Respiratory Decompensation and Immunization of Preterm Infants

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abstract

BACKGROUND: Concern for respiratory decompensation after immunization in premature infants, particularly those with bronchopulmonary dysplasia (BPD), may lead to delayed and altered immunization schedules.

METHODS: A retrospective cohort of premature infants at <32 weeks' gestational age cared for in a tertiary level 4 NICU and immunized during their hospital stay were evaluated for respiratory decompensation within 72 hours of immunization. Respiratory measurements including change in respiratory support, mean fraction of inspired oxygen, and apnea, bradycardia, and desaturation events were compared between those infants with BPD and those without. The primary outcome was the difference in respiratory decompensation defined as a composite of increased respiratory support or increased fraction of inspired oxygen ≥10% within 72 hours of immunization.

RESULTS: Of 403 infants admitted to the NICU and immunized, 240 met the study criteria. Of those infants, 172 had a diagnosis of BPD. There was no difference in the primary outcome of respiratory decompensation after immunization between groups (P = .65). There was also no significant difference in apnea, bradycardia, and desaturation events between groups (P = .51).

CONCLUSIONS: In this cohort, respiratory decompensation requiring clinical intervention after immunization of preterm infants both with and without BPD was uncommon and not significantly different between groups. Consideration for immunization of this vulnerable population should not be delayed out of concern for clinical deterioration.

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WHAT'S KNOWN ON THIS SUBJECT: There have been concerns that preterm infants with bronchopulmonary dysplasia (BPD) experience respiratory decompensation after immunization in greater proportion than those infants without BPD. Previous studies have identified comorbidities that may contribute to decompensation.

WHAT THIS STUDY ADDS: No previous studies have specifically evaluated preterm infants with BPD to identify if immunization is associated with respiratory decompensation in greater proportion than infants without BPD or if any comorbidities may predispose an infant to respiratory decompensation after immunization.

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Immunization programs in the United States have shown tremendous benefits over the past few decades, preventing illnesses, hospitalizations, and deaths.[1] The Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommend that preterm infants, with few exceptions and regardless of birth weight, be immunized at the same chronological age and according to the same schedule as full-term infants.[2,3] Despite these recommendations, previous studies have shown that a large number of preterm infants are delayed in receiving immunizations and are underimmunized at the time of discharge from the NICU.[4–10] Health care providers may have heightened concerns for adverse events after immunization in preterm infants, which may, in part, contribute to the delay in immunization administration. Previous studies have evaluated apnea, bradycardia, and desaturation (A/B/D) episodes after immunization of preterm infants with mixed results.[11–25] Infants with bronchopulmonary dysplasia (BPD) are often considered to be at highest risk of adverse events after immunization[24]; however, this population is known to be at highest risk of severe complications from developing vaccine-preventable illnesses.[4,5,9,26]

The objectives of this study were to determine if infants with BPD experience respiratory decompensation after immunization in greater proportion than those infants without BPD and to explore patient characteristics that may predispose infants to respiratory decompensation after immunization. We also sought to evaluate whether these patients have a clinically relevant concern for A/B/D events after immunization.

METHODS

Study Population

This retrospective observational study was conducted with the approval of the Children's Healthcare of Atlanta Institutional Review Board. The initial subject cohort consisted of all infants admitted to the NICU at Children's Healthcare of Atlanta at Egleston (a level 4, nonbirthing referral hospital) between January 1, 2008, and August 1, 2014, and who received any immunizations while inpatients. Only those infants who were born at <32 weeks' estimated gestational age and had data available for 72 hours before and 72 hours after immunization were included. Infants who were excluded were patients who were no longer located in the NICU at the time of immunization due to transfer to another floor or transfer to another hospital or who had been discharged from the NICU within 72 hours after immunization (n = 9) and those who underwent surgery within 72 hours after immunization (n = 3). In cases in whom vaccines were given over multiple days, data for each immunization were abstracted individually. If separate immunizations were given within 72 hours of one another, the 72-hour period of observation began after the first immunization was given. BPD was defined as an oxygen requirement at 36 weeks' corrected gestational age (cGA).[27] Infants who were immunized at <36 weeks (n = 69) were evaluated for oxygen requirement at the time of immunization to 36 weeks' cGA and were assigned the diagnosis of BPD if they continued to have an oxygen requirement at 36 weeks' cGA. Five of 12 patients who did not carry the diagnosis of BPD and were immunized at <36 weeks' cGA were receiving respiratory support at the time of immunization but had been weaned off respiratory support by 36 weeks' cGA. All patients with BPD were receiving respiratory support at the time of immunization.

Vaccines

The vaccines administered during the 6.5-year study period include inactivated polio vaccine (IPV; Ipol; Sanofi, Paris, France), diphtheria-tetanus-acellular pertussis (DTaP) vaccine (Infarix; GlaxoSmithKline Biologicals, Rixensart, Belgium), *Haemophilus influenzae* type b (Hib) vaccine (Pedvax; Merck, Kenilworth, NJ), hepatitis B vaccine (HBV; Engerix-B; GlaxoSmithKline Biologicals), pneumococcal conjugate vaccine (PCV13; Wyeth/Pfizer, New York, NY), influenza vaccine (Fluzone; Sanofi, Paris, France), rotavirus vaccine (Rotateq; Merck), and DTaP-IPV-HBV combination vaccine (Pediarix; GlaxoSmithKline Biologicals). On the basis of the Centers for Disease Control and Preventaion–recommended immunization schedule, the definition of 2-month immunizations included the following: HBV, Hib vaccine, pneumococcal conjugate vaccine, IPV, DTaP vaccine, and rotavirus vaccine.[28]

Cardiorespiratory Events

Apnea was defined as cessation of respiration for ≥20 seconds, bradycardia as a decrease in heart rate to ≤100 beats per minute for a period of ≥20 seconds, and desaturations as an oxygen saturation via pulse oximetry of <88%. A/B/D episodes were obtained from the chart as documented by nursing staff for a 72-hour period before and after immunization.

Fraction of Inspired Oxygen

For those infants receiving nasal cannula at the time of immunization, effective fraction of inspired oxygen

(FIO_2) measurements were calculated on the basis of the weight of the patient and nasal cannula flow by using the formula derived from the work of Benaron and Benitz[29] and used by the STOP-ROP Multicenter Study Group.[30] A clinically significant change in effective FIO_2 was defined as an increase of ≥10% above the mean effective FIO_2 24 hours before immunization.

Respiratory Support

Respiratory support was categorized as follows in increasing level of care: no support, low-flow nasal cannula (LFNC) defined as flow <2 L/minute, high-flow nasal cannula (HFNC) defined as flow ≥2 L/minute, continuous positive airway pressure (CPAP), noninvasive positive-pressure ventilation, and conventional mechanical ventilation (CMV) as delivered by endotracheal intubation. An increase in respiratory support was defined as a change to any greater level of respiratory support (eg, LFNC to HFNC).

Statistical Analysis

Characteristics of the study population were compared by using Pearson's χ^2 test or Fisher's exact test for categorical variables and Student's *t* test for continuous variables. Risk factors hypothesized to possibly predispose to respiratory decompensation after immunization (history of necrotizing enterocolitis or spontaneous intestinal perforation, grade III or IV intraventricular hemorrhage [IVH], BPD, or periventricular leukomalacia [PVL]) were analyzed. Generalized estimating equations were used to model the odds of an adverse outcome (either increased A/B/D events or increased respiratory support after immunization) for different potential risk groups while accounting for multiple observations per patient. Multivariable models for each outcome were constructed by using variables identified in univariate analyses or variables that were historically known to influence the outcome. Risk factors were quantified with odds ratios (ORs) and associated 95% confidence intervals (CIs). *P* values <.05 were considered significant. Statistical analyses were performed by using SAS 9.3 (SAS Institute, Cary, NC) and SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

RESULTS

A total of 403 patients were identified, of whom 240 met criteria for inclusion (170 with BPD and 70 without BPD). The characteristics of the patients are shown in Table 1. There was a statistically significant difference between study groups in gestational age, birth weight, history of requiring intubation at birth, and history of intraventricular hemorrhage. At the time of 2-month immunizations, those infants with BPD were more likely to be older in chronological age but similar in cGA, receiving greater respiratory support, receiving caffeine, and receiving a greater amount of oxygen than those infants without BPD.

There was no statistically significant difference in the composite primary outcome of respiratory decompensation within 72 hours of immunization or its individual components (increase in effective FIO_2 ≥10% above the previous 24-hour mean or increase in level of respiratory support) between the 2 groups (*P* = .65) (Table 2). There was also no difference in the individual outcomes of increase in effective FIO_2 ≥10% above the previous 24-hour mean (*P* = .58), increased respiratory support after immunization (*P* = .65), or increased number of A/B/D events within 72 hours of immunization (*P* = .51). Due to the possibility of influencing A/B/D events, if those infants who underwent retinopathy of prematurity eye examinations within 72 hours before (*n* = 63) or 72 hours after (*n* = 42) immunization were excluded, no statistical difference was found in either the primary outcome (OR: 1.33; 95% CI: 0.43–4.08; *P* = .79) or the incidence of increased A/B/D events (OR: 1.04; 95% CI: 0.56–1.89; *P* = 1) within 72 hours of immunization. In subgroup analysis of infants who received 2-month immunizations, there was no significant difference in the primary outcome (*P* = .63) or its individual components between groups. Although both groups of infants were noted to have increased A/B/D events, there was no statistically significant difference between the 2 groups (*P* = .19).

In univariate modeling, factors found to be predictive of respiratory decompensation after immunization included grade III or IV IVH (*P* = .04) and having a positive blood culture within 72 hours of immunization (Table 3). Younger cGA at immunization, younger chronological age at immunization, lower weight at immunization, and currently receiving caffeine at the time of immunization were all found to be significantly associated with increased A/B/D events after immunization. Conversely, having the diagnosis of BPD was not predictive of either requiring increased respiratory support or having more A/B/D events after immunization. The level of respiratory support before immunization was not predictive of an increase in A/B/D events after immunizations and could

TABLE 1 Demographic Characteristics and Clinical Conditions of Study Population

	BPD	No BPD	*P*	OR (95% CI)
Neonatal baseline characteristics[a]				
Gestational age at birth, wk	25.94 ± 2.15	27.79 ± 1.95	<.001	—
Birth weight, g	816 ± 279	1125 ± 355	<.001	—
Race, *n* (%)				
White	54 (31)	15 (22)	.52	—
Black	98 (57)	41 (60)		
Other	20 (12)	12 (18)		
Maternal age, y	27.60 ± 6.92	27.41 ± 7.44	.854	—
Antenatal steroids (≥1 dose before delivery), *n* (%)	109 (63)	40 (59)	.8	—
Intubated at birth, *n* (%)	161 (94)	43 (63)	<.001	8.51 (3.88–18.66)
IVH (any grade), *n* (%)	87 (51)	18 (27)	.001	2.84 (1.54–5.27)
Grade III or IV	46 (27)	7 (10)	.005	3.18 (1.36–7.46)
PVL, *n* (%)	37 (22)	10 (15)	.28	1.59 (0.74–3.41)
Necrotizing enterocolitis or spontaneous intestinal perforation, *n* (%)	104 (61)	45 (66)	.46	0.78 (0.43–1.41)
Characteristics at time of 2-month immunizations[b]				
Chronological age at 2-month immunizations, d	86.72 ± 28.79	71.55 ± 11.18	<.001	—
cGA at 2-month immunizations, wk	38.31 ± 4.50	38.04 ± 2.23	.65	—
Weight at 2-month immunizations, g	2407 ± 893	2626 ± 622	.08	—
Respiratory support, *n* (%)				
No support	25 (17)	58 (89)	<.001	—
LFNC	21 (15)	5 (8)	—	—
HFNC	54 (37)	2 (3)	—	—
CPAP	21 (15)	0	—	—
Noninvasive positive-pressure ventilation	7 (5)	0	—	—
CMV	17 (8)	0	—	—
Mean effective FIO_2 24 hours before immunization,%	26 ± 6	21 ± 1	<.001	—
Receiving caffeine, *n* (%)	76 (52)	16 (25)	<.001	3.37 (1.76–6.47)
History of A/B/D events 72 hours before immunization, *n* (%)	67 (46)	26 (40)	.25	1.29 (0.71–2.33)
Number of vaccines given per day, *n* (%)				
1	26 (18)	10 (15)	.02	—
2	36 (25)	9 (14)	—	—
≥3	83 (57)	46 (71)	—	—

Data are presented as means ± SDs unless otherwise indicated. Subjects were identified from a population immunized between January 1, 2008, and August 1, 2014, who were <32 weeks' gestational age at birth. BPD is defined as oxygen requirement at 36 weeks' cGA. *P* values and odds ratios were calculated when possible. *P* value for respiratory support calculated by comparison of no support vs. all other levels of support. *P* value for number of vaccines given per day calulcated by comparison of 1 vaccine vs. multiple vaccines per day.

[a] $n = 172$ and $n = 68$ for BPD and No BPD groups, respectively.

[b] $n = 145$ and $n = 65$ for BPD and No BPD groups, respectively. In the BPD group there were 145 subjects with 179 immunization events; in the No BPD group there were 65 subjects with 75 immunization events.

not be assessed for the outcome of increased respiratory support after immunization. In multivariate models, HFNC ($P = .04$) or CMV ($P = .01$) at the time of immunization was found to be significantly associated with increased A/B/D episodes after immunization. The number of vaccines administered in a day was not associated with having increased A/B/D events after immunization. Multivariate models were unable to assess factors related to respiratory decompensation after immunization due to the infrequency of events.

DISCUSSION

We found no significant difference in the incidence of respiratory decompensation within 72 hours after immunization of infants with BPD compared with those who did not have BPD. Even if the definition of respiratory decompensation were expanded to include A/B/D events after immunization, a statistically significant difference between the 2 groups was not found (data not shown). A subgroup analysis of infants who received their 2-month immunizations revealed no difference in respiratory decompensation between the 2 groups.

Univariate analysis found that infants who were smaller, more immature, and receiving caffeine at the time of immunization were more likely to experience increased A/B/Ds after immunization. Caffeine is given to premature infants to prevent apnea of prematurity and is also known to decrease the incidence of BPD.[31] In our sample, those infants in the BPD group were twice as likely as those in the group without BPD to be receiving caffeine at the

time of 2-month immunizations. One may assume that caffeine use is serving as a surrogate for infants who are more immature at the time of immunization and/or have a history of A/B/D events and that caffeine use itself is not an underlying factor that leads to increased likelihood for respiratory decompensation after immunization. Conversely, younger age and lesser weight at the time of immunization were not predictive of requiring increased respiratory support after immunization. Severe IVH was found to be predictive of respiratory decompensation after immunization, perhaps indicating a more vulnerable patient population. A positive blood culture within 72 hours of immunization was also found to be highly predictive of experiencing respiratory decompensation. In these cases, decompensation is likely secondary to the underlying infection. Further studies are needed to elucidate why positive blood cultures were noted after immunization. Multivariate models, when accounting for a history of necrotizing enterocolitis or spontaneous intestinal perforation, positive blood culture, positive urine culture, weight at immunization, cGA, and caffeine use at the time of immunization, found that infants receiving HFNC versus no support or CMV versus no support at the time of immunization were much more likely to experience increased A/B/D episodes after immunization. A larger sample size is needed to elucidate multivariate predictors of respiratory decompensation after immunization.

A study by DeMeo et al[17] found a higher incidence of a need for increased respiratory support after immunization (defined as either going from no support to any noninvasive support or going from any level of support to mechanical ventilation) in extremely low birth weight infants. Clinically, there is a marked difference in an infant who requires restarting nasal cannula versus an infant who requires reintubation. It is often the prospect of requiring reintubation that is of greatest concern to the clinician. In our cohort, there were 5 infants (2% of all immunization events) who required intubation after immunization, all of whom had BPD and a birth weight of <650 g. One infant developed necrotizing enterocolitis and *Klebsiella pneumoniae* bacteremia requiring bowel resection. The remaining patients were receiving respiratory support of at least 3 L/minute of HFNC at the time of immunization and were all reintubated due to increasing severity of A/B/D events.

Previous studies that included infants with BPD within their cohorts have evaluated cardiorespiratory events around the time of immunization. In an observational study in 78 very low birth weight infants (including 21 with BPD), 4 of 21 (5%) required increased FIO_2, CPAP, or LFNC.[15] Another study described 26 infants in a cohort of 45 infants who had BPD: 5 of 26 (19%) with BPD had increased A/B/D episodes requiring respiratory support.[24] Last, in a prospective study in 80 infants (63 with BPD), 21 (33%) subjects developed worsening A/B/D events requiring some level of intervention.[13] In our cohort, we found that 97 of 172 (29%) of the BPD group and 23 of 68 (25%) of the group without BPD developed increased A/B/D events after immunization. However, the proportion of infants requiring clinical intervention via increased respiratory support was far fewer: 26 (8%) in the BPD group and 5 (5%) in the group without BPD. This finding should allay concern that immunizing infants with BPD will lead to an increase in A/B/D events

TABLE 2 Outcomes After Immunization

	BPD	No BPD	OR (95% CI)	*P*
All patients and all immunization events[a]				
Primary outcomes				
Respiratory decompensation within 72 hours of immunization[b]	26 (8)	5 (5)	1.47 (0.55–3.94)	.65
Increased effective FIO_2 ≥10% above previous 24-hour mean	4 (1)	0	—	.58
Increased respiratory support within 72 hours of immunization	24 (7)	5 (5)	1.35 (0.50–3.64)	.65
Secondary outcome				
Increased A/B/D events within 72 hours of immunization	97 (29)	23 (25)	1.23 (0.73–2.08)	.51
Two-month immunization patients and events[c]				
Primary outcomes				
Respiratory decompensation within 72 hours of immunization[b]	16 (9)	5 (7)	1.37 (0.49–3.90)	.63
Increased effective FIO_2 ≥10% above previous 24-hour mean	0	0	—	
Increased respiratory support within 72 hours of immunization	16 (9)	5 (7)	1.37 (0.49–3.90)	.63
Secondary outcome				
Increased A/B/D events within 72 hours of immunization	64 (36)	20 (27)	1.53 (0.84–2.78)	.19

Data are presented as *n* (%) unless otherwise indicated. Odds ratios calculated when possible.

[a] In the BPD group there were 172 subjects with 337 immunization events; in the No BPD group there were 68 subjects with 93 immunization events.

[b] Respiratory decompensation within 72 hours of immunization is a composite score of increased effective FIO_2 ≥10% above the previous 24-hour mean or increased respiratory support within 72 hours of immunization.

[c] In the BPD group there were 145 subjects with 179 immunization events; in the No BPD group there were 65 subjects with 75 immunization events.

TABLE 3 Predictors of Respiratory Decompensation After Immunization

	Increased Respiratory Support After Immunization		Increased A/B/D Events After Immunization	
Characteristic	OR (95% CI)	*P*	OR (95% CI)	*P*
Univariate predictors[a]				
cGA (per decreasing week)	1.09 (1.00–1.18)	.06	1.10 (1.06–1.15)	<.001*
Age at immunization (per decreasing week)	1.06 (0.91–1.14)	.14	1.07 (1.04–1.11)	<.001*
Weight at immunization (per decrease of 100 g)	1.06 (1.00–1.14)	.06	1.06 (1.04–1.08)	<.001*
BPD	1.05 (0.38–2.92)	.92	1.23 (0.73–2.07)	.44
Necrotizing enterocolitis or spontaneous intestinal perforation	1.37 (0.52–3.56)	.52	1.58 (0.96–2.62)	.07
Number of vaccines per day	0.92 (0.64–1.33)	.66	0.99 (0.83–1.18)	.9
Previous respiratory support				
LFNC versus no support	Not enough events to estimate risk at each level of this variable		1.29 (0.70–2.36)	.42
HFNC versus no support			1.03 (0.59–1.81)	.92
CPAP versus no support			1.90 (0.94–3.86)	.08
Noninvasive positive-pressure ventilation versus no support			0.77 (0.15–3.91)	.75
CMV versus no support			0.46 (0.17–1.27)	.13
Grade III/IV IVH	2.59 (1.04–6.43)	.04*	1.50 (0.92–2.46)	.1
Grade III/IV IVH and PVL	2.20 (0.90–5.39)	.09	1.38 (0.87–2.19)	.18
Receiving caffeine at time of immunization	2.19 (0.85–5.69)	.11	2.40 (1.52–3.79)	<.001*
Positive blood culture within 72 hours of immunization	14.36 (3.38–60.91)	<.001*	1.96 (0.42–9.10)	.39
Positive urine culture within 72 hours of immunization	5.84 (0.58–58.61)	.13	2.61 (0.36–19.14)	.35
Multivariate models[b]				
Number of vaccines per day			1.06 (0.87–1.30)	.55
Previous respiratory support				
LFNC versus no support			1.01 (0.51–2.03)	.97
HFNC versus no support			0.47 (0.23–0.97)	.04*
CPAP versus no support			0.55 (0.24–1.26)	.16
Noninvasive positive-pressure ventilation versus no support	Not enough events to model		0.23 (0.04–1.16)	.07
CMV versus no support			0.23 (0.07–0.72)	.01*
Grade III/IV IVH			1.26 (0.73–2.16)	.41
Grade III/IV IVH and PVL			1.19 (0.72–1.95)	.50

[a] Models contain 1 predictor and are controlled for multiple vaccine cycles per patient.
[b] Each of the above risk factors were modeled one at a time in a multivariate model containing necrotizing enterocolitis/spontaneous intestinal perforation, positive blood culture, positive urine culture, weight at immunization, cGA, and caffeine use at time of immunization. Models were adjusted for multiple vaccine cycles per patient.
* Significant, $P < .05$.

that require significant clinical intervention such as intubation.

The results of this study included infants immunized at <36 weeks' cGA, which would preclude them from being defined as having BPD. All of the infants with BPD who were immunized at <36 weeks' cGA ($n = 57$) were receiving respiratory support at the time of immunization. Of the 12 infants without BPD who were immunized at <36 weeks, 5 were receiving respiratory support at the time of immunization but had been weaned to room air by 36 weeks' cGA.

Although multivariate analysis revealed that infants requiring HFNC versus no support and infants receiving CMV versus no support had more A/B/D events after immunization, infants receiving CPAP versus no support showed no statistical difference. This finding may represent a type 2 error or be a consequence of inadequate power to detect a difference in the CPAP versus no-support group (29 infants in the CPAP group vs 95 infants in the HFNC group). The hierarchy of respiratory support could also influence these results. The choice to represent HFNC as of lesser support than CPAP was chosen to reflect the severity of respiratory illness; however, the amount of CPAP provided by HFNC was not measured or reported.

The results of multivariate analysis revealed that infants with IVH alone were statistically more likely to experience respiratory decompensation after immunization. However, infants with both IVH and PVL did not show a similar statistically significant difference. There is no physiologic reason for this difference. We suspect this may possibly be due to a lack of power to detect a difference in the IVH and PVL combined group.

Due to the retrospective nature of this study we cannot account for biases that may be present. Due to a clinician's perception of possible vaccine-related adverse events, the timing of immunization and the number of vaccines administered at one time may have selected

for a healthier preimmunization population when compared with a similar unvaccinated population. This potential for selection bias has been previously described in the literature.[17] The infants who are transferred to our level 4 NICU often represent the sickest and most fragile patients; although we propose that these infants are likely to be at least as ill as those found in other NICUs, it is not possible to assess this confounder. An additional limitation is the data abstraction from health care providers' documentation. Respiratory therapists document static F_{IO_2} measurements, which do not account for frequent F_{IO_2} fluctuations, and nurses vary in their threshold to record A/B/D events. However, physicians rely on these recorded data to make clinical decisions. Therefore, these data reflect real-world analysis of day-to-day care.

CONCLUSIONS

Respiratory decompensation after immunization of preterm infants with BPD requiring clinical intervention is uncommon and does not differ significantly from preterm infants without BPD. Although there is an increase in A/B/D events after immunization in preterm infants both with and without BPD, most of these events are benign and resolve without significant clinical intervention. On the basis of our results, consideration to immunize this high-risk group should not be delayed out of concern for clinical deterioration.

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ABBREVIATIONS

A/B/D: apnea, bradycardia, and desaturation
BPD: bronchopulmonary dysplasia
cGA: corrected gestational age
CI: confidence interval
CMV: conventional mechanical ventilation
CPAP: continuous positive airway pressure
DTaP: diphtheria-tetanus-acellular pertussis
F_{IO_2}: fraction of inspired oxygen
HBV: hepatitis B vaccine
HFNC: high-flow nasal cannula
Hib: *Haemophilus influenzae* type b
IPV: inactivated polio vaccine
IVH: intraventricular hemorrhage
LFNC: low-flow nasal cannula
OR: odds ratio
PVL: periventricular leukomalacia

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