

Early Childhood Vaccination Status of Preterm Infants

Annika M. Hofstetter, MD, PhD, MPH,^{a,b} Elizabeth N. Jacobson, MD,^a M. Patricia deHart, ScD,^c Janet A. Englund, MD^{a,b}

abstract

BACKGROUND: Preterm infants are at increased risk for vaccine-preventable infections and associated complications. Limited studies describe timely vaccination of these vulnerable infants.

METHODS: This retrospective cohort study included Washington State infants with birth hospitalizations at an urban academic medical center between 2008 and 2013. Demographic, clinical, and visit data from electronic health records were linked to vaccine data from the Washington State Immunization Information System. Completion of the recommended 7-vaccine series by 19 months of age was compared between preterm infants (born at <37 weeks' gestation) and term/postterm infants (born at 37–43 weeks' gestation) by using Pearson's χ^2 test and multivariable logistic regression. Secondary outcomes included 7-vaccine series completion by 36 months of age and receipt of individual vaccines in the series. Rotavirus, hepatitis A, and influenza vaccination was also assessed.

RESULTS: Of study infants ($n = 10\,367$), 19.3% were born prematurely. Preterm infants had lower 7-vaccine series completion compared with term/postterm infants by 19 months (47.5% vs 54.0%; adjusted odds ratio 0.77 [95% confidence interval 0.65–0.90]) and 36 months (63.6% vs 71.3%; adjusted odds ratio 0.73 [95% confidence interval 0.61–0.87]). Early preterm (23–33 weeks' gestation) and late preterm (34–36 weeks' gestation) infants had a lower rate of 7-vaccine series completion compared with term/postterm infants. Full influenza vaccination coverage by 19 months also differed between groups (early preterm: 47.7%; late preterm: 41.5%; term/postterm: 44.7%; $P = .02$).

CONCLUSIONS: Over half of preterm infants were undervaccinated at 19 months; one-third failed to catch up by 36 months. Strategies to improve vaccination of these high-risk infants are needed.



^aDepartment of Pediatrics, University of Washington, Seattle, Washington; ^bSeattle Children's Research Institute, Seattle Children's Hospital, Seattle, Washington; and ^cOffice of Immunization and Child Profile, Washington State Department of Health, Olympia, Washington

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Address correspondence to Annika M. Hofstetter, MD, PhD, MPH, Department of Pediatrics, University of Washington, 1900 Ninth Ave, Mail Stop JMB-9, Seattle, WA 98101. E-mail: annika.hofstetter@seattlechildrens.org

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WHAT'S KNOWN ON THIS SUBJECT: Preterm infants are at an increased risk for vaccine-preventable infections and associated complications. Earlier work reveals that they may also be at risk for undervaccination, yet studies in which timely receipt of all currently recommended vaccines is examined in this population are lacking.

WHAT THIS STUDY ADDS: This study revealed that fewer preterm infants completed the recommended 7-vaccine series by 19 months of age compared with term/postterm infants. These high-risk infants continued to lag behind in vaccination coverage at 36 months of age.

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Approximately 1 in every 10 United States infants is born prematurely.¹ Preterm infants and infants with low birth weight are at an increased risk for vaccine-preventable infections and associated complications.²⁻⁵ The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of these high-risk infants on the basis of evidence that vaccines induce protective immunity and are safe and well tolerated in this population.⁶⁻⁸ Preterm infants who are medically stable should be vaccinated at the same chronological age and according to the same schedule as term infants. Exceptions include the hepatitis B birth dose, which should be deferred until hospital discharge or 1 month of age for infants born at <2000 g to mothers who are hepatitis B surface antigen-negative,⁹ and rotavirus vaccine, which should be deferred until or after hospital discharge for preterm infants.¹⁰ Despite these recommendations, earlier studies have revealed that preterm infants and infants with low birth weight are at an increased risk for delayed vaccination and undervaccination.¹¹⁻¹⁶ There are limited studies in which timely receipt of all recommended vaccines has been assessed in this high-risk population.

In this study, we compared early childhood vaccination among preterm and term/postterm infants born between 2008 and 2013. We hypothesized that preterm infants would have lower completion of the recommended 7-vaccine series compared with term/postterm infants by 19 months of age, and we hypothesized that this difference would remain at 36 months of age.

METHODS

Study Design, Population, and Setting

This retrospective cohort study included Washington State infants

with birth hospitalizations at an urban academic medical center between January 2008 and December 2013. Infants were excluded if they were admitted after the day of birth or if they died before 19 months of age. During the study period, the hospital policy was to administer vaccines to all patients according to ACIP recommendations. The hepatitis B vaccine was included in the routine newborn order set; no other vaccine-promoting strategies (eg, standing orders or electronic health record [EHR] prompts) were used. The study was approved by the Seattle Children's Hospital and Washington State Institutional Review Boards.

Data Sources

Demographic (sex, race and/or ethnicity, maternal language, and insurance type), clinical (gestational age and birth weight), and birth hospitalization (service and duration) data were abstracted from the EHR. Vaccine data (type and date), including doses administered during or after the birth hospitalization at the medical center or affiliated practices, were also obtained from the EHR. To capture doses administered at other health care facilities (ie, primary care practices) in Washington State, these data were linked to vaccine data (type and date) from the Washington State Immunization Information System (WAIS) by using select identifiers and an existing verification algorithm. During the study period, an estimated >95% of Washington State children <6 years old had ≥ 2 doses documented in WAIS.¹⁷ For this study, infants with no matching WAIS record, an inactive status in WAIS (ie, moved out of state), or <2 doses recorded in WAIS were excluded.

Measures

The primary outcome was completion of the 7-vaccine series, including 4 doses of the diphtheria-tetanus-pertussis (DTP)/diphtheria-tetanus-

acellular pertussis (DTaP) vaccine, 3 doses of the poliovirus vaccine, 1 dose of the measles-mumps-rubella (MMR) vaccine, 3 doses of the *Haemophilus influenzae* type b (Hib) vaccine, 3 doses of the hepatitis B vaccine, 1 dose of the varicella vaccine, and 4 doses of the pneumococcal conjugate vaccine (PCV), by 19 months of age (580 days). This age cutoff was selected a priori to reflect timely series completion, beyond which infants are considered delayed.¹⁸ Secondary outcomes included receipt of individual vaccines in the series by 19 months of age and 7-vaccine series completion as well as receipt of individual vaccines in the series by 36 months of age (1095 days). We also assessed recommended vaccines not included in the 7-vaccine series: (1) the rotavirus vaccine (2 doses by 19 months), (2) the hepatitis A vaccine (2 doses by 36 months), and the influenza vaccine (2-3 doses [depending on birth month] by 19 months and 4 doses by 36 months).

The main independent variable was preterm status, defined as birth at <37 weeks' gestation (versus 37-43 weeks' gestation). In a subgroup analysis, preterm infants were stratified into early preterm (23-33 weeks' gestation; ie, extremely, very, or moderately preterm) and late preterm (34-36 weeks' gestation) categories. Demographic variables included infant sex, infant race and/or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, and multiracial or other), maternal language (English, Spanish, and other), and insurance type (private, public, and uninsured). Only 1 subject was uninsured, so insurance was dichotomized into private and public or uninsured categories. Additional variables included birth weight (<1500, 1500-2499, and ≥ 2500 g), birth hospitalization service (newborn nursery, intermediate care nursery, and NICU), and birth

hospitalization duration (<24, 24–47, 48–95, and ≥96 hours).

Analyses

Completion of the 7-vaccine series by 19 and 36 months of age was compared by preterm status by using Pearson's χ^2 test and multivariable analysis, with adjustment for factors associated with the vaccine outcome at $P < .10$. Individual vaccine receipt and missing vaccine doses were examined among preterm and term/postterm infants by using Pearson's χ^2 test. Subgroup analyses were used to compare vaccine outcomes between early preterm, late preterm, and term/postterm infants. All 36-month outcomes were assessed among infants who were ≥36 months of age as of April 22, 2016 (data abstraction date). No known deaths occurred among infants between 19 and 36 months of age. Analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC). P values were based on 2-tailed tests and were considered significant at $P < .05$.

RESULTS

Of the 11 833 infants who fulfilled eligibility criteria, 10 367 (87.6%) had an active WAIS record and were included in the primary analytic sample. Infants were predominantly non-Hispanic white, publicly insured, and had English-speaking mothers (Table 1). Approximately 1 in 5 were born prematurely, 1 in 6 had a low birth weight (<2500 g), and 1 in 4 were cared for in the intermediate care nursery or NICU.

Overall, 52.7% of infants completed the 7-vaccine series by 19 months (range: 50.3% in 2008 to 55.5% in 2012). Fewer preterm infants completed the series by 19 months compared with term/postterm infants (47.5% vs 54.0%; $P < .001$). Both early and late preterm infants had lower series completion by 19 months compared with term/postterm infants (Fig 1).

Timely series completion differed by race and/or ethnicity (black: 50.0%; white: 51.4%; Hispanic: 57.6%; Asian: 66.1%; other or multiracial: 46.7%; $P < .001$), maternal language (English: 52.6%; Spanish: 61.7%; other: 53.2%; $P < .001$), insurance type (private: 57.2%; public or uninsured: 49.7%; $P < .001$), birth weight (<1500 g: 47.0%; 1500–2499 g: 49.0%; ≥2500 g: 53.6%; $P < .001$), birth hospitalization duration (<24 hours: 37.8%; 24–47 hours: 56.4%; 48–95 hours: 54.4%; ≥96 hours: 50.0%; $P < .001$), and birth hospitalization service (newborn nursery: 55.6%; intermediate care nursery: 52.6%; NICU: 37.2%; $P < .001$). In a multivariable model that included preterm status as the main independent variable, and with adjustment for race and/or ethnicity, maternal language, insurance type, and birth hospitalization duration, preterm infants had lower odds of completing the 7-vaccine series compared with term/postterm infants (Table 2). Birth weight and birth hospitalization service were not retained in this final multivariable model because of their strong correlation with preterm status (Spearman's $\rho = 0.6$ – 0.7). In an exploratory analysis, preterm status remained associated with series completion when birth weight, but not birth hospitalization service, was added to the multivariable model (Supplemental Table 4).

Compared with term/postterm infants, fewer preterm infants received each vaccine in the 7-vaccine series by 19 months, with the exception of the MMR and varicella vaccines for which no difference was appreciated (Table 3). A higher proportion of preterm infants were missing doses in the 7-vaccine series compared with term/postterm infants (1 dose: 16.5% vs 13.8% [$P = .002$]; 2 doses: 10.0% vs 9.6% [$P = .62$]; 3 doses: 4.9% vs 3.8% [$P = .03$]; ≥4 doses: 21.2% vs 18.8% [$P = .02$]). With respect to

recommended vaccines not included in the 7-vaccine series, rotavirus vaccination coverage was lower among preterm versus term/postterm infants, whereas influenza vaccination coverage was similar between groups. Among all vaccines recommended by 19 months, infants most commonly were missing a dose or doses of the DTP/DTaP vaccine (Supplemental Table 5).

In a subgroup analysis, early and late preterm infants had similar patterns of undervaccination for most vaccines by 19 months, although early preterm infants had particularly low hepatitis B and rotavirus vaccination coverage (Supplemental Table 6). For influenza, early preterm infants had higher vaccination coverage, whereas late preterm infants had lower coverage compared with term/postterm infants.

Among infants hospitalized ≥60 days ($n = 286$), most received ≥1 dose of the DTP/DTaP vaccine (84.6%), the PCV (84.6%), the Hib vaccine (84.3%), the poliovirus vaccine (84.3%), and the hepatitis B vaccine (84.3%) before discharge. Conversely, only 5 of 200 infants (2.5%) hospitalized between 60 and 104 days (ie, maximum age for rotavirus vaccine series initiation) and 3 of 86 infants (3.5%) hospitalized >104 days received the rotavirus vaccine before discharge. Infants hospitalized ≥60 days who received ≥1 (versus no) dose of a recommended vaccine before discharge had higher 7-vaccine series completion by 19 months (58.1% vs 21.1%; $P < .001$).

In a subset of children aged ≥36 months as of the data abstraction date ($n = 9211$), fewer preterm versus term/postterm infants completed the 7-vaccine series by 36 months (63.6% vs 71.3%; $P < .001$). Lower coverage was noted among early and late preterm infants compared with term/postterm infants (Fig 1). In a multivariable analysis that included

TABLE 1 Characteristics of Study Population

Characteristic	Total
Study population, <i>n</i> (%)	10 367 (100)
Sex, <i>n</i> (%)	
Male	5319 (51.3)
Female	5048 (48.7)
Race and/or ethnicity, <i>n</i> (%) ^a	
White, non-Hispanic	4414 (48.9)
Black, non-Hispanic	1914 (21.2)
Hispanic	1314 (14.6)
Asian	1183 (13.1)
Multiracial or other	197 (2.2)
Insurance, <i>n</i> (%) ^a	
Public	5467 (56.4)
Private	4229 (43.6)
Uninsured	1 (0.0)
Maternal language, <i>n</i> (%) ^a	
English	7412 (77.2)
Spanish	934 (9.7)
Other	1255 (13.1)
Gestational age, <i>n</i> (%) ^a	
37–43 wk	8302 (80.7)
<37 wk	1991 (19.3)
34–36 wk	1053 (10.2)
23–33 wk	938 (9.1)
Birth wt, <i>n</i> (%) ^a	
≥2500 g	8557 (83.3)
1500–2499 g	1146 (11.2)
<1500 g	568 (5.5)
Birth year, <i>n</i> (%)	
2008	1829 (17.6)
2009	1820 (17.6)
2010	1791 (17.3)
2011	1669 (16.1)
2012	1621 (15.6)
2013	1637 (15.8)
Birth hospitalization duration, median (interquartile range), h ^a	49.5 (33.0–78.4)
Birth hospitalization service, <i>n</i> (%)	
Newborn nursery	7458 (71.9)
Intermediate care nursery	1522 (14.7)
NICU	1387 (13.4)

^a Missing some data.

preterm status as the main independent variable, with adjustment for race and/or ethnicity, maternal language, and birth hospitalization duration, preterm infants had lower odds of series completion by 36 months (Table 2). This remained significant when we also adjusted for birth weight but not for birth hospitalization service (Supplemental Table 4). Compared with term/postterm infants, preterm infants had lower coverage for all individual vaccines except the MMR, varicella, and hepatitis A vaccines by 36 months (Table 3). Early and late preterm infants had similarly low coverage for most vaccines by 36

months, although hepatitis B vaccination coverage was especially low among early preterm infants (Supplemental Table 6).

DISCUSSION

In this large retrospective study that linked EHR and state immunization registry data from an 8-year period (2008–2016), fewer preterm infants were up-to-date with recommended vaccines by 19 months of age compared with term/postterm infants. Preterm infants continued to lag behind their term/postterm counterparts in vaccination coverage at 36 months of age, suggesting that

differential catch-up vaccination does not occur. All preterm infants, regardless of their degree of prematurity, were vulnerable to undervaccination. Indeed, late preterm infants had the lowest influenza vaccination coverage of all groups. These findings are worrisome given the increasing prevalence of preterm births¹ and the fact that preterm infants are particularly susceptible to vaccine-preventable diseases such as *Streptococcus pneumoniae*, pertussis, rotavirus, and influenza.^{2–5}

Approximately half of all study infants completed the recommended 7-vaccine series by 19 months, consistent with data indicating poor timely coverage in pediatric populations.^{19–21} Preterm infants were missing more doses and had lower odds of series completion by 19 months compared with term/postterm infants, which is concerning because timely vaccination is crucial for ensuring optimal protection of this vulnerable population. Rotavirus vaccination coverage, a separate outcome measure, was also markedly lower among preterm compared with term/postterm infants. Studies published in the 1990s and 2000s revealed that infants with low birth weight and other high-risk infants had a lower rate of receipt of select vaccines during early childhood.^{12–16} One study revealed that a lower proportion of infants born at <1500 g were up-to-date with DTP/DTPaP, poliovirus, Hib, and MMR vaccination at 18 months of age compared with term infants born at >2500 g (61%–68% vs 67%–75%, respectively).¹³ Authors of a more recent study conducted in the military health care system demonstrated that infants with low birth weight and preterm infants, identified by using *International Classification of Diseases, Ninth Revision* codes, had lower odds of vaccine receipt by 24 months of age.¹¹ In the current study, preterm

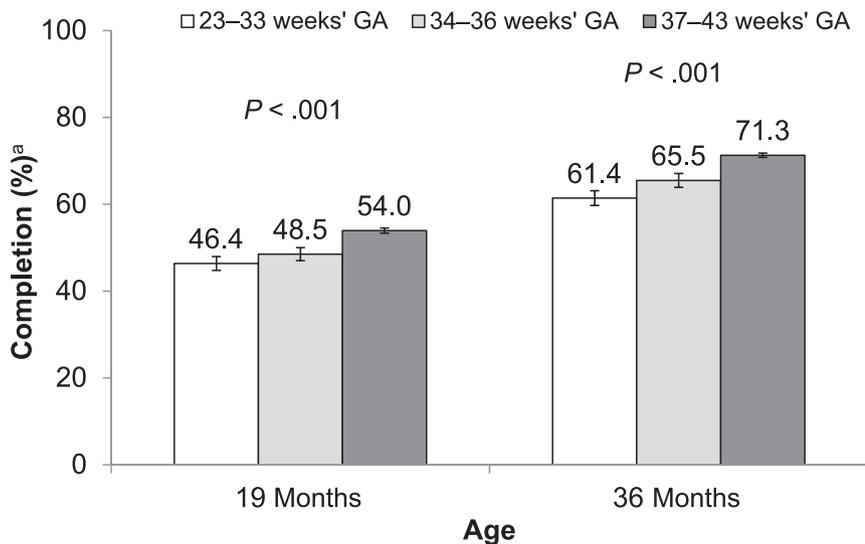


FIGURE 1 Seven-vaccine series completion by 19 and 36 months of age, by gestational age (GA). ^a Data are presented as percentage \pm SE.

infants did not catch up to term/postterm infants by 36 months of age. Authors of an earlier study reported that differences in up-to-date vaccination status by birth weight remained over time,¹⁴ whereas authors of other studies observed a persistent discrepancy only among infants with extremely low birth weight.^{12,13}

In an exploratory analysis, fewer early preterm and late preterm

infants completed the recommended 7-vaccine series by 19 and 36 months compared with term/postterm infants. These findings extend previous work indicating undervaccination among not only the highest-risk infants but also infants born with a low birth weight or infants born moderately to late preterm.^{11,14} In our study, these preterm groups had comparably low coverage levels for most individual vaccines, except rotavirus, hepatitis B,

and influenza vaccines. Lower rotavirus vaccination coverage among early preterm infants likely reflects the ACIP recommendation to delay receipt of the first dose until hospital discharge. Among infants hospitalized >104 days, only 3% received the rotavirus vaccine before discharge; the remaining infants were no longer age eligible for vaccination. We recently showed a lack of nosocomial transmission of rotavirus vaccine-type virus in the hospital setting.²² This study, along with work corroborating our finding²³ and previous studies indicating rotavirus vaccine safety among high-risk infants,^{24–28} suggests that rotavirus vaccination could be considered during hospitalization to avoid missed opportunities.^{22,29} Although infants ineligible for hepatitis B vaccination at birth (ie, because of birth weight <2000 g) can be vaccinated later in the hospitalization or after discharge, it is possible that being “off schedule” contributed to persistent delays. Supporting this, an earlier study found that hepatitis B vaccination in the first 7 days of postnatal life was associated with completion of the 3-dose series.³⁰

Interestingly, late preterm infants were noted to have the lowest

TABLE 2 Association Between Preterm Status and 7-Vaccine Series Completion by 19 and 36 Months of Age

Characteristic	19 Months		36 Months	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Preterm status (reference: term/postterm)	0.77 (0.70–0.85)*	0.77 (0.65–0.90)*	0.70 (0.63–0.78)*	0.73 (0.61–0.87)*
Race and/or ethnicity (reference: white, non-Hispanic)				
Black, non-Hispanic		1.09 (0.94–1.26)		1.41 (1.21–1.65)*
Hispanic		1.11 (0.92–1.35)		1.34 (1.07–1.67)*
Asian		1.90 (1.63–2.20)*		1.84 (1.54–2.20)*
Multiracial or other		0.93 (0.68–1.26)		0.97 (0.69–1.38)
Insurance (reference: private)				
Public or uninsured		0.63 (0.56–0.70)*		
Maternal language (reference: English)				
Spanish		1.92 (1.52–2.43)*		1.94 (1.45–2.60)*
Other		1.08 (0.93–1.26)		1.06 (0.88–1.27)
Birth hospitalization duration, h (reference: 24–47 h)				
<24		0.53 (0.44–0.63)*		0.41 (0.34–0.50)*
48–95		0.94 (0.85–1.05)		0.90 (0.80–1.02)
\geq 96		0.96 (0.81–1.14)		0.85 (0.70–1.03)

CI, confidence interval; OR, odds ratio.

* $P < .05$.

^a All variables included in multivariable logistic regression models were associated with 7-vaccine series completion in the bivariate analysis.

TABLE 3 Vaccination Coverage by 19 and 36 Months of Age Among Preterm and Term/Postterm Infants

Vaccine ^a	19 Months			36 Months		
	Preterm, <i>n</i> = 1991	Term/Postterm, <i>n</i> = 8302	<i>P</i> ^b	Preterm, <i>n</i> = 1727	Term/Postterm, <i>n</i> = 7426	<i>P</i> ^b
	No. (%)	No. (%)		No. (%)	No. (%)	
DTP/DTaP (4)	1159 (58.2)	5399 (65.0)	<.001	1313 (76.0)	6201 (83.5)	<.001
Poliovirus (3)	1600 (80.4)	7156 (86.2)	<.001	1437 (83.2)	6625 (89.2)	<.001
MMR (1)	1669 (83.8)	6809 (82.0)	.06	1540 (89.2)	6598 (88.9)	.70
Hib (3)	1737 (87.2)	7424 (89.4)	.005	1546 (89.5)	6815 (91.8)	.003
Hepatitis B (3)	1524 (76.5)	7005 (84.4)	<.001	1368 (79.2)	6457 (87.0)	<.001
Varicella (1)	1624 (81.6)	6617 (79.7)	.06	1521 (88.1)	6481 (87.3)	.37
PCV (4)	1407 (70.7)	6129 (73.8)	.004	1380 (79.9)	6126 (82.5)	.01
Rotavirus (2)	1387 (69.7)	6799 (81.9)	<.001	—	—	—
Hepatitis A (2)	—	—	—	1173 (67.9)	5112 (68.8)	.46
Influenza ^c	884 (44.4)	3708 (44.7)	.83	430 (24.9)	1916 (25.8)	.44

—, not applicable.

^a No. doses needed for each vaccine is listed in parentheses.

^b Coverage between preterm versus term/postterm infants was compared by using Pearson's χ^2 test.

^c Influenza: 2–3 doses (depending on birth month) by 19 mo and 4 doses by 36 mo.

influenza vaccination coverage, whereas early preterm infants had the highest coverage. The latter finding could reflect perceptions of risk for acute respiratory infections such as influenza. Reasons for lower coverage among late preterm infants are unclear and require further exploration.

Multiple factors could contribute to the persistent undervaccination of preterm infants. Parental decision-making that is based on beliefs and experiences could play a role. An earlier study revealed that parents of infants born before the due date were more likely to refuse or delay vaccines than parents of infants born on or after the due date.³¹ Parents commonly perceive their preterm infants as medically vulnerable even after their health has improved.^{32,33} Consistent with that, we found that vaccine outcomes differed by preterm status even among those hospitalized for only a few days (data not shown). One study revealed that some parents felt that their preterm infant was not developed enough to be vaccinated.³⁴ This could lead to heightened vaccine safety concerns. Although a recent study found that vaccine hesitancy did not differ between expectant mothers with high- versus low-risk pregnancies,³⁵ examination of vaccine

hesitancy among mothers of high-versus low-risk infants may be valuable. Additionally, providers caring for preterm infants may worry about vaccine adverse events. Studies have revealed an increased incidence of fever and cardiorespiratory events among high-risk infants in the immediate postvaccination period, leading to increased sepsis evaluations and increased need for cardiorespiratory monitoring or support.^{36,37} A previous study revealed that some providers deferred vaccination of high-risk infants because of concerns about neurologic injury and potential liability.¹⁶ Another study suggests, as we did, that initiating vaccination in the hospital setting was associated with future vaccination,³⁸ leading some to speculate that this helped to alleviate parent and provider vaccine safety concerns and helped to instill confidence in vaccinating high-risk infants after hospital discharge.³⁹

Earlier work has also indicated that parents and providers may have limited knowledge of and adherence to vaccine recommendations for preterm infants.^{15,34,40–43} One study revealed that less than half of parents knew that preterm infants should be vaccinated at the same age as term infants, 40% thought the extent of

prematurity influenced timing of vaccination, and 25% believed a minimum weight needed to be reached before vaccination.⁴⁰ Another study revealed that 16% of pediatricians and 40% of family physicians did not know the recommended timing of vaccination for preterm infants and that many reported using additional requirements for vaccination such as minimum weight limits.⁴¹ More recent data revealing recommendation knowledge and adherence among parents and providers are needed. Additionally, there have been few, if any, studies in which vaccine communication between providers and these high-risk families is examined. Further exploration is warranted given data demonstrating the critical importance of provider vaccine communication in pediatric populations.^{44–46}

Varied health care use patterns also could contribute to undervaccination of preterm infants. Authors of a small study from Switzerland reported that some parents of preterm infants desired a “rest” after hospital discharge.³⁴ Consistent with this, a US study revealed that only 43% of infants born at ≤ 35 weeks' gestation received all expected health supervision visits in the first

18 months and that lack of adherence was associated with undervaccination.⁴⁷ Conversely, high-risk infants have many non-well visits,⁴⁸ during which parents and providers may defer vaccination if the child is acutely ill.^{15,31} Additionally, preterm infants may have competing priorities during the visits because of their complex health care needs, leading to missed vaccination opportunities. They also may see multiple subspecialists. Evidence suggests that pediatric subspecialists often do not discuss or offer preventive health services,^{49,50} including needed vaccines.⁵¹

This study has several limitations. First, there may have been underreporting of vaccine administrations to WAIS. However, previous studies revealed that WAIS is highly accurate and complete.^{17,52,53} Moreover, we included only infants with active WAIS records and ≥ 2 doses documented, as is done routinely for immunization information system reports.¹⁷ Although some infants of parents who are vaccine hesitant may have been excluded as a result, this is likely a small number because $< 1\%$ of children nationally receive no vaccines.⁵² Individual vaccine receipt in this study resembled data from a nationally representative sample of children.²¹ Additionally, 67% of 19- to 35-month-old children in our study completed the 7-vaccine series in

2014 (data not shown), identical to Washington State estimates for 19- to 35-month-old children in 2014.⁵⁴ Second, misclassification of preterm status may have occurred (ie, because of inaccurate dating or because of data entry error). However, any misclassification likely would have been nondifferential and biased findings toward the null. Third, this study included infants from a regional tertiary care medical center that provides high-risk obstetric care. Thus, the proportion of preterm infants in this study was higher than that observed nationally (19% vs 10%).¹ Furthermore, the study was conducted in Washington State, which has a high vaccine exemption rate.⁵⁵ Therefore, the findings may be less generalizable to low-risk populations and to settings with lower vaccine hesitancy. Finally, as noted previously, we did not examine parental, provider, or systems-based factors that may have contributed to undervaccination in this study.

CONCLUSIONS

This large retrospective cohort study indicated that preterm infants, including those born between 34 and 36 weeks' gestation, had a lower rate of receipt of recommended vaccines by 19 months of age and failed to catch up on recommended vaccines by 36 months of age. The reasons for

this are unclear but could reflect parental and provider factors, such as perceptions of medical vulnerability, vaccine safety beliefs, understanding of current vaccine recommendations, and provider-family vaccine communication, as well as health care use patterns in these high-risk infants. Future work is needed to inform the design and implementation of interventions aimed at improving timely vaccination coverage of these high-risk infants.

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
DTaP: diphtheria-tetanus-acellular pertussis
DTP: diphtheria-tetanus-pertussis
EHR: electronic health record
Hib: *Haemophilus influenzae* type b
MMR: measles-mumps-rubella
PCV: pneumococcal conjugate vaccine
WAIS: Washington State Immunization Information System

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REFERENCES

- Centers for Disease Control and Prevention. Preterm birth. Available at: www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm. Accessed February 6, 2018
- Dennehy PH, Cortese MM, Bégué RE, et al. A case-control study to determine risk factors for hospitalization for

- rotavirus gastroenteritis in U.S. children. *Pediatr Infect Dis J*. 2006; 25(12):1123–1131
3. Hjuler T, Wohlfahrt J, Simonsen J, et al. Perinatal and crowding-related risk factors for invasive pneumococcal disease in infants and young children: a population-based case-control study. *Clin Infect Dis*. 2007;44(8):1051–1056
 4. Langkamp DL, Davis JP. Increased risk of reported pertussis and hospitalization associated with pertussis in low birth weight children. *J Pediatr*. 1996;128(5, pt 1):654–659
 5. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol*. 2012; 207(suppl 3):S3–S8
 6. Kroger AT, Duchin J, Vázquez M. Special Situations. General best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html. Accessed January 10, 2019
 7. Esposito S, Fumagalli M, Principi N. Immunogenicity, safety and tolerability of vaccinations in premature infants. *Expert Rev Vaccines*. 2012;11(10): 1199–1209
 8. Carbone T, McEntire B, Kissin D, et al. Absence of an increase in cardiorespiratory events after diphtheria-tetanus-acellular pertussis immunization in preterm infants: a randomized, multicenter study. *Pediatrics*. 2008;121(5). Available at: www.pediatrics.org/cgi/content/full/121/5/e1085
 9. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67(1):1–31
 10. Cortese MM, Parashar UD; Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Recomm Rep*. 2010;59(33):1074]. *MMWR Recomm Rep*. 2009;58(RR):1–25
 11. Nestander M, Dintaman J, Susi A, Gorman G, Hisle-Gorman E. Immunization completion in infants born at low birth weight. *J Pediatric Infect Dis Soc*. 2018;7(3):e58–e64
 12. Batra JS, Eriksen EM, Zangwill KM, et al; Vaccine Safety Datalink. Evaluation of vaccine coverage for low birth weight infants during the first year of life in a large managed care population. *Pediatrics*. 2009;123(3):951–958
 13. Davis RL, Rubanowice D, Shinefield HR, et al. Immunization levels among premature and low-birth-weight infants and risk factors for delayed up-to-date immunization status. Centers for Disease Control and Prevention Vaccine Safety Datalink Group. *JAMA*. 1999; 282(6):547–553
 14. Langkamp DL, Hoshaw-Woodard S, Boye ME, Lemeshow S. Delays in receipt of immunizations in low-birth-weight children: a nationally representative sample. *Arch Pediatr Adolesc Med*. 2001;155(2):167–172
 15. Magoon MW, Belardo LJ, Caldito G. Delays in immunizations of high-risk infants during the first two years of life: special care for the high-risk infant should not mean special immunization schedules. *J Perinatol*. 1995;15(3): 222–228
 16. Ruiz P, Nathanson R, Kastner T. Pertussis immunization patterns in special care nursery graduates. *J Dev Behav Pediatr*. 1991;12(1):38–41
 17. Centers for Disease Control and Prevention. Immunization Information Systems Annual Report (IISAR). Available at: www.cdc.gov/vaccines/programs/iis/annual-report-iisar/index.html. Accessed June 6, 2018
 18. Luman ET, Barker LE, Shaw KM, et al. Timeliness of childhood vaccinations in the United States: days undervaccinated and number of vaccines delayed. *JAMA*. 2005;293(10): 1204–1211
 19. Leeds M, Muscoplat MH. Timeliness of receipt of early childhood vaccinations among children of immigrants - Minnesota, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(42):1125–1129
 20. Smith PJ, Humiston SG, Parnell T, Vannice KS, Salmon DA. The association between intentional delay of vaccine administration and timely childhood vaccination coverage. *Public Health Rep*. 2010;125(4):534–541
 21. Kurosky SK, Davis KL, Krishnarajah G. Completion and compliance of childhood vaccinations in the United States. *Vaccine*. 2016;34(3):387–394
 22. Hofstetter AM, Lacombe K, Klein EJ, et al. Risk of rotavirus nosocomial spread after inpatient pentavalent rotavirus vaccination. *Pediatrics*. 2018; 141(1):e20171110
 23. Hiramatsu H, Suzuki R, Nagatani A, et al. Rotavirus vaccination can be performed without viral dissemination in the neonatal intensive care unit. *J Infect Dis*. 2018;217(4):589–596
 24. Goveia MG, Rodriguez ZM, Dallas MJ, et al; REST Study Team. Safety and efficacy of the pentavalent human-bovine (WC3) reassortant rotavirus vaccine in healthy premature infants. *Pediatr Infect Dis J*. 2007;26(12): 1099–1104
 25. Monk HM, Mottsney AJ, Wade KC. Safety of rotavirus vaccine in the NICU. *Pediatrics*. 2014;133(6). Available at: www.pediatrics.org/cgi/content/full/133/6/e1555
 26. Smith CK, McNeal MM, Meyer NR, Haase S, Dekker CL. Rotavirus shedding in premature infants following first immunization. *Vaccine*. 2011;29(45): 8141–8146
 27. Thrall S, Doll MK, Nhan C, et al. Evaluation of pentavalent rotavirus vaccination in neonatal intensive care units. *Vaccine*. 2015;33(39):5095–5102
 28. Javid PJ, Sanchez SE, Jacob S, et al. The safety and immunogenicity of rotavirus vaccination in infants with intestinal failure. *J Pediatric Infect Dis Soc*. 2014; 3(1):57–65
 29. Pahud B, Pallotto EK. Rotavirus immunization for hospitalized infants: are we there yet? *Pediatrics*. 2018; 141(1):e20173499
 30. Yusuf HR, Daniels D, Smith P, Coronado V, Rodewald L. Association between administration of hepatitis B vaccine at birth and completion of the hepatitis B and 4:3:1:3 vaccine series. *JAMA*. 2000; 284(8):978–983
 31. Gilkey MB, McRee AL, Brewer NT. Forgone vaccination during childhood

- and adolescence: findings of a statewide survey of parents. *Prev Med*. 2013;56(3-4):202-206
32. Perrin EC, West PD, Culley BS. Is my child normal yet? Correlates of vulnerability [published correction appears in *Pediatrics*. 1989;83(5):678]. *Pediatrics*. 1989;83(3):355-363
 33. Horwitz SM, Storfer-Isser A, Kerker BD, et al. A model for the development of mothers' perceived vulnerability of preterm infants. *J Dev Behav Pediatr*. 2015;36(5):371-380
 34. Tillmann BU, Tillmann HC, Nars PW, Weber P. Vaccination rate and age of premature infants weighing <1500 g: a pilot study in north-western Switzerland. *Acta Paediatr*. 2001;90(12):1421-1426
 35. Cunningham RM, Minard CG, Guffey D, et al. Prevalence of vaccine hesitancy among expectant mothers in Houston, Texas. *Acad Pediatr*. 2018;18(2):154-160
 36. DeMeo SD, Raman SR, Hornik CP, et al. Adverse events after routine immunization of extremely low-birth-weight infants. *JAMA Pediatr*. 2015;169(8):740-745
 37. Klein NP, Massolo ML, Greene J, et al. Vaccine Safety Datalink. Risk factors for developing apnea after immunization in the neonatal intensive care unit. *Pediatrics*. 2008;121(3):463-469
 38. Denizot S, Fleury J, Caillaux G, et al. Hospital initiation of a vaccinal schedule improves the long-term vaccinal coverage of ex-preterm children. *Vaccine*. 2011;29(3):382-386
 39. Sisson H, Gardiner E, Watson R. Vaccination timeliness in preterm infants: an integrative review of the literature. *J Clin Nurs*. 2017;26(23-24):4094-4104
 40. Langkamp DL, Langhough R. What do parents of preterm infants know about diphtheria, tetanus, and pertussis immunizations? *Am J Perinatol*. 1993;10(3):187-189
 41. Langkamp DL, Langhough R. Primary care physicians' knowledge about diphtheria-tetanus-pertussis immunizations in preterm infants. *Pediatrics*. 1992;89(1):52-55
 42. Crawford NW, Yeo V, Hunt RW, et al. Immunisation practices in infants born prematurely: neonatologists' survey and clinical audit. *J Paediatr Child Health*. 2009;45(10):602-609
 43. Gopal SH, Edwards KM, Creech B, Weitkamp JH. Variability in immunization practices for preterm infants. *Am J Perinatol*. 2018;35(14):1394-1398
 44. Gust DA, Darling N, Kennedy A, Schwartz B. Parents with doubts about vaccines: which vaccines and reasons why. *Pediatrics*. 2008;122(4):718-725
 45. Opel DJ, Heritage J, Taylor JA, et al. The architecture of provider-parent vaccine discussions at health supervision visits. *Pediatrics*. 2013;132(6):1037-1046
 46. Hofstetter AM, Robinson JD, Lepere K, et al. Clinician-parent discussions about influenza vaccination of children and their association with vaccine acceptance. *Vaccine*. 2017;35(20):2709-2715
 47. D'Agostino JA, Passarella M, Saynisch P, Martin AE, Macheras M, Lorch SA. Preterm infant attendance at health supervision visits. *Pediatrics*. 2015;136(4). Available at: www.pediatrics.org/cgi/content/full/136/4/e794
 48. Wade KC, Lorch SA, Bakewell-Sachs S, et al. Pediatric care for preterm infants after NICU discharge: high number of office visits and prescription medications. *J Perinatol*. 2008;28(10):696-701
 49. Britto MT, Garrett JM, Dugliss MA, et al. Preventive services received by adolescents with cystic fibrosis and sickle cell disease. *Arch Pediatr Adolesc Med*. 1999;153(1):27-32
 50. Britto MT, Rosenthal SL, Taylor J, Passo MH. Improving rheumatologists' screening for alcohol use and sexual activity. *Arch Pediatr Adolesc Med*. 2000;154(5):478-483
 51. Hofstetter AM, Lappetito L, Stockwell MS, Rosenthal SL. Human papillomavirus vaccination of adolescents with chronic medical conditions: a national survey of pediatric subspecialists. *J Pediatr Adolesc Gynecol*. 2017;30(1):88-95
 52. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Dietz V. Vaccination coverage among children aged 19-35 Months - United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(39):1065-1071
 53. Jackson ML, Henrikson NB, Grossman DC. Evaluating Washington State's immunization information system as a research tool. *Acad Pediatr*. 2014;14(1):71-76
 54. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kolasa M. National, state, and selected local area vaccination coverage among children aged 19-35 Months - United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(33):889-896
 55. Seither R, Calhoun K, Street EJ, et al. Vaccination coverage for selected vaccines, exemption rates, and provisional enrollment among children in kindergarten - United States, 2016-17 school year [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2017;66(42):1160]. *MMWR Morb Mortal Wkly Rep*. 2017;66(40):1073-1080

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