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Adverse Events After Routine Immunization of Extremely Low-Birth-Weight Infants

FREE ONLINE FIRST

Stephen D. DeMeo, DO[1]; Sudha R. Raman, PhD[2]; Christoph P. Hornik, MD, MPH[1,2]; Catherine C. Wilson, DNP, NNP-BC, FNP-BC[3]; Reese Clark, MD[4]; P. Brian Smith, MD, MPH, MHS[1,2]

[+] Author Affiliations

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ABSTRACT

Importance Immunization of extremely low-birth-weight (ELBW) infants in the neonatal intensive care unit (NICU) is associated with adverse events, including fever and apnea or bradycardia, in the immediate postimmunization period. These adverse events present a diagnostic dilemma for physicians, leading to the potential for immunization delay and sepsis evaluations.

Objective To compare the incidence of sepsis evaluations, need for increased respiratory support, intubation, seizures, and death among immunized ELBW infants in the 3 days before and after immunization.

Design, Setting, and Participants In this multicenter retrospective cohort study, we studied 13 926 ELBW infants born at 28 weeks' gestation or less who were discharged from January 1, 2007, through December 31, 2012, from 348 NICUs managed by the Pediatrix Medical Group.

Exposures At least one immunization between the ages of 53 and 110 days.

Main Outcomes and Measures Incidence of sepsis evaluations, need for increased respiratory support, intubation, seizures, and death.

Results Most of the 13 926 infants (91.2%) received 3 or more immunizations. The incidence of sepsis evaluations increased from 5.4 per 1000 patient-days in the preimmunization period to 19.3 per 1000 patient-days in the postimmunization period (adjusted rate ratio [ARR], 3.7; 95% CI, 3.2-4.4). The need for increased respiratory support increased from 6.6 per 1000 patient-days in the preimmunization period to 14.0 per 1000 patient-days in the postimmunization period (ARR, 2.1; 95% CI, 1.9-2.5), and intubation increased from 2.0 per 1000 patient-days to 3.6 per 1000 patient-days (ARR, 1.7; 95% CI, 1.3-2.2). The postimmunization incidence of adverse events was similar across immunization types, including

combination vaccines when compared with single-dose vaccines. Infants who were born at 23 to 24 weeks' gestation had a higher risk of sepsis evaluation and intubation after immunization. A prior history of sepsis was associated with higher risk of sepsis evaluation after immunization.

Conclusions and Relevance All ELBW infants in the NICU had an increased incidence of sepsis evaluations and increased respiratory support and intubation after routine immunization. Our findings provide no evidence to suggest that physicians should not use combination vaccines in ELBW infants. Further studies are needed to determine whether timing or spacing of immunization administrations confers risk for the developing adverse events and whether a prior history of sepsis confers risk for an altered immune response in ELBW infants.

INTRODUCTION

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Timely immunization of premature infants in the neonatal intensive care unit (NICU) is associated with improved immunization coverage throughout childhood.[1] However, the immunization of extremely low-birth-weight (ELBW; birth weight ≤1000 g) infants has been associated with adverse events, including fever and adverse cardiorespiratory events, such as apnea and bradycardia, in the immediate postimmunization period.[2-4] These adverse events can mimic serious diseases in ELBW infants, including true sepsis, presenting a diagnostic dilemma for physicians. Fever in ELBW infants after immunization can often lead to additional workup to rule out true sepsis, including collection of blood and urine cultures, and exposure to empirical antibiotic therapy. The risks of additional antibiotic use, exposing the infant to painful procedures, and the withholding of enteral feedings must be weighed against the risk of missing true sepsis in an ELBW infant.

Immunization delay has been reported in hospitalized premature infants.[5] This delay may be related to physicians waiting to immunize relatively well infants, concerns about adverse events, and misconceptions about the ability of an infant's immune system to tolerate multiple immunizations.[6] Better knowledge of the risk factors for and timing of adverse events after immunization in ELBW infants could lead to better monitoring, prevent unnecessary sepsis evaluations, and reduce immunization delay. To date, most studies describing the incidence of adverse events after immunization in ELBW have been small, single-center studies. In this study, we use a large, multicenter NICU database to investigate the incidence of sepsis evaluations and adverse cardiorespiratory events after immunization in ELBW infants, describe these events by immunization type, and assess potential risk factors for adverse events.

At a Glance

- This study investigated the incidence of adverse events after routine immunization in extremely low-birth-weight (ELBW) infants.
- We analyzed a large multicenter cohort of 13 926 ELBW infants born at 28 weeks' gestation or less.
- Infants had a higher incidence of sepsis evaluations (adjusted rate ratio [ARR], 3.7; 95% CI, 3.2-4.4), need for increased respiratory support (ARR, 2.1; 95% CI, 1.9-2.5), and intubation (ARR, 1.7; 95% CI, 1.3-2.2) in the 3 days after immunization relative to the 3 days before immunization.
- The incidence of adverse events was similar across immunization types, including combination vaccines when compared with single-dose vaccines.
- Lower gestational age (23-24 weeks) and a prior history of sepsis were associated with a higher rate of sepsis evaluation and need for intubation.

METHODS

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Data were obtained from an electronic medical record that prospectively captures information from daily progress notes generated by physicians from 348 NICUs managed by the Pediatrix Medical Group. These NICUs represent academic and private practice centers, encompassing all levels of NICU care. Information on multiple aspects of care is entered to generate admission notes, daily progress notes, procedure notes, and discharge summaries. Collected data include maternal history and demographic characteristics, medications, laboratory results, culture results, daily medications, respiratory support, and diagnoses. We defined *coagulase-negative* Staphylococcus *(CoNS) sepsis* as 2 positive blood culture results on the same day; *probable CoNS sepsis* as 2 positive cultures for CoNS within a 4-day period, 3 positive cultures for CoNS within a 7-day period, or 4 positive cultures for CoNS within a 10-day period; and *possible sepsis* as a culture positive for CoNS that did not meet criteria for definite or probable CoNS sepsis. We only included definite and probable CoNS sepsis in the analysis. We excluded sepsis episodes for organisms considered contaminants, including nonspeciated streptococci, *Bacillus* species, *Corynebacterium* species, *Diphtheroids* species, gram-positive rods (not including *Listeria* species), *Lactobacillus* species, *Micrococcus* species, *Stomatococcus* species, and *Bacteroides* species.

We identified all infants discharged from January 1, 2007, through December 31, 2012, with the following characteristics: (1) birth weight of 1000 g or less, (2) gestational age at birth of 28 weeks or less, and (3) receipt of at least one immunization (diphtheria, tetanus toxoids, and acellular pertussis [DTaP]; inactivated polio virus [IPV]; hepatitis B [HepB]; *Haemophilus influenzae* type B [HiB]; 7-valent and 13-valent pneumococcal conjugate; combination DTaP, IPV, and HepB; combination DTaP, IPV, and HiB; or combination HepB and HiB) between the ages of 53 and 110 days. This period allowed us to capture most immunizations administered at approximately 2 months (60 days) of age, the recommended age of scheduled immunizations, excluding the HepB vaccine. Combination products were treated as one immunization. Infants discharged during the 3-day observation window were excluded unless the discharge was due to death. The Duke University School of Medicine Institutional Review Board approved this study without the need for written informed consent because the data lacked patient identifiers.

The primary outcome measured was sepsis evaluation (blood culture obtained). Secondary outcomes were (1) the need for increased respiratory support (a recorded daily change in respiratory support increased from room air to noninvasive oxygen therapy [nasal cannula, continuous positive airway pressure, and nasal intermittent positive pressure ventilation] or the need for endotracheal intubation [room air or noninvasive therapy to a form of invasive mechanical ventilation—conventional ventilation or high-frequency ventilation]), (2) the need for endotracheal intubation (room air or noninvasive therapy to a form of invasive mechanical ventilation—conventional ventilation or high-frequency ventilation), (3) seizures, and (4) death. The incidence of adverse events, expressed in events per 1000 patient-days, was calculated in the preimmunization and postimmunization periods for each infant. Comparisons of the incidence of adverse events were made between two 3-day periods: the 3 days before immunization (preimmunization) and the 3 days after immunization (postimmunization; ie, day of immunization plus the following 2 days). For this main analysis, days that fell within both a preimmunization and postimmunization period for different immunization administrations were classified as a postimmunization day only. We also examined the daily incidence, expressed in events per 1000 patient-days, of each outcome measure from 30 days before to 30 days after the first immunization day. We used Poisson regression to compare the overall incidence of adverse events between the preimmunization and postimmunization periods for all immunizations. We further analyzed risk factors for postimmunization outcomes only, including infant gestational age at birth, small for gestational age status, history of sepsis, and postnatal age and postnatal weight at immunization in a multivariable Poisson regression. Prior history of sepsis was later subgrouped by history of gram-positive vs gram-negative sepsis for comparison. All variables in these models were categorical except postnatal age and weight.

In the analysis of adverse events by immunization type, days in the preimmunization period that were also postimmunization days for another type of immunization were excluded. The nonindependence of the observations within the same infant was accounted for using generalized estimating equations. We performed a sensitivity analysis comparing how varying lengths of observation periods in the preimmunization and postimmunization periods affected the measured incidence of the effect measures. Standard descriptive statistics were used to describe the study cohort. All data analyses were conducted using SAS statistical software, version 9.3 (SAS Institute Inc).

RESULTS

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We identified a total of 13 926 infants who received a total of 48 853 immunizations (Table 1); 12 703 infants (91.2%) received 3 or more immunizations. The median postnatal age at immunization was 64 days (interquartile range, 60-72 days). A history of sepsis before day 53 was observed in 2904 infants (20.9%). During the preimmunization and postimmunization periods, 5952 (42.7%) of 13 926 infants received caffeine therapy.

Table 1. Demographic Characteristics of the Study Patients[a]

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Characteristic	Finding (n = 13 926)
Gestational age, wk	
23-24	3113 (22.4)
25-26	6818 (49.0)
27-28	3995 (28.7)
Birth weight, g	
400-600	2019 (14.5)
601-800	5978 (42.9)
801-1000	5929 (42.6)
Small for gestational age	2486 (17.9)
Race/ethnicity	
White	5699 (40.9)
Black	4328 (31.1)
Hispanic	2622 (18.8)
Other	782 (5.6)
Male sex	6831 (49.1)
First immunization, median (IQR)	
Postnatal age, d	64 (60-72)
Weight, g	1988 (1735-2235)
No. of immunizations received	
1	559 (4.0)
2	664 (4.8)
3	9260 (66.5)
4	1096 (7.9)
≥5	2347 (16.9)
History of sepsis before day 53	2904 (20.9)

Abbreviation: IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

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The incidence of sepsis evaluation increased from 5.4 per 1000 patient-days in the preimmunization period to 19.3 per 1000 patient-days in the postimmunization period (adjusted rate ratio [ARR], 3.7; 95% CI, 3.2-4.4) (Table 2). Of the 235 sepsis evaluations performed in the preimmunization period, 5 (2.1%) yielded a positive blood culture result compared with 39 (3.8%) of 1035 evaluations performed after immunization. Analysis of the secondary outcomes revealed an increased incidence of respiratory support and intubations in the postimmunization period compared with the preimmunization period (Table 2). The incidence of seizure was 0.2 per 1000 infant-days in the preimmunization period and 0.1 per 1000 patient-days in the postimmunization period, but these occurrences represented only 9 and 3 total events in each period, respectively.

Table 2. Incidence of Events Before and After Immunization per 1000 Patient-days

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	Immunization			
Event	Before	After	RR (95% CI)	ARR (95% CI)[a]
Sepsis evaluation	5.4	19.3	3.5 (3.1-4.1)	3.7 (3.2-4.4)
Increased respiratory support	6.6	14.0	2.1 (1.9-2.4)	2.1 (1.9-2.5)
Intubation	2.0	3.6	1.8 (1.4-2.3)	1.7 (1.3-2.2)
Seizure	0.2	0.1	0.3 (0.1-1.0)	0.3 (0.1-1.1)

Abbreviations: ARR, adjusted rate ratio; RR, rate ratio.

[a] The ARR was adjusted for gestational age at birth, small for gestational age status, history of sepsis, postnatal age, and postnatal weight.

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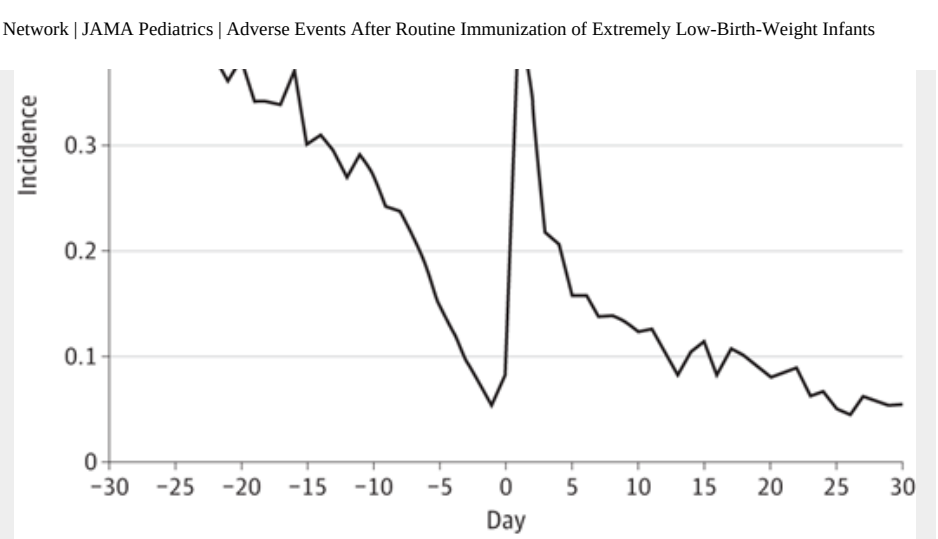
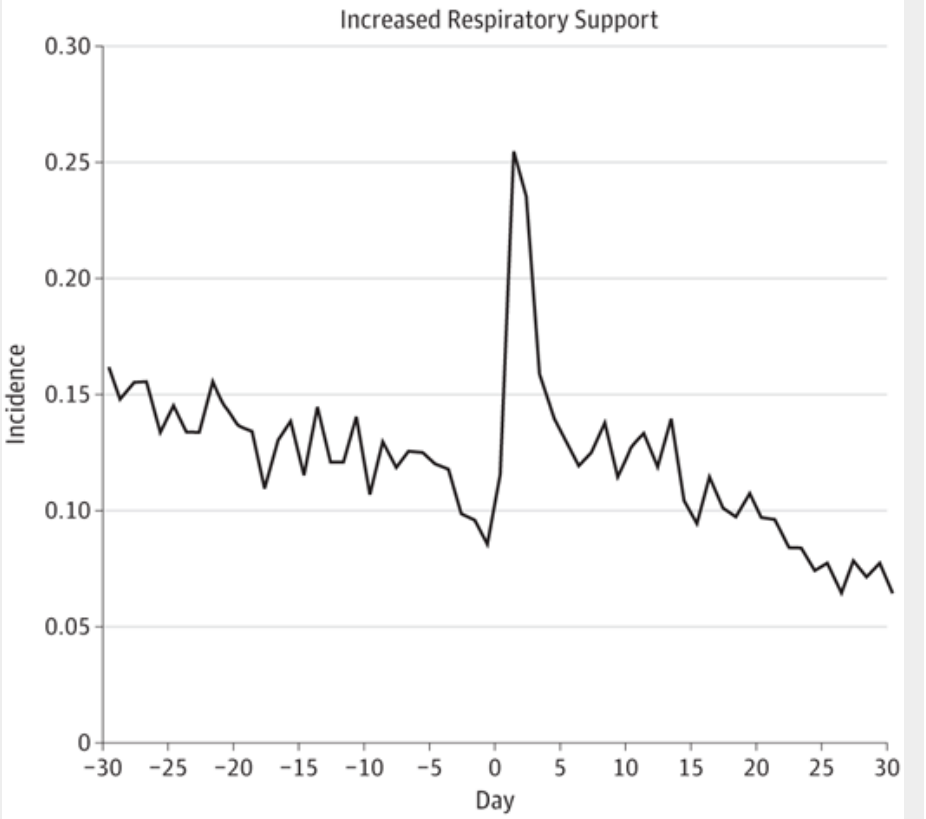
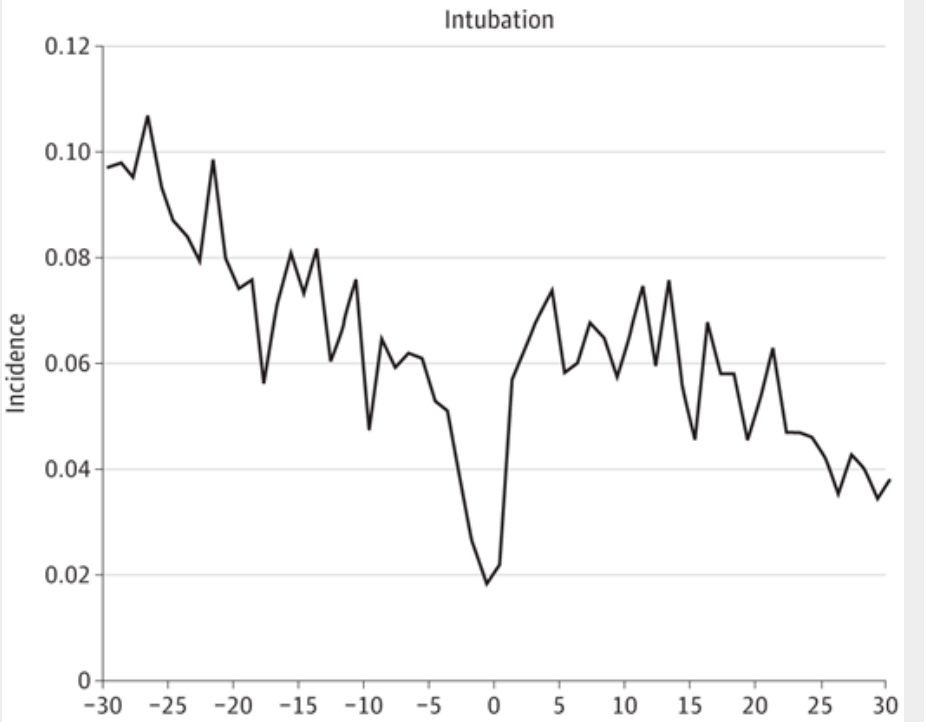
There were 5 deaths in the postimmunization period. Three of the 5 infants who died in the 3 days after immunization had a diagnosis associated with death available in the data set; 1 infant had a bowel perforation, 1 infant had necrotizing enterocolitis and presumed sepsis, and 1 infant had pneumonia and respiratory failure. The incidence of sepsis evaluations, increased respiratory support, and intubations measured by day, from 30 days before immunization to 30 days after immunization, revealed a steady decrease until 5 to 7 days before immunization, followed by a sharp decrease leading up to the day of immunization (Figure). After immunization, there was an increase in the daily incidence between day 0 and day 2 after immunization, most notably for sepsis evaluations (Figure). When analyzing adverse events grouped by type of immunization administered, we found pneumococcal conjugate to be the most commonly administered immunization (Table 3). The incidence of adverse events was similar across all immunization types, with the primary outcome (sepsis evaluation) again revealing a higher postimmunization incidence across all types of immunizations (Table 3).

Figure.

Daily Incidence of Sepsis Evaluation, Increased Respiratory Support, and Intubation in the 30-Day Period Before and After First Immunization (Day 0)


Incidence
0.3
0.2
0.1
0
−30 −25 −20 −15 −10 −5 0 5 10 15 20 25 30
Day


Increased Respiratory Support
Incidence
0.30
0.25
0.20
0.15
0.10
0.05
0
−30 −25 −20 −15 −10 −5 0 5 10 15 20 25 30
Day


Intubation
Incidence
0.12
0.10
0.08
0.06
0.04
0.02
0
−30 −25 −20 −15 −10 −5 0 5 10 15 20 25 30

Day

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Table 3. Postimmunization Incidence per 1000 Patient-days of Events and ARRs of Events by Immunization Type

Table 3. Postimmunization Incidence per 1000 Patient-days of Events and ARRs of Events by Immunization Type

Vaccine	No. of Patients	Sepsis Evaluation		Increased Respiratory Support		Intubated	
		Incidence	ARR (95% CI)[a]	Incidence	ARR (95% CI)[a]	Incidence	ARR (95% CI)[a]
HepB and HiB	560	22.7	6.0 (2.5-14.2)	15.6	1.4 (0.8-2.6)	4.8	1.8 (0.6-5.3)
DTaP, IPV, and HiB	1236	17.6	4.0 (2.3-6.9)	12.7	2.3 (1.3-4.0)	3.5	2.6 (0.8-7.9)
IPV	3278	15.5	3.0 (2.1-4.2)	13.9	2.1 (1.5-2.9)	4.3	2.5 (1.3-4.9)
DTaP	3391	13.9	3.2 (2.2-4.5)	12.3	1.9 (1.4-2.6)	3.6	2.5 (1.3-4.8)
HepB	4660	12.8	3.1 (2.3-4.1)	11.9	2.1 (1.6-2.8)	2.9	1.5 (0.9-2.6)
DTaP, IPV, and HepB	8558	24.6	4.3 (3.6-5.3)	16.4	2.6 (2.1-3.1)	3.6	1.8 (1.3-2.6)
HiB	11 166	21.6	4.0 (3.3-4.8)	14.2	2.1 (1.8-2.5)	3.3	1.6 (1.2-2.7)
PCV	13 004	22.0	4.4 (3.7-5.3)	14.7	2.2 (1.9-2.7)	3.6	2.0 (1.5-2.3)

Abbreviations: ARR, adjusted rate ratio; DTaP, diphtheria, tetanus toxoids, and acellular pertussis; HepB, hepatitis B; HiB, *Haemophilus influenzae* type B; IPV, inactivated polio virus; PCV, 7-valent and 13-valent pneumococcal conjugate vaccine.

[a] The ARR was adjusted for postnatal age and postnatal weight.

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In the postimmunization period, infants at 23 to 24 weeks' gestation had an increased incidence of sepsis evaluation (ARR, 1.2; 95% CI, 1.0-1.3) compared with older infants (27-28 weeks' gestation). In addition, infants in the 23- to 24-week group had a higher incidence of intubation (ARR, 1.5; 95% CI, 1.2-2.0) compared with older infants (27-28 weeks' gestation) in the postimmunization period. A prior history of sepsis was associated with an increased rate for sepsis evaluation (ARR, 1.4; 95% CI, 1.2-1.5) but not for intubation (ARR, 1.3; 95% CI, 1.0-1.9) or increased respiratory support (ARR, 1.0; 95% CI, 0.8-1.2). For infants with a prior history of sepsis, a history of gram-positive sepsis before day 53 was associated with an increased risk of sepsis evaluation after immunization (ARR, 1.3; 95% CI, 1.1-1.5). A history of gram-negative sepsis was not significantly associated with an increased risk of sepsis evaluation after immunization (ARR, 1.2; 95% CI, 0.9-1.5). Postnatal age at immunization, small for gestational age status, and postnatal weight at immunization were not significantly associated with any of the outcomes.

DISCUSSION

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In this large, multicenter cohort of ELBW infants, there was a significant increase in adverse events in the postimmunization period, including sepsis evaluations, need for increased respiratory support, and intubation. Despite the large number of sepsis evaluations after immunization, few infants had evidence of true sepsis (bacteremia). The pneumococcal conjugate vaccine represented the largest number of immunization administrations, likely because, for the other routine 2-month immunizations, the total number of administrations is split between those infants who received single-dose DTaP, HepB, HiB, or IPV vaccines and those who were administered combination products. In our cohort, all immunization types had similar ARRs comparing the preimmunization and postimmunization periods. There was no difference in the incidence of adverse events in combination vaccines vs single-dose vaccines. These data provide no evidence to suggest that physicians should not use combination vaccines in ELBW infants. Lower gestational age was associated with increased risk of sepsis evaluations and need for intubation in the postimmunization period. Postnatal age and postnatal weight at the time of immunization were not related to the risk of adverse events.

We observed a decrease in the incidence of several of the adverse events leading up to immunization day, especially in the several days before immunization. This occurrence is possibly explained by the so-called healthy vaccinated effect, by which physicians wait until infants are more stable to immunize, thus reducing the observed incidence of preimmunization adverse events and biasing the incidence rate ratios upward. Incidence rates of adverse events on the day of immunization in particular are likely to be

artificially low because physicians are unlikely to immunize infants on a day that they have had clinical instability. To address this potential bias, we performed several sensitivity analyses in which we varied the length of the preimmunization and postimmunization periods. Results from these analyses were similar to the primary results. Waiting for subjective markers of clinical stability might be a leading factor in immunization delay in ELBW infants. Although we did not assess for immunization delay in this study, a previous study[2] found that up to one-fifth of infants who were eligible for immunization were not vaccinated during that time frame, again pointing to the possibility of the healthy-vaccinated effect. Immunization delay burdens an already fragile patient population with the increased morbidity and mortality of vaccine-preventable diseases through the first year of life.[1,7,8]

Fever is a well-known adverse event after immunization. A previous retrospective cohort study[2] of 490 infants who were all inpatients in the NICU for more than 53 days observed increased rates of fever after immunization but found no increase in the rate of sepsis evaluations. Infants who had acute cardiorespiratory events in the immediate postimmunization period in combination with a febrile episode were more likely to undergo an evaluation to rule out sepsis—characterized as obtaining a blood culture and starting empirical antibiotic therapy—compared with those infants presenting with fever alone. In addition, there is some evidence that infants who receive all 3 routine 2-month immunizations at once rather than in 2 or 3 administrations have a higher risk of postimmunization fever.[9] The association between immunization and subsequent response to infection in ELBW infants is potentially significant. Premature infants have an altered immune response to immunization.[10] In one of the first studies[11] in neonates that examined the effects of sepsis on subsequent production of antibodies after immunization, very low-birth-weight (<1500 g) infants with a history of bacteremia had an alteration of immune response to specific serotypes of the pneumococcal vaccine. Others studies[12,13] have found that prior history of sepsis in ELBW infants was actually protective against future episodes of late-onset sepsis, with one preclinical study[13] suggesting a more robust innate immune response in immature mice. An important area of future research is to determine whether a causative relationship exists between sepsis in the neonatal period and subsequent alterations in the immune response to immunization in an already medically fragile population.

Apnea and bradycardia are also commonly observed adverse events in the postimmunization period.[14] The DTaP-containing vaccines have been of particular concern because the whole-cell pertussis vaccine has been cited as causing apnea and bradycardia in 7% of preterm infants,[15] and more recently, apnea and bradycardia have been observed after immunization with the acellular pertussis vaccine component.[16] Several studies[17,18] have found an increased risk of events leading to new requirements for respiratory support, especially in ELBW infants with significant lung disease, a history of sepsis during hospitalization,[17] and preimmunization apnea,[18] although other studies[19,20] have found no increased incidence in cardiorespiratory events after immunization among hospitalized infants in the NICU. These studies used much smaller cohorts than the current study. One randomized clinical trial[18] examining adverse events after DTaP vaccination reported no difference in the incidence of adverse cardiorespiratory events after only one immunization. When cardiorespiratory events occur, they are more likely to occur in populations similar to this study group of ELBW infants and those with more severe illness at birth.[21] Older infants with a diagnosis of chronic lung disease who were still hospitalized in the NICU at the time of immunization also had a higher incidence of adverse events.[22] Regarding the use of combination vaccines, a 2007 study[22] of the hexavalent DTaP, IPV, HiB, and HepB vaccine found that apnea and/or bradycardia occurred in 11% of study infants, demonstrating slightly higher rates of adverse events compared with single-dose vaccines. More recently, a retrospective study[3] in 2008 of 64 infants who received the combination DTaP, IPV, and HiB vaccine and the 7-valent pneumococcal conjugate vaccine found that 25% of study infants had clinically significant apnea and bradycardia. However, we do not have current information about the use of single-dose vs combination vaccines in US NICUs.

Although our study captured a large cohort of infants, we cannot be sure that clinical correlates documented in the electronic medical record, such as collection of a blood culture or an increase in respiratory support, truly reflect the occurrence of fever or sepsis evaluations or apnea and bradycardia, respectively. All deaths occurred after immunization because death before immunization would have excluded an infant from the study. Therefore, a true comparison before and after immunization cannot be made here. A potential bias also exists in the recording of events in the clinical record in that physicians may be more likely to document adverse events that are occurring in close proximity to the administration of immunizations. This potential for bias is reduced in the most serious adverse events (intubation and seizure) because we expect these serious events to be more consistently recorded, as opposed to apneic or bradycardic events in an otherwise stable infant. Although previous researchers have chosen to evaluate the presence of fever in the postimmunization period, we believed that blood culture was more likely to be specific for the occurrence of a sepsis evaluation because this was a laboratory test captured in the electronic record rather than a diagnosis that had to be observed and subsequently entered by a physician. We did not investigate whether specific timing or spacing of immunizations (such as all given in 1 day vs spaced during 72 hours) during the observation period contributed to an increased incidence of the study

outcomes. Finally, a retrospective observational study such as this can only provide evidence of correlation rather than causation.

CONCLUSIONS

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This study found an increase in adverse events after the routine immunization of ELBW infants in the NICU, specifically sepsis evaluations, need for increased respiratory support, and intubation. The incidence of these adverse events decreased sharply just before the first immunization day. Younger gestational age (23-24 weeks) was associated with a higher risk of sepsis evaluation and intubation after immunization. A prior history of sepsis was associated with a higher risk of sepsis evaluations after immunization. Further studies are needed to determine whether the order and timing of specific immunizations affect the incidence of adverse events in the postimmunization period and whether a prior history of sepsis confers risk for an altered immune response in ELBW infants.

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Corresponding Author: P. Brian Smith, MD, MPH, MHS, Duke Clinical Research Institute, Duke University School of Medicine, PO Box 17969, Durham, NC 27715 (brian.smith@duke.edu).

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Author Contributions: Drs DeMeo and Smith had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: DeMeo, Hornik, Clark, Smith.

Acquisition, analysis, or interpretation of data: DeMeo, Raman, Wilson, Clark, Smith.

Drafting of the manuscript: DeMeo.

Critical revision of the manuscript for important intellectual content: Raman, Hornik, Wilson, Clark, Smith.

Statistical analysis: Raman, Hornik, Smith.

Obtained funding: Smith.

Administrative, technical, or material support: Wilson, Clark.

Study supervision: Clark.

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