must have been exposed to the contact within 28 days (before or after) of onset of cough in the contact.

^cPositive immunohistochemistry (IHC) on respiratory tissue specimen (e.g., lung tissue) per CDC pathologist protocol.

and for developing a formal communication plan about how to be alerted when suspected pertussis cases are identified (e.g, via a form letter, email or other routine method).

Notification of the site PI should not in any way interfere with or inhibit communication activities with clinical staff caring directly for the patient or public health authorities. For example, if a case of pertussis is identified over the weekend by a nurse, contacting the site PI does not replace the need to contact the patient’s attending physician or physician on duty. Standard clinical and public health practices should be initiated per routine. Once alerted of a suspected case, it is the *sole responsibility of the site PI to decide how to act on the information and whether or not to communicate with other staff about this information* (e.g., to contact the patient’s attending physician, or NIH/CDC Federal PIs for advice). In addition, *it is the site PI’s responsibility to ensure a subject meets the enrollment criteria before initiating the consent and enrollment process.*

3.4.2 Case Finding through Passive Surveillance

All participating sites will use *passive surveillance* (e.g., suspected case is brought to attention through course of normal clinical care) to identify cases. All cases of suspected pertussis should be communicated to the site PI through the established “alert” channels (Section 3.4.1). Pertussis is suspected when a PICU clinical staff member voices strong suspicion for pertussis, when a case of pertussis is reported to any PICU staff member by any person using the word “pertussis” (e.g. health department), or when any pertussis lab test is ordered or result returned. Most likely, these cases would be reported from the hospital infection control department, laboratory, public health department, other patient care areas of the study hospital, or outside hospital and healthcare facilities. However, *the site PI should be alerted of any suspected case.* Some cases may be identified following discharge from the unit; the site PI should be alerted about these cases if it is possible that the child had pertussis during the PICU admission. Cases identified > 2 weeks after discharge will not be accepted in the prospective study. A case of pertussis with symptom onset after discharge from the PICU is not eligible for enrollment, unless the child requires re-admission to the intensive care unit.

3.4.3 Case Finding through Enhanced Surveillance

At all sites, enhanced surveillance will be conducted by 1) the site PI (or delegate) routinely contacting staff/departments to check for suspect cases and 2) using a simple method to ask the PICU attending on duty. To assure that the attending physician on duty remains aware of the study and to assure identification of all cases of pertussis, the site PI will assign a staff member (research coordinator, charge nurse, or other person selected at the site) to ask the attending physician a question like “*Were any patients with suspected pertussis admitted?*” on a routine basis (e.g., at the end of daily rounds). Once alerted, the site PI will enter the suspect case on a tracking form and review the case.

The site PI (or delegate, e.g., research nurse) at all participating centers must also communicate with the *hospital laboratory* and *infection control department* and hospital lab at least once a week, and with the *hospital pathologist* at least monthly regarding possible post-mortem evidence of pertussis in PICU patients.

3.5 Laboratory Testing for Pertussis

All pertussis testing prior to enrollment will be conducted as part of routine care if ordered by the treating physician (institutional or commercial laboratory, state health department). The enrollment case definition for pertussis described above, and the enrollment decision for a suspect case, are to be based on clinical criteria and lab findings available at the time of case identification. The preferred tests are culture and PCR.

If the clinical site isolates *B. pertussis*, the laboratory should retain the isolate until it can be shipped to an outside laboratory that is conducting research in strain genetics, to be identified by the NIH Program Scientist. These isolates will be identified solely with the study number, and not with identifiable patient information. Instructions for shipping will be provided to each site from the laboratory.

All clinical sites will obtain three nasopharyngeal swabs from each enrolled subject solely for the analysis of *B. pertussis* and other bacterial DNA. These isolates will be identified solely with the study number, and not with identifiable patient information. Instructions for shipping will be provided to each site from the laboratory.

All clinical sites will send organism samples (culture plates and/or nasopharyngeal swabs) to the outside central laboratory to be determined by the NIH Program Scientist.

3.6 Data to be Collected in the Study

Eligibility information will be collected for all patients who are identified using criteria described in Section 3.2 on page 13 and Table 2 on page 14. In-hospital data collection will be performed on all enrolled subjects, subject to informed consent restrictions that may be site-specific. Follow-up will be performed up to the 6-month contact for all enrolled and appropriately consented subjects alive at discharge. *The 1-year follow-up interview will only be performed on appropriately consented subjects who were under one year of gestational age at the time of their pertussis-related admission to the PICU.*

3.6.1 Responsibility for Data Collection

The CPCCRN Data Coordinating Center (DCC) will be responsible for data collection systems (described in Section 3.6.2 on the following page). Each Clinical Site will be responsible to collect all data in this study, and enter those data into the data system. The DCC will be responsible for monitoring data entry and sending data queries to each site to clarify unusual data values.

Each Clinical Site will obtain contact information when a subject is enrolled, to enable follow up at 6 months in all enrolled subjects, and follow up at 12 months for enrolled subjects < 12 months of gestational age at time of PICU admission who were discharged alive. This contact information will not be transmitted to the DCC.

When subject accrual is finished and the 12-month assessments are completed, the DCC will link the data together and will then de-identify the data for analysis purposes. Dates of events and birth will be recoded to provide age at each event, and identifiers such as names, medical record numbers, and account numbers, will be removed from the analytical database. This de-identified database will be used for all study analysis purposes.

3.6.2 Data Collection

Eligibility data are to be collected and retained for all subjects who are eligible for the study. If permission to participate in the study is not obtained from the parents or legal guardian, then no further data are to be collected. The eligibility data elements are detailed in Appendix A.1 on page 30.

The child with pertussis is the subject for this study; the data elements that will be collected will address questions about the impact of critical pertussis on the child under study. For subjects who are enrolled in the study,

data will be collected in the following categories:

1. Screening Phase
 - (a) Eligibility data
2. Acute Hospitalization Phase
 - (a) Contact information for follow-up
 - (b) Intake information from primary care giver (usually the parent or legal guardian)
 - (c) Initial PICU chart abstraction
 - (d) Immunization data
 - (e) Daily PICU data collection
 - (f) Pertussis-related laboratory data
 - (g) Discharge data at PICU discharge
 - (h) Data for deceased subjects, when applicable
3. Follow-up Phase
 - (a) Mail survey follow-up at approximately 6-months after PICU discharge
 - (b) Follow-up assessment approximately 12-months after PICU discharge

Detailed lists and definitions of the data elements are found in Appendix 7.4 on page 30.

When a subject is found to be eligible for the study, the site PI or research coordinator will enroll the patient using TrialDB, the electronic research software used by the Data Coordinating Center. It is necessary to have the patient's birthdate, gender, race, and ethnicity, in order to start a study record in this software. The software will automatically assign a Study ID that is used to identify the subject in TrialDB. If permission to participate in this study is not obtained, as described in Section 7.1 on page 25, then only eligibility data will be entered into the TrialDB system.

4 Site Education

Site education will be the joint responsibility of the NIH/CDC Federal PIs and the Data Coordinating Center. In addition, training in developmental assessment at all sites will be designed and supervised by a pediatric neurologist and developmental psychologist, both with expertise in evaluating children following critical illness or injury.

4.1 Personnel Requirements

It is expected that at CPCCRN sites, the site PI and the study research nurses will perform screening, recruitment, data collection, and data submission. At non-CPCCRN centers, an appropriate person is to be identified who will undergo study training, be responsible for IRB approval of this study at their site, and be responsible that the screening requirements detailed above for non-CPCCRN centers are met.

4.2 Training for 1-Year Assessment

A key component of education will be training for the 1-year developmental assessment 12-months after PICU discharge. This assessment must be performed by appropriately credentialed medical personnel e.g., developmental physician, site pediatric intensivist, child psychologist, neurodevelopmental neurologist, or a pediatric research nurse. Individuals who will perform this assessment *must be initially approved by the study Federal Principal Investigators* on the basis of a submitted CV and letters of support. In addition, these individuals *must attend an off-site training session and pass certification testing* at the end of that session. This training will be provided at study expense, but *travel and lodging expenses will be the responsibility of each clinical site.*

It is expected that CPCCRN PI or research coordinator will perform this testing. Non-CPCCRN site PIs may designate off-site personnel who meet the above qualifications, with approval of the Federal Principal Investigators, or perform the testing themselves.

5 Data Management and Site Monitoring

5.1 Data Entry

Study data will be entered on-site by research coordinators using an electronic data collection system developed by the Data Coordinating Center.

The software for data collection will enable online entry of data. This software will incorporate a battery of electronic checks to avoid entry of incorrect or inappropriately missing data. If inconsistent data are entered, Data Coordinating Center staff will contact the respective site with a data “query” to resolve the issue.

5.2 Site Monitoring

Study personnel, including representatives of the Data Coordinating Center and the NICHD, CDC, and study investigators, may perform routine and non-routine site visits as required. During these visits, relevant hospital records and study-specific documents will be examined to ensure compliance with all study requirements. Activities during these visits may include, but not be limited to:

- Review of medical records of enrolled patients to ensure eligibility, as well as complete and accurate entry of study data
- Review of consent documents for patients in the follow-up portion of the study
- Review of PICU admission data and Infection Control Office records to ensure that all potentially eligible subjects have been enrolled.

6 Statistical Analysis Plan

This study will enroll a cohort of approximately 200 children with severe pertussis. A major goal of this study is to provide **descriptive information** about what treatments and support these children receive in the PICU, their status at time of PICU discharge, and how those who survive critical pertussis as infants are faring at up to one year after their illness. A second overarching goal of this study is to **generate hypotheses** about factors predictive of adverse outcomes in these children, both acutely and longer-term. In line with these broad-ranging study goals, the following sections outline the outcomes and analytic approach for the Specific Aims of the study.

6.1 Characterize acute PICU hospital course

Specific Aim 1. Characterize children’s presentation and acute course of critical pertussis during the PICU admission. Assess severity of illness

(Pediatric Risk of Mortality (PRISM III)) at the time of PICU admission, provision of selected modalities of therapy, lengths of ventilatory support, duration of PICU stay, and disposition, including neurologic status, at the time of discharge.

The analytic approaches for this Aim will be primarily descriptive, involving appropriately summarized univariate distributions of the clinical outcomes derived from information collected during PICU admission. These summary measures include key information about distributions. For example, outcome measures with approximately normal distributions can be summarized by mean, standard deviation, and possibly minimum and maximum. Substantially skewed measures are more appropriately described using median, interquartile range, and minimum and maximum. Graphical approaches such as histograms summarizing overall distributions, and boxplots comparing distributions between patient subgroups, are often of high utility to clinical audiences and readers. Various PICU hospital course data elements to be reported, and relevant analytic concerns, are discussed below.

PICU Admission Data (Appendix A.4 on page 43). PICU admission data includes demographic data, birth history data, baseline laboratory and immunization data, pertussis confirmation data, and presentation and symptoms data. This information will be collected during the PICU admission from the primary caregiver (usually the parent or legal guardian) and the medical record. Immunization data may be obtained by contacting the child's primary care healthcare provider.

The presentation and symptoms data include severity of illness, as measured by the Pediatric Risk of Mortality (PRISM III) score.^{32,33} The PRISM III score is a predictive marker, based on 17 physiologic variables subdivided into 26 ranges, that measures risk of mortality. The PRISM III score can range from 0 to 74.

PICU Daily Data (Appendix A.5 on page 50). Daily data collection will focus on key laboratory and physiological parameters, as well as invasive support therapies. The occurrence of rescue therapies will also be noted on a daily basis. Daily data collection will end after 28 days in the PICU, if the subject is still in the PICU.

PICU Outcome. While death may occur at any time during PICU admission, mortality is likely to be a relatively rare outcome in this study. The overall death rate in PICUs has been estimated to be 6%.³⁴ In a Canadian

study, the estimated case fatality rate due to pertussis in PICUs was 5.7% (10/175).⁸ One recent U.S. study of pertussis hospitalizations reported a case fatality rate of 1.9% (6/317) among case-infants admitted to the intensive care unit.¹⁴ If we assume a case fatality rate of 6%, we estimate that 12 deaths might occur among 200 children enrolled in our study.

For binary outcome variables such as acute mortality, the number and percent of subjects with an event will be calculated. Univariate analyses may also be performed to identify factors associated with adverse PICU outcomes, although for rare events, relevant techniques such as Fisher's Exact Test have very limited power. Results of such testing will be reported as exploratory, especially for instances where a factor has not shown association with mortality in other published reports.

6.2 Assess reported health status after discharge

Specific Aim 2. Assess reported health status and family impact in children following discharge from the PICU.

We will perform a primarily descriptive analysis of health status information collected following discharge from PICU:

Health status and family impact will be assessed in the hospital, at 6 months after discharge from PICU, and for infants only, again at 12 months after discharge from PICU. The instruments are obtained from HealthActCHQ. The interview tool is age dependent:

- For subjects who are 5 years or older, the Child Health Questionnaire (CHQ) PF28; OR
- For subjects under 5 years, the Infant Toddler Quality of Life Questionnaire (ITQOL)

Clinical status will be measured on the day of PICU discharge, and for infants only, one year after PICU discharge.

6.3 Developmental outcomes of critical pertussis

Specific Aim 3. Assess developmental sequelae and quality of life 12 months after discharge from the PICU, for infants who were admitted to the PICU at < 12 months of gestational age, using standardized tools.

Developmental sequelae will be assessed in infants who were < 12 months of gestational age at the time of PICU admission. The specific standardized

instrument used for developmental assessment will be the Mullen Scales of Early Learning.³⁵ The Mullen Scales have not been translated and validated in Spanish, but for this study, assessment of children with Spanish speaking primary caregivers will be done by a bilingual examiner or an examiner with translator assistance. The scores derived from the Mullen Scales have been standardized using a nationally representative sample: a composite score (mean=100, SD=15), and four subscale scores (visual reception, fine motor, receptive language, and expressive language) (mean=50, SD=10). These scores are appropriate for 0-68 month olds. An additional subscale score, appropriate for 0-33 month olds, is gross motor (mean=50, SD=10). We will thus be able to identify subjects whose development 12 months after discharge is delayed according to well-defined, age-specific norms.

It should be pointed out that the Mullen is a relatively new instrument not yet in wide use. Similar older instruments such as the Bayley Mental Developmental Index have been used in published reports and can help guide the Mullen analysis.³⁶⁻³⁸ These reports created a binary outcome (abnormal versus normal) by defining abnormality as a score more than two standard deviations below the mean. For instance, using the composite score derived from the Mullen Scales, a subnormal score will be defined as $< 70 [= 100 - 2(15)]$. Other cutoff points may be used based on percentiles or other measures.

Subjects who died in the PICU or during follow-up may be incorporated into a developmental analysis by creation of additional categorical outcomes, such as death versus survival, and an ordered outcome (death during hospital stay, death after discharge, survival with at least one abnormal score, survival with all normal scores). In addition to such categorical outcomes, the neurodevelopmental, clinical status, and Mullen scores can be considered as continuous outcomes, whose distributions can be summarized graphically and to discern any patterns or differences between subgroups of children.

6.4 Risk factors for developmental sequelae

Specific Aim 4. Assess risk factors associated with developmental sequelae in children who were admitted to the PICU at < 12 months of gestational age.

A secondary aim of the study is to identify characteristic factors associated with developmental sequelae. The developmental sequelae described for Aim 5 will be considered as the dependent variables in this analysis, and the independent variables will be derived from information collected during

the study. Univariate analysis will be performed to test the null hypothesis of no association between each independent variable and each dependent variable. The primary measure of association for this part of the analysis will be the risk ratio. A key point in this analysis is that results be considered exploratory, and that in any publications a clear indication be given of the number of variables examined. Clinicians will likely give more weight to a factor that previously showed a significant association in other published reports. In general, results of all analyses will need to be confirmed in future studies of different patients in different settings by different clinicians.

Potential risk factors for adverse outcomes have been identified from the pertussis literature and included in the data collection tools (*e.g.*, prematurity, leukocytosis at PICU admission). These factors will be evaluated in the analysis. We may be limited in assessing the independent effects of age and vaccination status because they are correlated variables; among infants, DTaP vaccine is recommended to be administered at two, four, and six months of age. Most infants with critical pertussis are less than 2 months old and unimmunized. One way to assess the independent effects is to stratify on both age and vaccination status, but too few subjects may exist in the resulting strata (*e.g.*, age two months with or without vaccination).

Various statistical techniques or combinations of techniques may be used to identify factors potentially associated with adverse outcomes. For categorical outcomes, these include classification tree analysis^{39–41} and logistic regression. For continuous outcomes, additional techniques such as regression tree analysis and linear regression may be used. Classification and regression trees can be useful for describing associations in the data and identifying distinct subgroups at risk for adverse outcomes, possibly subgroups defined by a combination of clinical variables. Logistic and linear regression analyses are useful for estimating the net effects of risk factors on the adverse outcomes.

One important consideration for all multivariable analyses is the total sample size and final number of outcome events (abnormal outcomes). If these numbers are too small (as they will likely be for mortality), then problematic results may occur. For instance, simulation studies of logistic regression analysis have suggested that the number of the less common of the two possible outcomes (*e.g.*, abnormal vs. normal) divided by the number of predictor variables should be at least ten.⁴² This condition for valid results may limit our ability to identify independent risk factors for adverse outcomes. A similar sample size consideration applies to classification and regression tree analyses, which are large sample techniques.

7 Human Subjects Protection

7.1 Informed Consent Issues

The Data Coordinating Center and each clinical site (CPCCRN and non-CPCCRN) must obtain approval from their respective IRB prior to participating in the study. The DCC will track the IRB approval status at all participating centers.

7.1.1 Waiver of Consent for Retaining Screening Data

Waiver of consent is requested for retaining screening data that is collected about patients to determine eligibility for enrollment in this study. The data elements collected to determine eligibility are limited, and are listed in Appendix A.1 on page 30. Briefly, the data elements include date of birth, data of PICU admission, gender, race, ethnicity, type of eligibility (from Table 2 on page 14), critical nature of the illness, whether the child was enrolled for further participation, and whether the child is alive or deceased. Retaining this eligibility data from all eligible subjects is important to the scientific integrity of the study. Failure to include all cases would invalidate estimation of the burden of critical pertussis, a primary purpose of the study. Demographic data (gender, race, and ethnicity) are included in screening data in order to assess generalizability of results from the study population. For example, if the screened eligible population includes a greater proportion of Hispanic cases than the consented population, the study findings may not be generalizable. The DCC tracks the gender, race and ethnicity of subjects screened and recruited into all CPCCRN studies and reports these data to NICHD.

The justification for waiver of consent for this eligibility data collection includes the following:

1. Collection of this information does not require patient contact.
2. There is no intervention or any variation from usual patient care. Declining to participate in this study will not change the course of patient care or affect the patient's rights or welfare.
3. There is no required patient contact, intervention, or variation from normal care, so collecting and retaining these data pose minimal risk to the patient or family of loss of confidentiality.

4. The data will be de-identified by the Data Coordinating Center. The age will be calculated from dates of birth and admission, but investigators will not have access to the actual dates of birth or admission.
5. Failure to include all cases of critical pertussis would impair the scientific validity of the study.

7.1.2 Waiver of Consent for Analysis of Bacterial Isolates

Waiver of consent is requested for analyses of bacterial isolates that are identified as *B. pertussis*. These analyses will be carried out at an outside laboratory to be identified by the NIH, and specimens will be solely identified with a study number. The analyses involve genomic analysis of the organism, and no biologic markers from subjects are involved. Justification for waiver of consent includes the following:

1. Bacterial isolates were obtained in course of normal care, and shipping of the isolates to a specialized laboratory does not require patient contact and poses no patient risk.
2. There is no intervention or any variation from usual patient care. Declining to participate in this study will not change the course of patient care or affect the patient's rights or welfare.
3. There is no required patient contact, intervention, or variation from normal care, so collecting and retaining these isolates from the hospital laboratory pose no risk to the patient or family.
4. Clinical data provided, for correlation with bacterial genomic analyses, will be restricted to de-identified data.

7.1.3 Obtaining consent for live eligible subjects

Cases that meet any of the pertussis case definitions 1 to 4 in Table 2 on page 14 will be considered confirmed cases. Cases that meet definition 5 in the Table will be considered probable cases. Subjects must be probable or confirmed cases in order to be eligible for this study. The site investigator or research coordinator should approach the patient's family to enroll them for the purpose of doing the long term functional outcome assessment as soon as possible after eligibility has been determined.

It is possible that the parent or legal guardian may not be present to sign the consent form, or that an eligible case may occasionally escape detection

until after PICU discharge. In these situations, the research coordinator at CPCCRN sites should contact the parent or legal guardian by telephone, and obtain verbal informed consent by telephone. The telephone call and its outcome will be documented. If permission is granted, the coordinator should schedule a time to interview the primary caregiver (usually the parent or legal guardian) by telephone or in person, to obtain the intake data and contact information. If indicated, PICU data would be obtained by retrospective medical record abstraction.

7.1.4 Obtaining permission for dead eligible subjects

For PICU subjects who were not enrolled during the PICU admission, but die and are found to have autopsy evidence of pertussis, a different approach will be used to obtain permission for enrollment in the study.

When the investigator or research coordinator identify a deceased subject who meets the eligibility criteria for this study, a letter will be sent to the parents or legal guardian of the subject. This letter will provide information about the study, and will indicate that they will receive a telephone call from the research coordinator to discuss whether they would be interested in participating in the study. It will also provide an option for parents to notify study staff that they do not wish to be contacted. Within approximately two weeks of sending this informational letter, the research coordinator will telephone the parents or legal guardian, and ask if they would be willing to participate in the study. If the parents or legal guardian agree to participate, then a time will be scheduled for a subsequent telephone call, during which he or she will be asked all the questions that comprise the intake information from the primary care giver of the subject (Appendix A.3 on page 31). This methodology has successfully been used at CPCCRN sites with bereaved parents.⁴³

Waiver of written informed consent is requested for these activities; verbal consent will be obtained and documented at the time of the first telephone call, and at any point during these telephone calls, parents or legal guardian have the ability to terminate participation by hanging up. Written HIPAA authorization should not be required, because the subject is deceased. In addition, all analytical data sets for this project are de-identified by the Data Coordinating Center in Utah (see Section 7.3 on page 29).

7.1.5 Subject Reimbursement Issues

Subjects may be reimbursed for travel expenses to attend follow-up. Generally \$60 will be provided as reimbursement but the amount may vary depending on travel circumstances. Reimbursement policies will be explicitly stated on the parental consent instruments, and are subject to approval by each Institutional Review Board (IRB).

7.2 Data Security

The Data Coordinating Center at the University of Utah has a dedicated, locked server room within its offices, and the building has 24 hour on-site security guards. The Data Coordinating Center has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the Data Coordinating Center with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. TrialDB is the clinical trials software used at the Data Coordinating Center in Utah, and eRoomTM is used for communications about the study. TrialDB, eRoomTM and other web applications use the SSL protocol to transmit data securely over the Internet.

Direct access to Data Coordinating Center computers is only available while physically located inside the Data Coordinating Center offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the Data Coordinating Center are fully committed to the security and confidentiality of all data collected for CPC-CRN studies. All personnel at the Data Coordinating Center at the Uni-

versity of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with Data Coordinating Center data systems have received Human Subjects Protection and HIPAA education.

7.3 Health Insurance Portability and Accountability Act

Registration of research subjects in the TrialDB system used by the DCC at the University of Utah requires a date of birth, race, ethnicity, and gender. These demographic data are held in database tables that are separate from coded research data (including clinical data). The demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For patients who are screened but whose parents do not wish to enroll them in the study, the data will be de-identified by the Data Coordinating Center. The only identifiers collected in the screening data are the dates of birth and admission, and these will be recoded into the patient's age, in days. The analysis database will not include the dates of birth or admission.

For patients who are enrolled in the study, authorization for access to medical records, including the outpatient immunization record, will be obtained as part of the initial informed consent process. It is permissible to combine this authorization with the informed consent documents, but this is subject to approval by each Institutional Review Board and, if applicable, relevant privacy boards at clinical sites. The purpose of this authorization is to allow on-going access to the medical record during the daily hospital course and during follow-up. For deceased subjects who are identified after their death (Section 7.1.4 on page 27), it is requested that authorization not be required because the analytical data sets will be de-identified (see below), and the patient is deceased.

Contact information will be collected to permit follow-up at 6 months, and 12 months after PICU discharge. These data will be retained at the Clinical Site and will not be transmitted to the DCC. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude patient identifying information. The analytical data set will be de-identified as defined by HIPAA regulations.

The Data Coordinating Center produces the de-identified research data sets that will be used for all analyses in this project. Since the raw data includes potential identifiers, such as dates of birth and admission, as well as contact information for patients, all CPCCRN sites have been offered a

Business Associate Agreement (BAA) with the University of Utah. Similar Business Associate Agreements will be offered to non-CPCCRN sites that participate in this study. The BAA explains that the Data Coordinating Center is producing the de-identified data using the data submitted by the site, and the University of Utah assumes responsibility to preserve the confidentiality of the original data. Copies of executed Business Associate Agreements are maintained at the Data Coordinating Center in Utah.

All analyses will be conducted with de-identified data sets created by the Data Coordinating Center. Investigators and statisticians will only have access to these de-identified data sets.

7.4 Record Retention

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

A Study Data Points

A.1 Eligibility Data

These data elements should be collected on *all* patients who fulfill eligibility for enrollment in this study. Waiver of informed consent is requested for these data elements. If parental permission is not obtained for enrollment into the study, then no further data collection will be undertaken.

1. Date of birth
2. Date and time of admission to PICU
3. Gender
4. Race - from the chart only
5. Ethnicity - from the chart only

6. Type of eligibility (definition of each type is from Table 2 on page 14)
 - (a) Type 1 - positive culture with or without a positive PCR test
 - (b) Type 2 - positive PCR
 - (c) Type 3 - epidemiologic link
 - (d) Type 4 - post-mortem evidence
 - (e) Type 5 - clinical syndrome
7. Critical nature of illness
 - (a) Spent at least 24 consecutive hours in PICU
 - (b) Spent any time in the PICU and died in the unit.
8. Vital status when eligibility determined
 - (a) Alive
 - (b) Deceased
9. Enrollment consent obtained
 - (a) Yes
 - (b) No

If enrollment consent is not obtained, no further data will be collected and retained for the patient.

A.2 Contact Information

If enrollment consent is obtained, contact information should be obtained from the family, including the name, address, telephone numbers, and email address for the parents, primary caregiver, and legal guardians, as appropriate. The child's name should also be recorded on this contact sheet. These data will be used to enable followup at six months, and 12 months, and to arrange the neurodevelopmental assessment at 12 months following PICU discharge.

A.3 Intake Data from Parent / Guardian / Primary care giver

Data in this section should be obtained by interviewing the parent or guardian of the subject. If the parent or guardian is not the primary care giver for the subject, the parent or guardian may direct the interviewer to obtain

this information from the person they designate as the primary care giver. Therefore, this interview will usually be with a parent or guardian, but may be with a grandmother, or other relative, etc.

A.3.1 Demographic Information

1. Method of interview
 - (a) In person
 - (b) By telephone
2. Name of patient - not to be transmitted, for worksheet only
3. Date of birth of subject
4. Gender of subject
5. Race of subject

American Indian or Alaska Native A person having origins in any of the original peoples of North and South America, including Central America, and who maintains tribal affiliation or community attachment.

Asian A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American A person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Other (provide text) Should provide text description.

Stated as Unknown Explicitly stated as unknown.

6. Ethnicity of subject
 - (a) Hispanic or Latino
 - (b) Not Hispanic or Latino

- (c) Stated as Unknown
7. Subject born in the United States
- (a) Yes
 - (b) No - please identify where subject was born
 - i. Mexico
 - ii. Central America other than Mexico
 - iii. Caribbean
 - iv. South America
 - v. Europe
 - vi. Africa
 - vii. Asia
 - viii. Australia
 - ix. Pacific Islands
 - x. Other
 - (c) Unknown
8. Relationship of *person being interviewed*, to subject
- (a) Mother biological
 - (b) Father biological
 - (c) Mother by adoption or stepmother
 - (d) Father by adoption or stepfather
 - (e) Grandmother
 - (f) Grandfather
 - (g) Other relative
 - (h) Guardian or foster parent
 - (i) Babysitter, nanny, governess
 - (j) Other
9. Race of biological mother
10. Ethnicity of biological mother
11. Relationship of *primary care giver*, to subject
- (a) Mother biological

- (b) Father biological
 - (c) Mother by adoption or stepmother
 - (d) Father by adoption or stepfather
 - (e) Grandmother
 - (f) Grandfather
 - (g) Other relative
 - (h) Guardian or foster parent
 - (i) Babysitter, nanny, governess
 - (j) Other
12. Race of primary care giver
13. Ethnicity of primary care giver
14. Age of primary care giver (years)
15. Highest education of *primary care giver* (*Choose one*)
- (a) Some high school or less
 - (b) High school diploma or GED
 - (c) Vocational school or some college
 - (d) College degree
 - (e) Graduate or doctoral degree
 - (f) Unknown
16. Work situation of *primary care giver* (*Choose one*)
- (a) Working or attending school ≥ 30 hours per week
 - (b) Working or attending school < 30 hours per week
 - (c) Full time care giver of subject, not looking for work
 - (d) Looking for work

A.3.2 Birth Information

1. Subject born premature (< 37 weeks gestation)
- (a) Yes
 - (b) No

2. Gestational age at birth (weeks)
3. Birth weight
4. Multiple births?
 - (a) No, single birth
 - (b) Yes, twins
 - (c) Yes, triplets
 - (d) Yes, more than triplets
5. Medical complications for the baby during pregnancy, labor, or delivery
 - (a) No complications
 - (b) Unknown if there were complications
 - (c) Yes, but they did not require hospitalization
 - (d) Yes, and they required hospitalization of baby
 - (e) List complications (free text entry)
6. Subject required special medical care due to problems during pregnancy, labor, or delivery
 - (a) No special medical care was required
 - (b) Unknown if special medical care required
 - (c) Yes, special medical care was required temporarily
 - (d) Yes, and special medical care continues to be required
 - (e) List special medical care (free text entry)
7. Subject age at discharge after birth (days)
8. Biological mother's age at birth of subject (years)
9. Were there any problems with the baby during pregnancy?
 - (a) No
 - (b) Unsure
 - (c) Yes
 - i. Poor fetal movement
 - ii. Growth retardation

- iii. Other problem (free text entry)
10. Did a healthcare provider diagnose any congenital abnormalities (birth defects)?
- (a) Yes
 - (b) No
 - (c) Unsure
11. Did the baby have to stay in the neonatal intensive care unit (NICU) before discharge home?
- (a) Yes
 - (b) No
 - (c) Unsure
12. If the baby was in the NICU, was mechanical ventilation (breathing machine) required?
- (a) Yes
 - (b) No
 - (c) Unsure

A.3.3 Immunization History

For all age patients, ask parent/guardian if child ever received a pertussis (whooping cough) vaccine, also called DTP?

If answer is yes, ask how many doses were received, or if this is unknown.

List all locations where child has received vaccines and/or primary care (list phone number of medical practice and name of provider, if known).

Chronological age of child:

1. < 3 months of age
2. \geq 3 months of age

If the child is less than 3 months of age, skip the remainder of questions in this section, because by definition the immunizations are not considered delayed. If the child is \geq 3 months of age, then ask the following questions:

The reported shot status for the subject:

1. The subject has received all shots on time; this includes babies who had shots in the nursery before discharge but are not due for their next shots

2. The subject has missed some shots
3. The interviewee does not know about the subject's shot history

Did subject miss any pertussis (whooping cough) shots?

1. No, received all shots on time
2. Unsure
3. Yes, missed one or more shots

A.3.4 Onset of Acute Pertussis

1. When did the child become ill or appear less well than usual? (Date)
2. If date not known, estimated number of days the child was ill before the PICU admission? (Number of days)

A.3.5 Baseline neurodevelopmental status

These questions refer to *prior to* the beginning of the current pertussis illness.

1. Did the child seem behind, compared with other infants or children of the same age?
 - (a) Yes
 - (b) No
 - (c) Unsure
2. What were the results of the newborn hearing screening test?
 - (a) Normal
 - (b) Abnormal
 - (c) Indeterminate
 - (d) Not done
3. Was the caregiver told by a healthcare provider that the child had developmental delay?
 - (a) Yes
 - (b) No
 - (c) Unsure

4. Was the caregiver told by a healthcare provider that the child had hearing problems?
 - (a) Yes
 - (b) No
 - (c) Unsure

5. Was the caregiver told by a healthcare provider that the child had vision problems?
 - (a) Yes
 - (b) No
 - (c) Unsure

6. Was the child receiving early intervention for developmental delay, hearing, or vision problems?
 - (a) Yes
 - (b) No
 - (c) Unsure

A.3.6 Subject Health Status Before Pertussis Illness

The parent's perception of the subject's quality of life *prior to onset of pertussis* will be assessed as early as possible after enrollment in the study. The instruments are obtained from HealthActCHQ. The interview tool is age dependent:

- For subjects who are 5 years or older, the Child Health Questionnaire (CHQ) PF28; OR
- For subjects under 5 years, the Infant Toddler Quality of Life Questionnaire (ITQOL)

Indicate if the parents were told by a healthcare provider that the subject had any of the following conditions *prior to onset of pertussis*:

1. Asthma or reactive airway disease
 - (a) Yes
 - (b) No
 - (c) Unsure

2. Chronic lung disease other than asthma

- (a) Yes
 - (b) No
 - (c) Unsure
3. Heart disease, congenital or acquired
- (a) Yes
 - (b) No
 - (c) Unsure
4. Metabolic or hormone disease, such as diabetes
- (a) Yes
 - (b) No
 - (c) Unsure
5. Suppressed immune system
- (a) Yes
 - (b) No
 - (c) Unsure
6. Allergy
- (a) Yes
 - (b) No
 - (c) Unsure
7. Blood or hemoglobin disease
- (a) Yes
 - (b) No
 - (c) Unsure
8. Kidney disease
- (a) Yes
 - (b) No
 - (c) Unsure
9. Gastrointestinal disease, such as reflux
- (a) Yes
 - (b) No
 - (c) Unsure
10. Epilepsy or seizures

- (a) Yes
- (b) No
- (c) Unsure

11. Receiving anticonvulsants

- (a) Yes
- (b) No
- (c) Unsure

12. Other neurologic or neuromuscular disorder

- (a) Yes
- (b) No
- (c) Unsure

13. Genetic anomaly or congenital malformation

- (a) Yes
- (b) No
- (c) Unsure

14. Cancer

- (a) Yes
- (b) No
- (c) Unsure

15. Trauma requiring hospitalization

- (a) Yes
- (b) No
- (c) Unsure

Before the pertussis illness, did the subject have any of the following medical devices:

1. Gastrostomy tube

- (a) Yes
- (b) No
- (c) Unsure

2. Other feeding tube

- (a) Yes
- (b) No

(c) Unsure

3. Tracheostomy

(a) Yes

(b) No

(c) Unsure

4. Home ventilator

(a) Yes

(b) No

(c) Unsure

5. Ventricular shunt (CSF)

(a) Yes

(b) No

(c) Unsure

A.3.7 History of Pertussis Illness

Did the child have a cough during the acute pertussis illness?

1. Yes
2. No

If the child had a cough during the acute pertussis illness:

1. What date did the cough start? (Date)
2. If date unknown, how many days prior to PICU admission?
3. When did the cough stop?
 - (a) Still coughing at time of PICU admission
 - (b) Cough stopped on specific date (Date)
 - (c) Cough stopped, but timing uncertain
 - (d) Unsure if cough has stopped
4. Was cough associated with any of the following symptoms before coming to the PICU?
 - (a) Couldn't stop coughing or hard to catch breath
 - i. Yes

- ii. No
- iii. Unsure
- (b) High pitched noise (whoop) between spells
 - i. Yes
 - ii. No
 - iii. Unsure
- (c) Vomiting after the coughing
 - i. Yes
 - ii. No
 - iii. Unsure
- (d) Fainting or passing out during or after coughing spell
 - i. Yes
 - ii. No
 - iii. Unsure

Did the child have any of the following other symptoms during the acute pertussis illness, prior to admission to the PICU?

1. Stopped breathing for 20 sec or longer, unassociated with cough
 - (a) Yes
 - (b) No
 - (c) Unsure
2. Tongue or face turned blue, unassociated with cough
 - (a) Yes
 - (b) No
 - (c) Unsure
3. Runny nose or nasal congestion
 - (a) Yes
 - (b) No
 - (c) Unsure
4. Fever above 101 degrees F
 - (a) Yes
 - (b) No
 - (c) Unsure
5. Difficulty with feeding

- (a) Yes
- (b) No
- (c) Unsure

6. Seizures or convulsions

- (a) Yes
- (b) No
- (c) Unsure

A.4 Initial PICU Chart Abstraction

For purposes of this protocol Day 0 is the day of admission to the PICU, and lasts until 23:59 of that day. If the subject is admitted after 18:00, then Day 0 extends to 23:59 of the subsequent calendar day.

Some subjects will have multiple PICU admissions, and whether to include these admissions in the study is subject to the following rules:

1. PICU admissions prior to the PICU admission during which the patient is identified as eligible for this study are *not* to be included.
2. Following a PICU admission during which a subject is identified as eligible for this study, subsequent PICU admissions (“bounce backs”) will *not* be included as part of the acute PICU course *unless they occur within 72 hours of initial discharge from the PICU*.

A.4.1 Demographic Data

1. Date and Time of Admission to PICU

A.4.2 Birth History Data

1. Birth weight (kg)
2. Gestational age at birth
3. NICU admission
 - (a) Yes
 - (b) No
 - (c) Unknown
4. NICU mechanical ventilation or CPAP (if there was NICU admission)
 - (a) Yes

- (b) No
- (c) Unknown

A.4.3 Immunization Status

The immunization history should be obtained from medical records from the vaccination site (or immunization registry, if available) whenever this is possible. Parent records (e.g., shot card) may be copied if available but should only be used to verify immunization status if the information is not available from the vaccination site. The usual vaccination schedule includes administration of up to six points in time. Table 3 summarizes the usual vaccination schedule (since 2006).

Table 3: Routine Pediatric and Adolescent Pertussis Vaccine Schedule, 2007

Dose	Chronological Age	Usual Formulation
1	2 months (as early as 6 weeks)	DTaP
2	4 months	DTaP
3	6 months	DTaP
4	15 to 18 months	DTaP
5	4 to 6 years	DTaP
6	11 to 12 years	Tdap

Data are collected for each dose that has been administered to the child. For each dose, collect the following information:

1. Source of information:
 - (a) Regular primary care providers office/clinic
 - (b) Public health clinic
 - (c) Hospital records, including emergency department
 - (d) Urgent care records
 - (e) Immunization registry
 - (f) Parent record (immunization card)
 - (g) Other (specify, free text)
2. Date of administration
3. Type of vaccine:

- (a) DTaP
 - i. DTaP alone
 - ii. DTaP-Hib
 - iii. DTaP-HepB-IPV
 - iv. DTaP-Hib-IPV
 - v. Other (specify, free text)
- (b) DTP
- (c) DTP/DTaP
- (d) DT
- (e) Tdap
- (f) Td
- (g) None
- (h) Unknown
- (i) Other (specify, free text)

It is important to try to validate the immunization history rigorously. Please document all pertussis, tetanus and diphtheria toxoid-containing vaccinations as they are recorded in medical records. Record as much information as is available. If it is not apparent whether the child received DTP (whole cell) or DTaP (acellular) vaccine, then choose DTP/DTaP. It is not necessary to abstract information about other vaccines.

Please note the source for each dose entry, using the codes provided above. For infants < 6 weeks of chronological age at the time of PICU admission, it is not necessary to obtain verification of zero doses unless the parent reported that the baby *did* receive a DTaP vaccination. If a parent reports that a baby < 6 weeks old received a pertussis vaccination, verbal communication with the physician office may be used to confirm that this did not happen. Written documentation from the physician office is desirable for all other situations, to assure the most accurate information about the precise vaccines administered.

A.4.4 Pertussis Laboratory Data

The laboratory tests used to diagnoses pertussis are reported here. All applicable tests should be reported.

1. Type of test:

- (a) Culture
 - (b) PCR
 - (c) Serology
 - (d) Direct fluorescent antibody (DFA)
 - (e) Other - specify in free text
2. Collection date and time
3. Laboratory facility:
- (a) Hospital laboratory
 - (b) Commercial laboratory
 - (c) Public health department
 - (d) CDC
 - (e) Other - specify in free text
4. Specimen type:
- (a) Nasopharyngeal (NP) swab
 - (b) Nasopharyngeal (NP) dry aspirate
 - (c) Nasopharyngeal (NP) wash
 - (d) Nasopharyngeal (NP) - unspecified
 - (e) Blood
 - (f) Lung biopsy
 - (g) Fiberoptic bronchoalveolar lavage (BAL)
 - (h) Deep alveolar lavage
 - (i) Endotracheal suctioning
 - (j) Post-mortem specimens - specify in free text
 - (k) Other - specify in free text
 - (l) Unknown
5. Result:
- (a) Positive
 - (b) Negative
 - (c) Equivocal
6. Comments (free text)

A.4.5 Documented Past Medical History

1. Asthma or reactive airway disease
 - (a) Yes
 - (b) No
 - (c) Not documented
2. Chronic lung disease other than asthma
 - (a) Yes
 - (b) No
 - (c) Not documented
3. Heart disease, congenital or acquired
 - (a) Yes
 - (b) No
 - (c) Not documented
4. Metabolic or hormone disease, such as diabetes
 - (a) Yes
 - (b) No
 - (c) Not documented
5. Suppressed immune system
 - (a) Yes
 - (b) No
 - (c) Not documented
6. Allergy
 - (a) Yes
 - (b) No
 - (c) Not documented
7. Blood or hemoglobin disease
 - (a) Yes
 - (b) No
 - (c) Not documented
8. Kidney disease
 - (a) Yes
 - (b) No

- (c) Not documented
- 9. Gastrointestinal disease, such as reflux
 - (a) Yes
 - (b) No
 - (c) Not documented
- 10. Chronic epilepsy or seizures
 - (a) Yes
 - (b) No
 - (c) Not documented
- 11. Seizures associated with current illness
 - (a) Yes
 - (b) No
 - (c) Not documented
- 12. Receiving anticonvulsants
 - (a) Yes
 - (b) No
 - (c) Not documented
- 13. Other neurologic or neuromuscular disorder
 - (a) Yes
 - (b) No
 - (c) Not documented
- 14. Genetic anomaly or congenital malformation
 - (a) Yes
 - (b) No
 - (c) Not documented
- 15. Cancer
 - (a) Yes
 - (b) No
 - (c) Not documented
- 16. Trauma requiring hospitalization
 - (a) Yes
 - (b) No
 - (c) Not documented

A.4.6 Admission Presentation and Symptoms Data

1. Symptoms present at time of admission
 - (a) Cough
 - i. Yes
 - ii. No
 - (b) Cyanosis
 - i. Yes
 - ii. No
 - (c) Apnea
 - i. Yes
 - ii. No
 - (d) Bradycardia
 - i. Yes
 - ii. No
 - (e) Respiratory distress
 - i. Yes
 - ii. No
 - (f) Seizures
 - i. Yes
 - ii. No
 - (g) Altered mental status
 - i. Yes
 - ii. No
2. Admission vital signs
 - (a) Length / Height (cm) and percentile for age
 - (b) Weight (kg) and percentile for age
 - (c) Head circumference (cm) and percentile for age
 - (d) Temperature (Celsius)
 - (e) Respiratory rate
 - (f) Heart rate
 - (g) Oxygen saturation % (first reading in PICU)
 - (h) FiO₂ at time of oxygen saturation measurement

3. Neurological findings (age wnl, altered tone/posturing/movements)
 - (a) Grossly normal for age
 - (b) Altered tone, posturing, or abnormal movements
 - (c) Unable to assess because of heavy sedation or muscle relaxant
4. Status on Admission to PICU
 - (a) Muscle relaxant
 - i. Yes
 - ii. No
 - (b) Intubated
 - i. Yes
 - ii. No
 - (c) Mechanical ventilation
 - i. Yes
 - ii. No
5. PRISM III
6. PICU admission diagnosis (free text)

In addition to the data items listed above, the data elements to be collected on a daily basis (Appendix A.5) will also be collected on Day 0.

A.5 PICU Information Collected on a Daily Basis

This data is to be collected for each day that the subject is in the PICU, beginning with the day of PICU admission. Since the study days are based on calendar dates, the research coordinator will be reviewing data for the previous day, as the recorded data should reflect the most abnormal or severe value for the respective study day.

Neurological Parameters

1. Neuromuscular blockade (any time during the day)
 - (a) Yes
 - (b) No
2. Receiving anticonvulsants

- (a) Yes
- (b) No
- 3. Seizure
 - (a) Yes
 - (b) No
- 4. Abnormal posturing
 - (a) Yes
 - (b) No
- 5. Evidence of CNS bleed
 - (a) Yes
 - (b) No
- 6. Altered mental status
 - (a) Yes
 - (b) No
- 7. Other abnormal neurological observations noted
 - (a) Yes
 - (b) No

Respiratory Parameters

- 1. Cough (yes, no, or intubated)
- 2. Cyanosis
 - (a) Yes
 - (b) No
- 3. Apnea
 - (a) Yes
 - (b) No
- 4. Chest X-ray (Normal, abnormal, not done)
- 5. Nasal cannula
 - (a) Yes
 - (b) No

6. Nasal CPAP

- (a) Yes
- (b) No

7. Other non-invasive ventilatory support

- (a) Yes
- (b) No

8. Conventional mechanical ventilation

- (a) Yes
- (b) No

9. High frequency ventilation

- (a) Yes
- (b) No

10. ECMO or ECLS

- (a) Yes
- (b) No

11. Inhaled nitric oxide

- (a) Yes
- (b) No

Cardiovascular Parameters

1. Evidence of cardiac failure

- (a) Yes
- (b) No

2. Poor perfusion

- (a) Yes
- (b) No

3. Arrhythmia

- (a) Yes
- (b) No

4. Bradycardia

- (a) Yes

- (b) No
- 5. Hypotension
 - (a) Yes
 - (b) No
- 6. Use of vasoactive drips
 - (a) Yes
 - (b) No
- 7. Pulmonary Hypertension
 - (a) Yes
 - (b) No

Renal Parameters

- 1. Creatinine (worst value of day), mg/dL
- 2. Renal replacement therapy
 - (a) Yes
 - (b) No

Bacterial and Fungal Microbiology

- 1. Endotracheal tube culture
 - (a) Not done
 - (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result
- 2. Tracheal gram stain
 - (a) Not done
 - (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result
- 3. Broncho-alveolar lavage
 - (a) Not done

- (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result
4. Blood culture
- (a) Not done
 - (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result
5. CSF culture
- (a) Not done
 - (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result
6. Urine culture
- (a) Not done
 - (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result
7. Other sterile site culture (indicate site)
- (a) Not done
 - (b) Negative
 - (c) Positive
 - i. If positive, specify results (free text)
 - (d) Unknown or inconclusive result

Immunologic/Hematologic Parameters

1. On Day 0 - Collect all hematology labs prior to PICU admission or on Day 0.
 - Date of collection
 - Time of collection

- Was a differential obtained? (Yes/No)
 - Hematology labs to be collected include: white blood cell (WBC) count, platelet count, absolute lymphocyte (ALC), neutrophil (ANC), and phagocyte (APC) counts.
 - Exchange transfusion or leukopheresis (Yes/No)
 - RBC transfusion (Yes/No)
 - Abnormal bleeding (Yes/No)
 - Use of antibiotics (Yes/No)
2. On Days 1 through 28 - Collect hematology labs associated with the highest WBC and lowest WBC counts observed on this study day.
- Date of collection
 - Time of collection
 - Was a differential obtained? (Yes/No)
 - Highest WBC count and all associated hematology labs from the report.
 - Associated hematology labs include values for: platelet, ALC, ANC, and APC.
 - Lowest WBC count and all associated hematology labs from the report.
 - Associated hematology labs include values for: platelet, ALC, ANC, and APC.
 - Exchange transfusion or leukopheresis (Yes/No)
 - RBC transfusion (Yes/No)
 - Abnormal bleeding (Yes/No)
 - Use of antibiotics (Yes/No)

Complications Noted During Study Day

1. Cardiac arrest
 - (a) Yes
 - (b) No
2. Respiratory arrest
 - (a) Yes

- (b) No
- 3. Development of pneumonia (new)
 - (a) Yes
 - (b) No
- 4. Pneumothorax
 - (a) Yes
 - (b) No
- 5. Death
 - (a) Yes
 - (b) No
- 6. Other (specify free text field)

A.6 Information Collected at Time of PICU Discharge

1. Date and time of PICU discharge For subjects discharged alive, the time of physically leaving the unit is recorded. For subjects who expire in the PICU, the time of death is recorded.
2. Alive at PICU Discharge
 - (a) Yes
 - (b) No
3. If died in PICU, withdrawal of support
 - (a) Yes
 - (b) No
4. If died in PICU, was the patient DNR at the time of admission to the PICU?
 - (a) Yes
 - (b) No

For subjects who are discharged alive from the PICU, the following data elements will be obtained within 24 hours of discharge. The head circumference, weight, and height may be obtained from the medical record if measured within the 24 hours prior to discharge; otherwise these should be measured. The chart should be reviewed to determine the presence or absence of seizures, use of anticonvulsants, and mode of feeding. The bedside nurse may also be consulted to collect this information.

1. Head circumference (cm) and percentile for age
2. Weight (kg) and percentile for age
3. Length / Height (cm) and percentile for age
4. Receiving anticonvulsants
 - (a) Yes
 - (b) No
5. Seizure assessment
 - (a) No seizures occurred during the PICU admission
 - (b) Seizures documented during PICU admission
6. Feeding assessment
 - (a) Oral feeding only
 - (b) Oral plus tube feeding (NG, NJ, or gastrostomy)
 - (c) NG or NJ tube feeding only
 - (d) Gastrostomy feeding only
 - (e) No enteral feeding
7. Arousal assessment
 - (a) Awake, alert, or looks to clapping
 - (b) Arouses but does not localize sound
 - (c) Responds to pain with agitation or withdrawal
 - (d) Non-responsive
8. Communication assessment
 - (a) Age-appropriate vocalization, facial expressiveness, gestures
 - (b) Slightly decreased vocalization or non-verbal interaction
 - (c) Moderately decreased vocalization or non-verbal
 - (d) No reactivity to speech, gestures, or touch
9. Motor strength assessment
 - (a) Normal activity for age
 - (b) Asymmetric limb activity or withdrawal to stimulation

- (c) Withdraws from pain
- (d) No response to stimulation

10. Motor tone assessment

- (a) Normal tone for age
- (b) Increased or decreased tone for age
- (c) Moderately floppy or spastic, including poor head control for age
- (d) No response to stimulation, severe diffuse spasticity, posturing

A.7 Information Collected for Deceased Subjects

1. Autopsy

- (a) Autopsy not performed
- (b) Autopsy performed, results not obtainable
- (c) Autopsy performed, results to be sent to DCC

For subjects who expire and have an autopsy performed, a full autopsy report should be sent to the DCC. The report should be converted into a PDF document.

A.8 Information Collected 6 Months after PICU Discharge

The date of collection of information and the six-month followup will be collected. This evaluation is primarily aimed at the quality of life of the subject. The interview tool is age dependent:

- For subjects who are 5 years or older, the Child Health Questionnaire (CHQ) PF28; OR
- For subjects under 5 years, the Infant Toddler Quality of Life Questionnaire (ITQOL)

A.9 Information Collected at One-Year Follow-up Visit

The data below are to be collected at the time of each subject's follow-up 12 months after PICU discharge.

1. Date of followup visit
2. Parent perception of status at time of followup

- (a) Alive with apparently intact neurodevelopment
 - (b) Alive with apparent neurodevelopmental impairment
 - (c) Alive but unable to assess neurodevelopment
 - (d) Deceased
3. If deceased at time of followup, date of death.
 4. If deceased at time of followup, withdrawal of support?
 - (a) Yes
 - (b) No
 5. If deceased at time of followup, autopsy performed? If an autopsy was performed, please obtain a copy of the autopsy report and send it to the DCC.
 - (a) Yes
 - (b) No

For subjects who are alive at the time of followup, obtain the following data.

1. Head circumference (cm) and percentile for age
2. Weight (kg) and percentile for age
3. Length / Height (cm) and percentile for age
4. Seizure assessment
 - (a) No seizures have ever occurred since PICU discharge
 - (b) Seizures have occurred since PICU discharge but the child is not on anticonvulsants
 - (c) Seizures have occurred since PICU discharge and the child is on anticonvulsants
5. Feeding assessment
 - (a) Oral feeding only
 - (b) Oral plus tube feeding (NG, NJ, or gastrostomy)
 - (c) NG or NJ tube feeding only
 - (d) Gastrostomy feeding only

- (e) No enteral feeds
- 6. Arousal assessment
 - (a) Awake, alert, or looks to clapping
 - (b) Arouses but does not localize sound
 - (c) Responds to pain with agitation or withdrawal
 - (d) Non-responsive
- 7. Communication assessment
 - (a) Age-appropriate vocalization, facial expressiveness, gestures
 - (b) Slightly decreased vocalization or non-verbal interaction
 - (c) Moderately decreased vocalization or non-verbal
 - (d) No reactivity to speech, gestures, or touch
- 8. Motor strength assessment
 - (a) Normal activity for age
 - (b) Asymmetric limb activity or withdrawal to stimulation
 - (c) Withdraws from pain
 - (d) No response to stimulation
- 9. Motor tone assessment
 - (a) Normal tone for age
 - (b) Increased or decreased tone for age
 - (c) Moderately floppy or spastic, including poor head control for age
 - (d) No response to stimulation, severe diffuse spasticity, posturing
- 10. Vision assessment by asking parent "Does your child have any problems with vision?"
 - (a) Normal
 - (b) Abnormal
 - (c) Parent can't tell

Quality of life will be reassessed at the time of the 12 month followup. The interview tool is:

- Infant Toddler Quality of Life Questionnaire (ITQOL)

Finally, at the followup visit, the subject should be assessed with the Mullen scores (Composite Score and Subscales) (Appendix B on the next page).

B Mullen Scales Description

The Mullen Scales³⁵ have been adopted for this project after consultation with Drs. Linda Ewing-Cobbs and Elizabeth Gills, active participants in development of this protocol.

Developmental outcomes will be assessed one year post-admission in children who were < 12 months of age on admission to the PICU for critical pertussis (window +/- 2 weeks). The Mullen Scales of Early Learning³⁵ will be administered. This measure was selected to 1) provide broad coverage of cognitive, motor, and adaptive behavior outcomes that may be adversely affected by critical pertussis and 2) to provide measures that minimize measurement and site-specific error variance when used in multiple sites.

The Mullen Scales yield the Early Learning Composite Score, a standard score (M=100; SD=15) based on age norms for ages birth-68 months that reflects the child's learning competencies in several domains: visual reception, fine motor, receptive language, and expressive language abilities. The domain scores yield Individual Scale Scores. These are normalized T-scores (M=50; SD=10). A gross motor scale yields a T-score for ages 0-33 months, separate from the composite score. Advantages of the Mullen include: relatively short testing time (average about 45-60 minutes for age 1 to 2 years), engaging testing materials, well-written manual, excellent inter-tester reliability, and multiple scores assessing different developmental areas. Reliability studies indicated excellent internal consistency of items.

Test-retest reliability is high, with stability coefficients ranging from 0.82 to 0.96 for ages 1 to 24 months across individual scales. Interscorer reliability coefficients ranged from 0.91 to 0.99, indicating that the Mullen Scales are extremely well-suited for multicenter studies; different observers rate the child's behavior similarly, evidence of reduced inter-tester error.

Construct validity is indicated by the developmental progression of scores, indicating sensitivity to developmental change across ages. Concurrent validity studies indicate correlation of 0.70 of the Mullen Composite Score and the Bayley Scales of Infant Development Mental Development Index; correlation of the Mullen gross motor scale and the Bayley Physical Developmental Index was 0.76. The composite score was correlated with other established measures of language and fine motor skills. Factor analyses showed that each individual Mullen scale loaded on a general ability factor as expected. In addition, each scale has reasonable unique variance, suggesting that they measure different abilities. Use of a test with several scales is advantageous because critical pertussis may differentially affect specific developmental outcomes.

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