Cognitive Development One Year After Infantile Critical Pertussis*

John T. Berger, MD[1]; Michele E. Villalobos, PhD[2]; Amy E. Clark, MS[3]; Richard Holubkov, PhD[3]; Murray M. Pollack, MD[1]; Robert A. Berg, MD[4]; Joseph A. Carcillo, MD[5]; Heidi Dalton, MD[6]; Rick Harrison, MD[7]; Kathleen L. Meert, MD[8]; Christopher J. L. Newth, MD, FRCPC[9]; Thomas P. Shanley, MD[10]; David L. Wessel, MD[1]; Kanwaljeet J. S. Anand, MBBS, PhD[11]; Jerry J. Zimmerman, MD, PhD[12]; Ronald C. Sanders Jr, MD, MS[13]; Teresa Liu, MPH, CCRP[3]; Jeri S. Burr, MS, RN-BC, CCRC[3]; Douglas F. Willson, MD[14]; Allan Doctor, MD[15]; J. Michael Dean, MD, MBA[3]; Tammara L. Jenkins, MSN, RN[16]; Carol E. Nicholson, MD, MS[16]; on behalf of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network

***See also p. 161.**

[1]Department of Pediatrics, Children's National Medical Center, Washington, DC.

[2]Department of Psychiatry, University of North Carolina at Chapel Hill, Asheville, NC.

[3]Department of Pediatrics, Univesity of Utah, Salt Lake City, UT.

[4]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, PA.

[5]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA.

[6]Department of Child Health, Phoenix Children's Hospital, Phoenix, AZ.

[7]Department of Pediatrics, Mattel Children's Hospital UCLA, Los Angeles, CA.

[8]Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI.

[9]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA.

[10]Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, Ann Arbor, MI.

[11]Department of Pediatrics, Le Bonheur Children's Hospital, Memphis. TN.

[12]Department of Pediatrics, Seattle Children's Hospital, Seattle, WA.

[13]Department of Pediatrics, Arkansas Children's Hospital, Little Rock, AR.

[14]Department of Pediatrics, Virginia Commonwealth University, Richmond, VA.

[15]Departments of Pediatrics and Biochemistry, St. Louis Children's Hospital, St. Louis, MO.

[16]Pediatric Trauma and Critical Illness Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD.

Supported, in part, by cooperative agreements from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services (U10HD05009, U10HD049945, U10HD050096, U10HD049981, U10HD049983, U10HD050012, U10HD063108, U10HD063106, U10HD063114, U01HD049934). Initial support was provided by the National Vaccine Program Office at the U.S. Department of Health and Human Services.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Dr. Berger's institution received funding from *Eunice Kennedy Shriver* National Institute of Child Health and Development and Association for Pediatric Pulmonary Hypertension. He received support for article research from the National Institutes of Health (NIH). Dr. Clark's institution received funding from the NIH. She received support for article research from the NIH. Dr. Holubkov's institution received funding from the NIH. He disclosed other support from Data Safety Monitoring Board (DSMB) member for Fibrocell Inc (past), American Burn Association (past), and Armaron Bio (current). He received support for article research from the NIH. He received funding from St. Jude Medical (biostatistical consulting), Pfizer Inc (DSMB), and DURECT Corporation (biostatistical consulting). Dr. Pollack's institution received funding from the NIH. He received support for article research from the NIH. Dr. Berg's institution received funding from the National Institute for Child Health and Human Development (NICHD). He received support for article research from the NIH. Dr. Carcillo's institution received funding from the NICHD. He received support for article research from the NIH. Dr. Dalton's institution received funding from the NIH. She received funding from Innovative extracorporeal membrane oxygenation Concepts and Maquet. She received support for article research from the NIH. Dr. Harrison's institution received funding from the NIH. He received support for article research from the NIH. Dr. Meert's institution received funding from the NIH. She received support for article research from the NIH. Dr. Newth's institution received funding from the NICHD. He received support for article research from the NIH. Dr. Shanley's institution received funding from the NIH. He received support for article research from the NIH. He received funding from International Pediatric Research Foundation Dr. Wessel's institution received funding from the NIH. He received support for article research from the NIH. Dr. Anand received support for article research from the NIH. Dr. Zimmerman's institution received funding from the NIH and Immunexpress, Seattle (research funding). He received support for article research from the NIH. He received funding from Society of Critical Care Medicine (travel reimbursement to attend board meetings) and from Elsevier Publishing (royalties for coediting the textbook, Pediatric Critical Care). Dr. Sanders Jr received support for article research from the NIH. Dr. Liu's institution received funding from the NIH/NICHD. She received support for article research from the NIH. Dr. Burr's institution received funding from the NICHD. He received support for article research from the NIH. Dr. Doctor received support for article

DOI: 10.1097/PCC.0000000000001367

research from the NIH. His institution received funding from the NIH, Department of Defense, and Children's Discovery Institute. Dr. Dean's institution received funding from the NICHD. He received support for article research from the NIH. Dr. Jenkins disclosed government work: I completed this work as part of official duties as a Federal Employee of the National Institutes of Health. Dr. Nicholson disclosed government work. She received support for article research from the NIH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: jberger@childrensnational.org

Objectives: Pertussis can cause life-threatening illness in infants. Data regarding neurodevelopment after pertussis remain scant. The aim of this study was to assess cognitive development of infants with critical pertussis 1 year after PICU discharge.

Design: Prospective cohort study.

Setting: Eight hospitals comprising the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development Collaborative Pediatric Critical Care Research Network and 18 additional sites across the United States.

Patients: Eligible patients had laboratory confirmation of pertussis infection, were less than 1 year old, and were admitted to the PICU for at least 24 hours.

Interventions: The Mullen Scales of Early Learning was administered at a 1-year follow-up visit. Functional status was determined by examination and parental interview.

Measurements and Main Results: Of 196 eligible patients, 111 (57%) completed the Mullen Scales of Early Learning. The mean scores for visual reception, receptive language, and expressive language domains were significantly lower than the norms ($p < 0.001$), but not fine and gross motor domains. Forty-one patients (37%) had abnormal scores in at least one domain and 10 (9%) had an Early Learning Composite score 2 or more SDs below the population norms. Older age ($p < 0.003$) and Hispanic ethnicity ($p < 0.008$) were associated with lower mean Early Learning Composite score, but presenting symptoms and PICU course were not.

Conclusions: Infants who survive critical pertussis often have neurodevelopmental deficits. These infants may benefit from routine neurodevelopmental screening. (*Pediatr Crit Care Med* 2018; 19:89–97)

Key Words: child development; intensive care; neurologic complications; outcome assessment; pertussis

Pertussis outbreaks, with over 28,000 cases in 2014, occur in the United States despite high vaccine rates (1). Critical pertussis, defined as infections with sufficient severity to merit PICU admission, primarily affects infants less than 3 months old and is associated with hospital mortality rates ranging between 5.5% and 14% (2–5). Factors associated with mortality include pulmonary hypertension and hyperleukocytosis (5, 6). Acute neurologic complications of critical pertussis include seizures and encephalopathy.

Long-term outcome data for infants with critical pertussis are scant. A few small series reported neurodevelopmental problems including lower IQ scores, developmental delay, seizures, and school performance problems; these were associated with lymphocytosis, apnea, seizures, and encephalopathy during the acute illness (2, 7, 8). Other studies, however, have not found cognitive impairment, even in children with acute neurologic complications during the acute illness (9, 10).

The Mullen Scales of Early Learning (MSEL) was a developed as specific measure of early development for children ages birth to 68 months (11). The test was designed for administration by professionals who have experience working with infants and has a short administration time. Interscorer reliability coefficients range from 0.91 to 0.99 (11). The MSEL assesses multiple domains of cognitive and motor functions, making it useful for conditions which may have differential effects on development. The MSEL has good internal validity and has been used in infant follow-up studies including premature infants and children with congenital heart disease (11–17).

The aim of this study was to assess cognitive development of infants with critical pertussis 1 year after PICU discharge. The cohort consisted of those infants with laboratory-confirmed pertussis hospitalized in a PICU from 2008 to 2013 as part of a prospective cohort study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN). We hypothesized that these infants were at risk for lower developmental scores compared with age-adjusted normalized scores.

METHODS

The study was conducted at seven sites (one site had two hospitals) in the NICHD CPCCRN network and 18 additional PICUs across the United States. Details of screening, enrollment, patient inclusion, and the acute illness have been published (5), and the study protocol is available (http://www.cpccrn.org/documents/PertussisProtocolVersion4.0109Aug12.pdf). Briefly, children 0–18 years were enrolled if they had laboratory-confirmed evidence of pertussis infection (polymerase chain reaction [PCR] and/or positive culture) and were hospitalized in the PICU for at least 24 hours or died. Patients were enrolled from June 2008 to May 2013. For analyses of the 1-year outcomes, additional inclusion criteria were age less than 1 year when hospitalized and completion of the MSEL at 1 year after PICU discharge. The protocol was approved by the institutional review board at each participating institution, and written parental consent was obtained prior to enrollment.

Clinical data were collected through chart abstraction and parental and staff interviews. Data included demographics, prematurity, pertussis vaccinations, chronic conditions, illness history, and aspects of the PICU course including apnea, bradycardia, seizures, cardiac arrest, CNS hemorrhage, pulmonary hypertension, extracorporeal membrane oxygenation (ECMO) use, and WBC count. Severity of illness was assessed using the Pediatric Risk of Mortality III score (18). Functional status of feeding, arousal, communication, motor strength, and motor tone and use of anticonvulsants were assessed on PICU discharge and at the 1-year follow-up visit. Clinical and laboratory data were collected from admission until PICU discharge, 28 days, or death, whichever occurred earlier.

Cognitive development was assessed with the MSEL 1 year after PICU discharge. The MSEL evaluates gross motor, fine motor, visual reception, and receptive and expressive language based on a nationally representative sample of U.S. children. Raw scores from each scale are converted to a T-score based on the patient's age and have a population mean of 50 and a SD of 10 (11). A summary measure termed as the Early Learning Composite score is derived from the visual reception, fine motor, receptive language, and expressive language T scores and has mean of 100 and a SD of 15. Scores that were 2 SDs or more below the mean were defined as abnormal. The patient's chronologic age used for MSEL testing was adjusted for those who were premature at birth ($n = 24$) as described in MSEL administration instructions (11). The MSEL was administered in person by trained neuropsychologists, developmental pediatricians, developmental psychologists, or neurologists. The MSEL is available only in English. Twenty-five MSELs were administered by a bilingual examiner (24 Spanish, one other language), and three with an interpreter (two Spanish, one other language) when the parent did not speak English ($n = 28$).

We descriptively characterized the acute illness and initial PICU course for all patients eligible for 1-year follow-up and compared those who completed the MSEL with those who did not. Continuous data were summarized as median and interquartile range (25 and 75th percentiles). Associations between demographic and clinical variables and whether or not follow-up was completed were evaluated using the Pearson chi-square or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

We evaluated change in functional assessment status (from PICU discharge to one year) using the McNemar test for paired data. MSEL scale T scores were summarized graphically using a box-and-whisker plot, and the observed mean scores were compared with the population mean (from the normative sample) using a one-sample *t* test. The Early Learning Composite score was summarized overall and within demographic and clinical subgroups as mean ± SD. The overall mean was compared with the population mean using a one-sample *t* test. Univariable associations with the Early Learning Composite outcome were evaluated based on *t* test or analysis of variance for categorical variables and simple linear regression for continuous measures. Clinical events that occurred in fewer than five patients were not included in the univariable analyses including cardiac arrest, evidence of a CNS hemorrhage, pulmonary hypertension, and ECMO use. A multivariable linear regression model was constructed including any variable with *p* value of less than 0.15 in univariable analyses. A sensitivity analysis was conducted excluding non-English speaking patients. A significance level of 0.05 was used for all analyses. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 225 patients with critical pertussis were enrolled based on their PICU admission and positive culture or PCR. The enrollment diagram is shown in **Figure 1**. Nineteen patients died, 17 during the acute hospitalization, and two prior to the 1-year follow-up (one from blunt force trauma and one from respiratory syncytial viral pneumonitis). Seven patients were greater than 1 year old on enrollment, parental permission was withdrawn in three, and 85 were lost to follow-up or did not complete the MSEL. Of the 111 patients who completed the MSEL, two had a cardiac arrest, one had CNS hemorrhage, four had pulmonary hypertension, and three received ECMO during the acute hospitalization.

Patient demographics and clinical information are shown in **Table 1**. There were no statistically significant differences between those lost to follow-up and those who completed the MSEL. Of those who completed the MSEL, 86% were less than 3 months old on presentation, 23% had a history of prematurity, and 19% had received one or more vaccinations. Apnea occurred in 60%, bradycardia in 69%, seizures in 7%, 35% received mechanical ventilation, and 7% received a therapy to reduce their WBC count.

The functional status at PICU discharge and 1 year after discharge are shown in **Table 2** for feeding, arousal, communication, and motor assessments. There were no statistically significant differences in PICU discharge assessments in those with and without 1-year follow-up. For the MSEL cohort at PICU discharge, 35% of patients were receiving some or all of their feeds from a nasogastric, nasojejunal, or gastrostomy tube. Very few patients (< 5%) had dysfunction in the other areas of

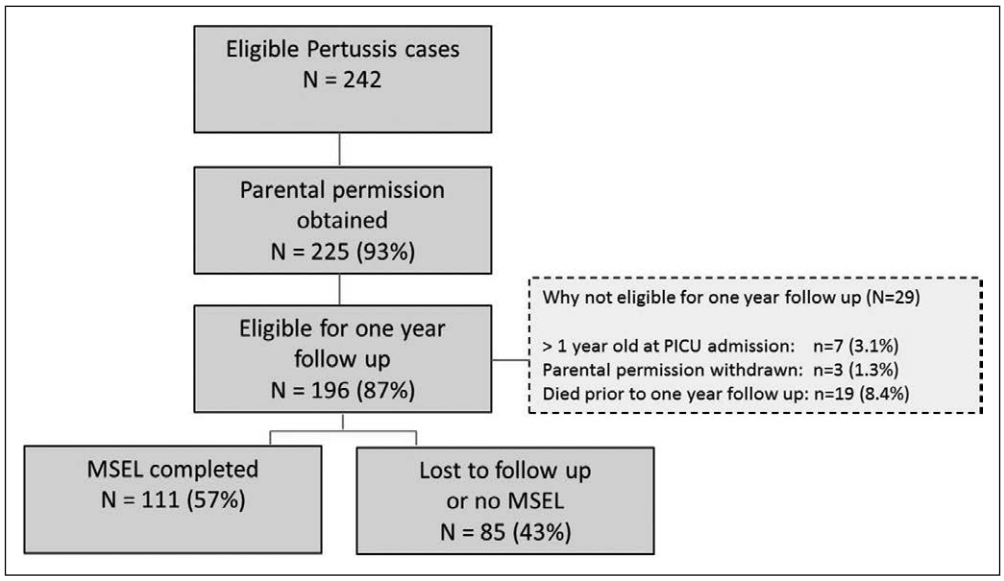

Figure 1. Enrollment and follow-up flow diagram. MSEL = Mullen Scales of Early Learning.

TABLE 1. Demographic and Clinical Data

Clinical Characteristics	Lost to Follow-Up, *n* = 85	MSEL Completed, *n* = 111	*p*
Demographics, *n* (%)			
Age < 3 mo at PICU admission	70 (82)	96 (86)	0.43
Female	43 (51)	66 (59)	0.22
Race			0.10
Black or African American	14 (16)	13 (12)	
White	48 (56)	81 (73)	
Other	8 (9)	7 (6)	
Recorded as unknown	15(18)	10 (9)	
Hispanic ethnicity	48 (57)	57 (52)	0.50
Prematurity (< 37 wk gestation)	21 (25)	25 (23)	0.69
Pertussis vaccinations	21 (25)	21 (19)	0.33
Chronic medical condition	19 (22)	16 (14)	0.15
History of apnea	55 (65)	61 (55)	0.17
History of seizures	5 (6)	6 (5)	1.00
History of bradycardia	25 (29)	36 (32)	0.65
PICU course			
Pediatric Risk of Mortality III score, median (IQR)	0 (0–3)	0 (0–3)	0.67
WBC (× 10^3/uL), median (IQR)	23 (15–36)	22 (16–34)	0.60
Apnea, *n* (%)	48 (56)	67 (60)	0.58
Seizure, *n* (%)	5 (6)	8 (7)	0.71
Bradycardia, *n* (%)	52 (61)	77 (69)	0.23
Mechanical ventilation, *n* (%)	35 (41)	39 (35)	0.39
Exchange transfusion or leukopheresis, *n* (%)	4 (5)	8 (7)	0.47
PICU length of stay, median (IQR)	6 (3–12)	6 (3–12)	0.99

IQR = interquartile range.

functional assessment. By the 1-year follow-up, 98% of patients were feeding without a device, but a significantly larger numbers were demonstrating decreased communication function (p = 0.002). Four percent (n = 4) were receiving anticonvulsants on PICU discharge compared with less than 1% (n = 1) at 1-year follow-up. Hearing assessments were performed after hospital discharge in 26 patients of which 24 were judged as normal.

The Mullen domain scores obtained at 1-year follow-up are shown in **Figure 2**. The mean scores for visual reception, receptive language, and expressive language domains were significantly lower than the norms ($p < 0.001$), but the motor domains were not. Forty one patients (37%) had abnormal scores (≤ 2 SDs below the mean) in at least one domain. The most common area of impairment was in one of the two language development domains. Twenty-three patients (21%) had expressive language delay and 16 (14%) had delays in the receptive language domain. The Mullen Early Learning Composite Score is shown in **Figure 3**. Consistent with the impairment in the domain scores, the composite score was significantly lower than the norm (mean 90.3 ± 16.8; $p < 0.001$). The range of composite scores was 49–134 with 10 patients (9%) having a composite score 2 or more SDs below the population mean.

Table 3 shows the univariable associations of the demographic and clinical factors with the Mullen Early Learning Composite score. Older age (3–11 mo), Hispanic or Latino ethnicity, and previous pertussis vaccinations were significantly associated with decreased performance. Because age and documented pertussis vaccinations were highly collinear, we included age but not vaccination in the multivariable model as this was the stronger predictor. Otherwise, the multivariable model included all variables in Table 3 with p value of less than 0.15 from univariable analyses. In this model, only older age (p = 0.003) and Hispanic ethnicity (p = 0.008) were significantly associated with decreased Mullen Early Learning Composite scores when corrected for these covariates.

We performed a sensitivity analysis by repeating the analysis after excluding the 28 patients whose families did not speak English. The mean scores for scores for visual reception, receptive

TABLE 2. Functional Status at PICU Discharge and at 1-Year Follow-Up

Functional Domains	PICU Discharge, ($n = 110$)[a], n (%)	Status at 1 Yr, ($n = 110$)[a], n (%)	p (PICU d/c Vs 1 Yr)[b]
Feeding assessment			< 0.001
Oral feeding only	72 (65)	108 (98)	
Oral plus tube feeding (NG, NJ, or gastrostomy)	15 (14)	0 (0)	
NG, NJ, or gastrostomy tube feeding only	23 (21)	2 (2)	
Arousal assessment			0.56
Awake, alert, or looks to clapping	108 (98)	109 (99)	
Arouses but does not localize sound	2 (2)	1 (1)	
Communication assessment			0.002
Age-appropriate vocalization, facial expressiveness, gestures	106 (96)	92 (84)	
Decreased vocalization or nonverbal interaction	4 (4)	18 (16)	
Motor strength assessment			0.08
Normal activity for age	109 (99)	106 (96)	
Asymmetric limb activity or withdrawal to stimulation	1 (1)	4 (4)	
Withdraws from pain	0 (0)	0 (0)	
Motor tone assessment			0.56
Normal tone for age	107 (97)	108 (98)	
Increased or decreased tone for age	3 (3)	2 (2)	

NG = nasogastric, NJ = nasojejunal.

[a]One patient had incomplete 1 yr data and is not included.

[b]p value based on McNemar test for paired data (normal vs abnormal).

language, and expressive language domains were still significantly lower than the norms ($p \leq 0.001$). On univariable analysis, older age, Hispanic ethnicity, and previous pertussis vaccinations remained significantly associated with decreased Mullen Early Learning Composite scores ($p < 0.05$) as seen in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A548). In a revised multivariable model that included age, sex, ethnicity, and history of bradycardia, only older age ($p = 0.02$) and ethnicity ($p = 0.04$) remained significantly associated with lower Mullen Early Learning composite scores.

DISCUSSION

In this report of the developmental status of 111 survivors of critical pertussis, 37% of patients had abnormal MSEL scores in at least one domain, and 9% had an Early Learning Composite score 2 or more SDs below the population norm 1 year after PICU discharge. The results of testing can be described as an age equivalent (i.e., the age at which the child's raw score is the median score) (11). For example, a 15-month-old child who has an expressive language score 2 SDs below the norm has the age equivalent performance of 10–11 months old in that domain and gross motor domain the equivalent age would be 12–13 months. The most frequent abnormal scores occurred in the language domains, and communication was the most frequent abnormal functional assessment. Survivors of critical pertussis who were 3–12 months old when they presented had worse neurodevelopmental outcomes than those who were 0–3 months old. Clinical factors such as presenting symptoms, occurrence of pulmonary hypertension or shock, and peripheral WBC counts were not associated with worse neurodevelopmental scores.

The frequency of neurodevelopmental dysfunction in this cohort of patients with critical pertussis is comparable with that reported in critically ill patients with sepsis or meningoencephalitis (19–21). Although this study did not investigate the pathophysiologic processes associated with neurodevelopment dysfunction, clinical pertussis often includes inflammation as well as other processes more specific to pertussis including primary injury from pertussis toxin or other neurotoxins (22, 23), hypoxia, hemorrhage, and vascular occlusion. In two case series, MRI studies have demonstrated the occurrence of acute demyelination in pertussis (24, 25). In the United States, seizures are reported in 2.2% of patients hospitalized with pertussis (26) and in 4–18 % with critical pertussis (4–6, 9). Acute seizures have been associated with mortality and an increased occurrence rate of epilepsy (5, 6, 8).

Older infants were at higher risk for lower MSEL scores. Older infants may have had a single dose of pertussis vaccine which appears to reduce the risk of death, hospitalization, and pneumonia but not encephalopathy and seizures during the acute hospitalization (27) and may not protect against long-term neurodevelopmental problems.

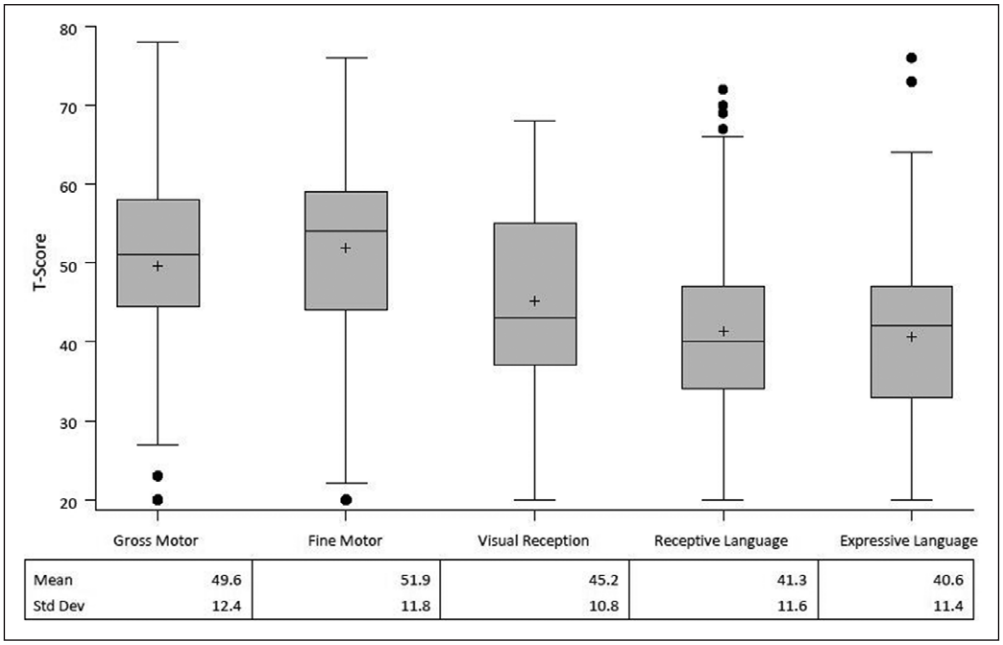

Figure 2. Mullen domain scores. Box-and-whisker plots show summary statistics as minimum (with outliers depicted by *filled circles*), 25th percentile, median, 75th percentile, maximum, and mean (+).The T-score is a standardized score with a population mean of 50 and SD of 10. The scores for visual reception, receptive and expressive language ($p < 0.001$) but not motor were significantly lower than the population norms.

Previously identified associations of mortality including pulmonary hypertension, shock, or elevated WBC count were not associated with the developmental outcome in this cohort. This contrasts with previously reported associations of seizures and apnea with developmental outcomes (2, 7). The difference may be due to differences in study design. In a retrospective study of critical pertussis, 10% of survivors had neurodevelopmental problems identified through medical record review (2). All of the patients were abnormal during the acute illness. A composite outcome that included death and respiratory disability as well as neurologic disability was used to test for possible associations. Additionally, if formal developmental testing was not used, more subtle forms of dysfunction may not have been detected. The second case-control study compared patients with apnea or seizures to patients with uncomplicated pertussis who may not have required critical care (7). In this cohort, 48% of the patients with complicated pertussis required remedial help during school compared with 20% without complicated pertussis. A case series for 14 patients with acute seizure or encephalopathy did not find any abnormalities on long-term follow-up, but formal developmental testing was not performed (9). Our data suggest that a significant proportion of patients with critical pertussis regardless of specific symptoms appear to be at risk for neurodevelopmental problems which may only be evident with formal screening.

Our follow-up assessments were completed after only 1 year in infants, so further developmental problems could present or some problems may resolve. For instance, most patients no longer required artificial feeding methods at the 1-year follow-up visit while communication dysfunction was more frequently recognized. We speculate that this is due to recovery from critical illness and/or ability to recognize dysfunction rather than pertussis illness. Longitudinal developmental studies of critically ill patients have shown changes in the incidence and types of abnormalities. For example, in patients with repaired transposition of the great arteries, the incidence of detected developmental abnormalities was substantially higher at school age compared with age 1–5 years (28, 29). Determining the frequency and length of developmental surveillance

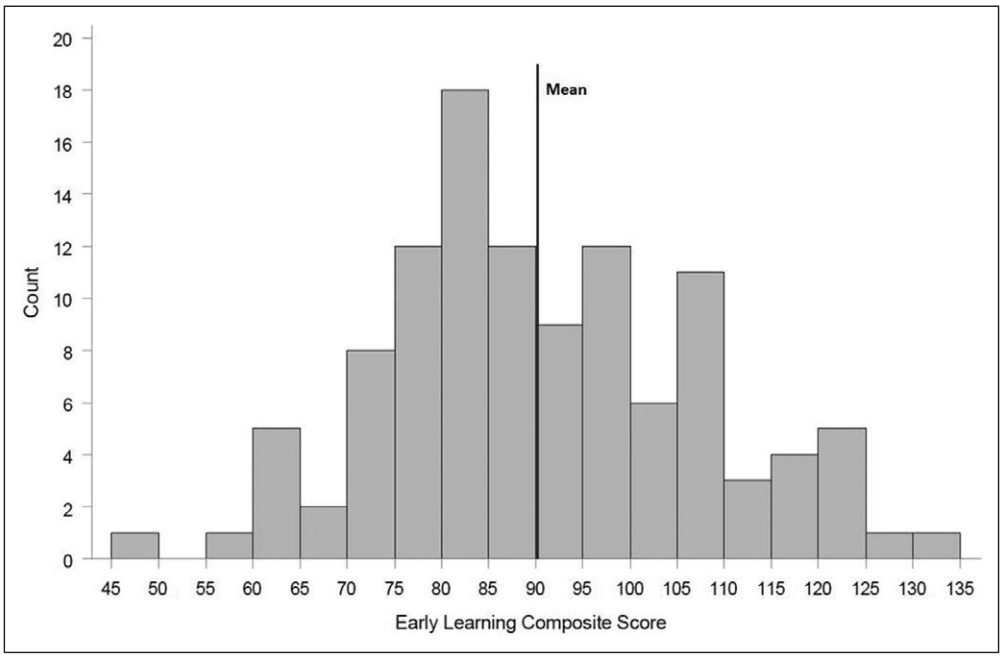

Figure 3. Distribution of the Mullen Early Learning Composite Score. The early learning composite is derived from the four cognitive scales (fine motor, visual reception, receptive language, and expressive language) and is normalized to have a mean of 100 and a SD of 15. The mean observed in the study cohort is significantly different from the population mean ($p < 0.001$).

TABLE 3. Univariable Associations With Mullen Early Learning Composite Score

Clinical Characteristics	Mullen Early Learning Composite Score (1) Mean ± SD	*p*
Demographics		
Chronologic age at PICU admission (mo)		0.003
< 3	92.1 ± 16.1	
3–11	78.4 ± 16.9	
Sex		0.08
Female	92.5 ± 16.9	
Male	86.9 ± 16.4	
Race		0.75
Black or African American	88.8 ± 15.8	
White	91.2 ± 15.8	
Other	87.4 ± 18.1	
Ethnicity		0.004
Hispanic or Latino	86.1 ± 15.4	
Not Hispanic or Latino	95.3 ± 17.3	
Prematurity (< 37 wk gestation)		0.47
Yes	92.4 ± 17.1	
No	89.6 ± 16.8	
Pertussis vaccinations		0.006
Yes	81.3 ± 16.0	
No	92.3 ± 16.4	
Chronic medical condition		0.50
Yes	87.6 ± 14.6	
No	90.7 ± 17.2	
History of apnea		0.83
Yes	90.6 ± 18.1	
No	89.9 ± 15.3	
History of seizures		0.31
Yes	83.5 ± 19.6	
No	90.6 ± 16.7	
History of bradycardia		0.11
Yes	93.9 ± 18.6	
No	88.5 ± 15.8	
PICU course		
Pediatric Risk of Mortality III score, correlation (*r*)	−0.075	0.44
WBC (× 10^3/uL), correlation (*r*)	−0.13	0.20
Apnea		0.69
Yes	90.8 ± 16.6	
No	89.5 ± 17.4	
Seizure		0.13
Yes	81.5 ± 18.2	
No	90.9 ± 16.6	
Bradycardia		0.52
Yes	89.6 ± 16.6	
No	91.8 ± 17.5	
Mechanical ventilation		0.26
Yes	87.8 ± 16.3	
No	91.6 ± 17.1	
Exchange transfusion or leukopheresis		0.11
Yes	81.1 ± 12.5	
No	91.0 ± 17.0	

[a]Data are mean ± SD except for the Pediatric Risk of Mortality III score, correlation III scores and WBC counts, which are Pearson correlations (*r*).

after pertussis and other major pediatric critical illness remains a research need. The lack of factors associated with developmental dysfunction suggests that all survivors of critical pertussis should undergo neurodevelopmental surveillance and screening.

Hispanic ethnicity, which has been associated with mortality in some pertussis studies and decreased functional status after sepsis, was associated with lower MSEL scores (19, 27, 30). The association is likely multifactorial. Although the MSEL has been used in non-English speaking populations, we found lower scores in the language domains which may reflect the effects of using translated materials and interpreters (31–34). Alternatively, true language delays are seen in multilingual children when compared with monolingual children, which may also explain lower scores (34, 35). Finally, there may be cultural or socioeconomic factors accounting for the association. The MSEL was chosen for its ease of administration in a multicenter study, short administration time, and ability to assess multiple domains in the age range. Other common tests of infant development such as the Bayley Scales of Infant and Toddler Development and the Battelle Development Inventory are likewise not validated in non-English speakers. Although language differences may account for the association of Hispanic ethnicity and lower MSEL scores, the results from univariable and multivariable analysis were not substantially changed after excluding non-English speaking patients.

There are some limitations to this study. First, a substantial portion of patients were lost to follow-up over the 1 year. However, demographics, illness course, nor discharge assessments appeared to be different between the groups. Second, we did not collect information regarding other confounding variables such as exposure to sedative medications in the PICU or parental socioeconomic status; therefore, we could not adjust for this in our associations with outcome. Additionally, it is not possible to separate the effects of pertussis from general critical illness. Third, the lack of association with clinical features may have been, in part, due to inadequate power. For example, only four patients tested 1 year after PICU discharge had pulmonary hypertension and two had a cardiac arrest.

CONCLUSIONS

In this prospective cohort study of critical pertussis, over one third of survivors had significantly abnormal neurodevelopmental scores in one or more domains. Neither illness characteristics nor PICU course was associated with lower developmental scores. Our results suggest that all survivors of critical pertussis like survivors of sepsis and other major critical illness may benefit from routine neurodevelopmental screening.

ACKNOWLEDGMENTS

Members of the CPCCRN participating in this study—University of Utah (Data Coordinating Center), Salt Lake City, UT: Linda Herrera, MPH; Children's Hospital of Pittsburgh, Pittsburgh, PA: Michael Bell, MD, Alan Abraham, BA, CCRC; Children's National Medical Center, Washington, DC: Jean Reardon, MA, BSN, RN; Elyse Tomanio, BSN, RN; Children's Hospital of Michigan, Detroit, MI: Ann Pawluszka, BSN, RN; Children's Hospital Los Angeles, Los Angeles, CA: Jennifer Yuen Kwok, JD; Arkansas Children's Hospital, Little Rock, AR: Glenda C. Hefley, MNSc, CCRP; Seattle Children's Hospital, Seattle, WA: Stephanie Hamilton, BSN, CCRP; Children's Hospital of Philadelphia, Philadelphia, PA: Athena F. Zuppa, MD, MSCE, Mary Ann DiLiberto, BS, RN, CCRC, Carolann Twelves, RN, BSN, CCRC; Children's Hospital of Phoenix, Phoenix, AZ: Aimee La Bell, MS, RN; and Mott Children's Hospital, Ann Arbor, MI: Frank W. Moler, MD, Monica S. Weber, RN, BSN, CCRP, and Lauren Conlin, BSN, RN. Collaborating Sites contributing to this study—Centers for Disease Control and Prevention, Atlanta, GA: Fatima Coronado, MD, MPH; Children's Healthcare of Atlanta at Egleston, Atlanta, GA: James Fortenberry, MD, Richard Toney, RN, Cheryl L. Stone, RN; Miller Children's Hospital Long Beach, Long Beach, CA: Kevin C. O'Brien, MD, FAAP; Children's Hospital of Orange County, Orange, CA: Patricia P. Liao, MD, Tiffany Patterson, BS, CRC; Children's Hospitals and Clinics of Minnesota, Minneapolis, MN; Children's Hospital and Research Center Oakland, Oakland, CA: Heidi R. Flori, MD, Julie Simon, BSN, RN; Children's Hospital of Wisconsin, Milwaukee, WI: Rainer G. Gedeit, MD, Melissa Christensen, BS; Dell Children's Medical Center of Central Austin, Austin, TX: Renee A. Higgerson, MD, LeeAnn Christie, MSN, RN; Dartmouth-Hitchcock Medical Center, Lebanon, NH: Daniel L. Levin, MD, J. Dean Jarvis, BSN, MBA, CCRN; Miami Children's Hospital, Miami, FL: Balagangadhar R. Totapally, MBBS, DCH, MD, MRCP; New York Presbyterian Hospital Cornell University, New York, NY: Chani S. Traube, MD, Charlene S. Carlo; Penn State Hershey Children's Hospital, Hershey, PA: Neal J. Thomas, MD, MSc, Debbie Spear, RN, CCRN; St. Louis Children's Hospital, St. Louis, MO: Jose A. Pineda, MD, Tina Day, CCRC; Stollery Children's Hospital, University of Alberta, Alberta, Canada; Texas Children's Hospital and Baylor College of Medicine, Houston, TX: Moushumi S. Sur, MD, Nancy Jaimon, BSN, RN; University of Nebraska Medical Center/Children's Hospital, Omaha, NE: Edward J. Truemper, MD, Machelle A. Zink, MEd, BSN, RN, CCRC; and University of Virginia, Charlottesville, VA: Robin L. Kelly, RN.

REFERENCES

1. National Center for Immunization and Respiratory Disease, Centers for Disease Control and Prevention: Pertussis Cases by Year (1922–2014). Available at: http://www.cdc.gov/pertussis/surv-reporting/cases-by-year.html. Accessed February 9, 2016
2. Surridge J, Segedin ER, Grant CC: Pertussis requiring intensive care. *Arch Dis Child* 2007; 92:970–975
3. Gillis J, Grattan-Smith T, Kilham H: Artificial ventilation in severe pertussis. *Arch Dis Child* 1988; 63:364–367
4. Namachivayam P, Shimizu K, Butt W: Pertussis: Severe clinical presentation in pediatric intensive care and its relation to outcome. *Pediatr Crit Care Med* 2007; 8:207–211
5. Berger JT CJ, Shanley TP, Wessel DL, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN): Critical pertussis ilness in children: A multicenter prospective cohort study. *Pediatr Crit Care Med* 2013; 14:354–365
6. Murray EL, NIeves D, Bradley JS, et al: Characteristics of severe bordetella pertussis infection among infants ≤ 90 days of age admitted to pediatric intensive care units - Southern California, September 2009-June 2011. *J Pediatric Infect Dis Soc* 2013; 2:1–6
7. Anonymous: Study of intellectual performance of children in ordinary schools after certain serious complications of whooping cough. Swansea Research Unit of the Royal College of General Practitioners. *Br Med J (Clin Res Ed)* 1987; 295:1044–1047
8. Olsen M, Thygesen SK, Østergaard JR, et al: Hospital-diagnosed pertussis infection in children and long-term risk of epilepsy. *JAMA* 2015; 314:1844–1849
9. Incorpora G, Pavone L, Parano E, et al: Neurological complications in hospitalized patients with pertussis: A 15-year Sicilian experience. *Childs Nerv Syst* 1996; 12:332–335
10. de Greeff SC, van Buul LW, Westerhof A, et al: Pertussis in infancy and the association with respiratory and cognitive disorders at toddler age. *Vaccine* 2011; 29:8275–8278
11 .Mullen EM: Mullen Scales of Early Learning, AGS Edition. Minneapolis, MN, NCS Pearson, 1995
12. Bassan H, Limperopoulos C, Visconti K, et al: Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics* 2007; 120:785–792
13. Bolduc ME, Du Plessis AJ, Sullivan N, et al: Spectrum of neurodevelopmental disabilities in children with cerebellar malformations. *Dev Med Child Neurol* 2011; 53:409–416
14. Caudle SE, Katzenstein JM, Karpen S, et al: Developmental assessment of infants with biliary atresia: Differences between boys and girls. *J Pediatr Gastroenterol Nutr* 2012; 55:384–389
15. Ungerleider RM, Shen I, Yeh T, et al: Routine mechanical ventricular assist following the Norwood procedure–improved neurologic outcome and excellent hospital survival. *Ann Thorac Surg* 2004; 77:18–22
16. Wachtel EV, Zaccario M, Mally P: Impact of respiratory morbidities on neurodevelopmental outcome of late preterm infants. *Am J Perinatol* 2015; 32:1164–1168

17. Schraeder BD: Assessment of measures to detect preschool academic risk in very-low-birth-weight children. *Nurs Res* 1993; 42:17–21
18. Pollack MM, Patel KM, Ruttimann UE: PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med* 1996; 24:743–752
19. Farris RW, Weiss NS, Zimmerman JJ: Functional outcomes in pediatric severe sepsis: Further analysis of the researching severe sepsis and organ dysfunction in children: A global perspective trial. *Pediatr Crit Care Med* 2013; 14:835–842
20. Als LC, Nadel S, Cooper M, et al: Neuropsychologic function three to six months following admission to the PICU with meningoencephalitis, sepsis, and other disorders: A prospective study of school-aged children. *Crit Care Med* 2013; 41:1094–1103
21. Bronner MB, Knoester H, Sol JJ, et al: An explorative study on quality of life and psychological and cognitive function in pediatric survivors of septic shock. *Pediatr Crit Care Med* 2009; 10:636–642
22. Davis LE, Burstyn DG, Manclark CR: Pertussis encephalopathy with a normal brain biopsy and elevated lymphocytosis-promoting factor antibodies. *Pediatr Infect Dis* 1984; 3:448–451
23. Grant CC, McKay EJ, Simpson A, et al: Pertussis encephalopathy with high cerebrospinal fluid antibody titers to pertussis toxin and filamentous hemagglutinin. *Pediatrics* 1998; 102:986–990
24. Budan B, Ekici B, Tatli B, et al: Acute disseminated encephalomyelitis (ADEM) after pertussis infection. *Ann Trop Paediatr* 2011; 31:269–272
25. Hiraiwa-Sofue A, Ito Y, Mori H, et al: Pertussis-associated encephalitis/encephalopathy with marked demyelination in an unimmunized child. *J Neurol Sci* 2012; 320:145–148
26. Farizo KM, Cochi SL, Zell ER, et al: Epidemiological features of pertussis in the United States, 1980–1989. *Clin Infect Dis* 1992; 14:708–719
27. Tiwari TS, Baughman AL, Clark TA: First pertussis vaccine dose and prevention of infant mortality. *Pediatrics* 2015; 135:990–999
28. Hövels-Gürich HH, Seghaye MC, Schnitker R, et al: Long-term neurodevelopmental outcomes in school-aged children after neonatal arterial switch operation. *J Thorac Cardiovasc Surg* 2002; 124:448–458
29. McGrath E, Wypij D, Rappaport LA, et al: Prediction of IQ and achievement at age 8 years from neurodevelopmental status at age 1 year in children with D-transposition of the great arteries. *Pediatrics* 2004; 114:e572–e576
30. Haberling DL, Holman RC, Paddock CD, et al: Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. *Pediatr Infect Dis J* 2009; 28:194–198
31. Krakowiak P, Walker CK, Bremer AA, et al: Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics* 2012; 129:e1121–e1128
32. Walker CK, Krakowiak P, Baker A, et al: Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. *JAMA Pediatr* 2015; 169:154–162
33. Koura KG, Boivin MJ, Davidson LL, et al: Usefulness of child development assessments for low-resource settings in francophone Africa. *J Dev Behav Pediatr* 2013; 34:486–493
34. Chaidez V, Hansen RL, Hertz-Picciotto I: Autism spectrum disorders in Hispanics and non-Hispanics. *Autism* 2012; 16:381–397
35. Carlson SM, Meltzoff AN: Bilingual experience and executive functioning in young children. *Dev Sci* 2008; 11:282–298