Immunization Completion in Infants Born at Low Birth Weight

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Background. Low birth weight (LBW) has been associated with underimmunization. We sought to understand the effect of LBW on immunization completion after controlling for previously hypothesized mediators, including prematurity, neonatal illness, well-child care, non–well-child visits, and provider consistency.

Methods. We formed a retrospective cohort of infants born between 2008 and 2011 with ≥2 years of military healthcare follow-up. International Classification of Diseases, Ninth Revision codes were used to identify LBW, preterm birth, neonatal illnesses, well-child visits, non–well-child visits, provider consistency, and parental rank in the inpatient and outpatient records. Immunization records were extracted from both records. Logistic regression determined the odds of immunization completion and well-child care completion (ie, having had ≥2 WCC visits by 15 months of age).

Results. Of 135,964 included infants, 116,521 (85.7%) were completely immunized at the age of 2 years. In adjusted analysis, the odds of immunization completion were significantly decreased in infants born at LBW (odds ratio [OR], 0.88 [95% confidence interval (CI), 0.79–0.97]), very LBW (OR, 0.61 [95% CI, 0.48–0.77]), or extremely LBW (OR, 0.45 [95% CI, 0.33–0.63]) or at ≤32 weeks’ gestation (OR, 0.76 [95% CI, 0.63–0.92]), infants with chronic lung disease (OR, 0.63 [95% CI, 0.45–0.88]), male infants (OR, 0.96 [95% CI, 0.93–0.99]), and infants who experienced decreased provider consistency (OR, 0.92 [95% CI, 0.91–0.92]). The rate of immunization completion increased with the overall number of healthcare visits (OR, 1.02 [95% CI, 1.02–1.03]) and complete well-child care (OR, 1.80 [95% CI, 1.75–1.86]). However, children born LBW or preterm were significantly less likely to have complete well-child care.

Conclusions. After adjustment for preterm birth, comorbid neonatal conditions, and early childhood patterns of healthcare use, LBW was significantly associated with immunization noncompletion in a universal healthcare system. Provider consistency and well-child care seem important for increasing immunization completion in LBW infants.

Keywords. immunization; immunization completion; low birth weight; prematurity.

The ability of vaccines to prevent illness and death in infants is well documented, and vaccines are recommended almost universally [1, 2]. Infants are at increased risk for vaccine-preventable illnesses because of their relatively immature immune system [3–5]. Risk is even higher for infants with a low birth weight (LBW) (<2500 g), whose immunoglobulin levels are lower than those in normal-birth-weight (NBW) infants, and for infants born preterm before adequate immunoglobulin transfer [3–12]. These infants are more likely to suffer morbidity and death from vaccine-preventable illnesses than term-born NBW infants, which makes immunization particularly important for them [13–15]. Current recommendations state that infants should receive each immunization on the basis of their chronological age without adjustment, with the exception of hepatitis B vaccine, which is recommended for only if newborns weigh >2000 g or are 30 days old [1, 3, 6].

Despite proven benefit from immunization and increased risk without immunization, LBW and preterm-born infants are underimmunized relative to their term-born NBW peers [16–21]. Researchers have hypothesized that lack of health insurance, lower socioeconomic status, medical fragility that results from complications of prematurity, and decreased well-child care (WCC) because of increased sick or specialist care might contribute to decreased rates of immunization. The effect of these factors on immunization completion has not been evaluated fully. In addition, the potential independent effect of LBW on immunization completion has yet to be distinguished from that seen in infants born both prematurely and at LBW [17–19, 22].

We hypothesized that LBW infants will continue to be at risk for underimmunization at 2 years of age in an open-access healthcare system after accounting for the effects of other hypothesized mediators, including prematurity, WCC, neonatal illnesses, consistency of pediatric care, socioeconomic status, and overall healthcare utilization.
METHODS

We formed a retrospective cohort using the Military Healthcare System (MHS) database. The MHS provides healthcare to nearly 9.5 million military members, retirees, and dependents [23]. Care is delivered at military treatment facilities (MTFs) and civilian facilities in the United States and abroad. Dependent children can receive care at MTFs, civilian treatment facilities, or a combination of the two types of facilities [23]. The MHS database includes member medical records of all inpatient and outpatient care and houses a military-wide database of immunizations.

The retrospective cohort included infants born between October 1, 2007, and September 30, 2011. Included children had a birth record in the MHS database and a record in the MHS immunization database. Inclusion in the immunization database indicated contact with at least 1 MTF and excluded infants seen solely by civilian providers. To indicate use of the MHS, included children also had at least 1 WCC visit in the MHS during each of their first 2 years of life. Immunizations given at an MTF are entered into the MHS immunization database automatically. In addition, any record of immunizations provided during outpatient visits at MTFs or civilian facilities were extracted from the medical record and merged with immunization database records to find all immunization records. This process served as a cross-check for military records. Immunizations were identified by Current Procedural Terminology codes in the outpatient setting, International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification codes in the inpatient setting, and immunization/trade name in the immunization record. Records were truncated to exclude immunizations given after 2 years of age and cross referenced for duplicates; any immunization of the same type on the same date recorded in multiple records was flagged as a duplicate and counted only once.

Immunization status was evaluated for completeness at 2 years of age and was defined by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommended 4:3:3:1:3:1 immunization schedule (ie, 4 doses of diphtheria, tetanus, and pertussis vaccine, 3 doses of polio vaccine, 1 dose of measles, mumps, and rubella vaccine, 3 doses of Haemophilus influenza type B vaccine, 3 doses of hepatitis B vaccine, and 1 dose of varicella vaccine) [1]. H influenza type B immunization status was excluded when determining completeness because of the vaccine shortage from 2007 to 2009, which resulted in a 4:3:1:3:1:1 schedule [24].

The inpatient record included admissions initiated during the neonatal period (first 28 days of life); ICD-9 codes identified LBW/preterm-birth categories, neonatal illness, and any inpatient immunizations given during those hospitalizations. Infants were categorized as LBW (1500–2499 g), very LBW (VLBW) (1000–1499 g), or extremely LBW (ELBW) (<1000 g). The estimated gestational age (EGA) for each infant was categorized as ≤32 weeks, 33 to 36 weeks, or ≥37 weeks (term). The included neonatal illnesses expected to require ongoing care were neonatal sepsis, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and chronic lung disease (CLD).

The outpatient record included all MHS encounters in the first 2 years of life at MTFs and civilian treatment facilities. Outpatient visits for WCC were identified by ICD-9 codes, and WCC was considered complete if the infant met the Healthcare Effectiveness Data and Information Set (HEDIS) standard of having had ≥26 WCC visits by 15 months of age [25]. All other healthcare encounters were considered non-WCC and were counted until the age of 2 years. Outpatient provider change was defined as the number of distinct facilities each patient had visited by the age of 2 years. Each facility was counted once, and having had different providers at a facility was not considered a change.

The military family member's rank was used as a surrogate for socioeconomic status. Military members were classified as junior enlisted or senior military on the basis of rank at the time of the infant’s birth. Junior enlisted was defined as a pay grade ≤E-4. With a maximum base pay of $28,000, this number equated to 125% of the 2011 federal poverty level for a family of 4 [26]. Dual military parents were classified as senior military.

Analysis using the χ² statistic determined group differences between the included and excluded infants. Logistic regression determined adjusted and unadjusted odds of immunization completion. Two partially adjusted models were used. One model evaluated the association of LBW and preterm birth with immunization completion without other variables, and the other model evaluated the effect of LBW and preterm birth on meeting the HEDIS standard for WCC. The fully adjusted model calculated the odds of immunization completion at 2 years of age and accounted for sex, LBW category, preterm birth category, neonatal illnesses, WCC completion by 15 months of age, non-WCC encounters, provider consistency, and military-parent rank. Stepwise models and the Akaike inclusion criterion were used to build and evaluate the model. A variance inflation factor tested for collinearity. Stata Intercooled 13 software (Stata Corp, College Station, Texas) was used for statistical analysis; a P value of <.05 was considered statistically significant. This study was reviewed and approved by the appropriate institutional review boards.

RESULTS

A total of 313,262 infants were born in the MHS during fiscal years 2008 through 2011; of these children, 135,964 met inclusion criteria. The primary reason for exclusion was loss to follow-up. Included children were more likely to have been born to parents of junior enlisted rank and less likely to have had sepsis or IVH and to have been born preterm or LBW than were the excluded...
infants. Included and excluded children did not differ according to sex, CLD, ROP, or NEC (Table 1). There were 6668 (4.9%) infants born in any LBW category and 9740 (7.2%) infants born in any preterm category. Table 2 shows more details of LBW and preterm categories along with associated infant immunization rates.

In our cohort, 2727 (2.0%) infants were diagnosed with sepsis, 335 (0.3%) with IVH, 252 (0.2%) with ROP, 123 (0.1%) with NEC, and 292 (0.2%) with CLD. Of the included infants, 72734 (53.5%) met the HEDIS standard for WCC by 15 months of age, 69887 (51.4%) were male, and 41940 (30.9%) were born to junior enlisted parents. In the first 2 years of life, the children received care at a median of 3 (interquartile range [IQR], 2–4) facilities. NBW infants had a median of 15 (IQR, 10–23), LBW infants had 23 (IQR, 14–34), VLBW infants had 52 (IQR, 31–79), and ELBW infants had 88 (IQR, 40–133) non-WCC encounters by the age of 2 years. Term-born infants had a median of 15 (IQR, 10–23), infants born at ≤32 weeks’ EGA had 48 (IQR, 31–79), and ELBW infants had 88 (IQR, 40–133) non-WCC encounters by the age of 2 years.

In unadjusted analysis, LBW infants were 13% less likely, VLBW infants were 30% less likely, and ELBW infants were 41% less likely than NBW infants to be completely immunized. Infants born at 33 to 36 weeks’ EGA were 8% less likely and those born at ≤32 weeks’ EGA were 27% less likely to be fully immunized than were term-born infants. Meeting the HEDIS standard for WCC and additional non-WCC encounters was associated with increased odds of immunization completion, whereas provider changes led to reduced odds of immunization completion. Male sex, ROP, and NEC were not associated with immunization completion in the unadjusted analyses, whereas CLD, IVH, and sepsis were (Figure 1).

In the partially adjusted model, in which we examined the effects of prematurity and birth weight on immunization completion, LBW was associated with an 11% decreased odds, VLBW with a 25% decreased odds, and ELBW with a 37% decreased odds of immunization completion. Preterm birth was not significantly associated with immunization completion (Table 3). In the partially adjusted analysis, in which we examined birth weight, prematurity, and WCC, LBW infants had a 9% decreased odds, VLBW infants a 30% decreased odds, ELBW infants a 67% decreased odds, and infants born at ≤32 weeks’ EGA a 19% decreased odds of meeting the HEDIS WCC standard (Table 4). Birth at 33 to 36 weeks’ EGA was not significantly associated with meeting the HEDIS WCC standard.

The fully adjusted model revealed that LBW was associated with a 12% decreased odds, VLBW with a 39% decreased odds, and ELBW with a 55% decreased odds of immunization completion by the age of 2 years. Birth at 33 to 36 weeks’ EGA was not associated with immunization completion, whereas birth at ≤32 weeks’ EGA was associated with a 24% decreased odds of immunization completion. In an adjusted analysis, male sex was associated with a 4% decreased odds and CLD with a 37% decreased odds of immunization completion. For each change in provider, infants were 8% less likely to complete immunization by the age of 2 years. Meeting the HEDIS standard for WCC by the age of 15 months was associated with an 80% increased odds of immunization completion by the age of 2 years, and each additional non-WCC encounter was associated with a 2% increase in the odds of immunization completion (Figure 2). A history of neonatal sepsis, IVH, or ROP and being born to a parent of junior enlisted rank were not significantly associated with immunization completion by the age of 2 years.

**DISCUSSION**

In a cohort of infants with access to comprehensive healthcare coverage, all LBW subcategories were significantly associated with decreased odds of immunization completion. Infants born at the lowest weight had the greatest odds of noncompliance. Birth at ≤32 weeks’ EGA, CLD, male sex, and changes in

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**Table 1. Comparison of Included and Excluded Children Born Between Fiscal Years 2008 and 2011**

| Demographic | 135 964 Included | 177 298 Excluded | P |
|-------------|-----------------|-----------------|---|
| Junior enlisted parents | 41 940 (30.9) | 48 551 (27.4) | <.001 |
| Male | 69 887 (51.4) | 90 885 (51.3) | .45 |
| Born preterm | 97 401 (71.6) | 13 125 (7.40) | .011 |
| Born at LBW | 6688 (4.90) | 9188 (5.18) | .001 |
| CLD | 292 (0.21) | 417 (0.24) | 23 |
| IVH | 355 (0.26) | 541 (0.31) | .022 |
| Sepsis | 2727 (2.01) | 3827 (2.16) | .003 |
| ROP | 252 (0.19) | 308 (0.17) | .45 |
| NEC | 123 (0.09) | 171 (0.10) | .59 |

Abbreviations: CLD, chronic lung disease; IVH, intraventricular hemorrhage; LBW, low birth weight; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

*Excluded infants were born in the Military Healthcare System but either did not receive care in the Military Healthcare System or were never accessed well-child care at a military treatment facility.

**Table 2. Birth Weights, Estimated Gestational Ages, and Immunization Rates in Study Cohort**

| Demographic | n (%) | Immunization Rate (%) |
|-------------|-------|-----------------------|
| All included infants | 135 964 (100) | 85.7 |
| Birth weight Status |       |                       |
| Normal birth weight | 129 296 (95.1) | 85.8 |
| Low birth weight | 5408 (4.0) | 84.0 |
| Very low birth weight | 828 (0.6) | 81.0 |
| Extremely low birth weight | 439 (0.3) | 78.2 |
| Gestational age |       |                       |
| ≤37 wk EGA | 126 224 (92.8) | 95.8 |
| 33–36 wk EGA | 7811 (5.7) | 84.8 |
| ≤32 wk EGA | 1929 (1.4) | 81.5 |

Abbreviation: EGA, estimated gestational age.
healthcare providers were also associated with immunization noncompletion at the age of 2 years. Meeting the HEDIS standard of ≥6 WCC visits in the first 15 months of life and overall increased number of healthcare encounters were associated with immunization completion.

The overall immunization-completion rate of 85.7% by the age of 2 years in our study is higher than a reported health maintenance organization immunization rate of 78.5% to 78.8% for 2-year-olds [27], higher than a 78% rate reported from a study that used the same 4:3:1:1:3 immunization schedule [28], and higher than previously reported military children immunization rates, which range from 54% to 84% [29–31]. Potential factors related to differences in observed immunization rates might relate to access to no-cost healthcare, use of the survey methodologies in previous studies, or a lack of access to the full complement of military immunization records in military-specific studies.

Although LBW and prematurity are linked, previous studies have not examined these factors together as they relate to immunization. Woestenberg et al [16] reported that both prematurity and LBW decreased immunization timeliness, but they analyzed the infants in separate models, which makes comparisons impossible. In our partially and fully adjusted models, LBW seemed to be the more salient characteristic for immunization completion relative to gestational age, which might relate to the recommendation that infants weigh >2000 g for their initial hepatitis B vaccine and to the perceived association between LBW and neonatal illness.

Previous researchers have theorized that factors commonly associated with LBW, including neonatal illness, the need for ongoing postneonatal specialist care, and decreased use of WCC, are the cause for the link between LBW and immunization.
noncompletion. Investigators hypothesized that neonatal illness would increase parents’ concern that their child is too fragile for immunization and that increased sick-child care required for those with neonatal illnesses could result in decreased contact with WCC providers and lead to subsequent decreased immunization rates [5, 18, 32]. Our finding that IVH, sepsis, ROP, and NEC were not associated with immunization noncompletion might suggest that neonatal illness is not the principal route by which LBW decreases immunization-completion rates. However, finding that CLD was associated with a decreased odds of immunization completion might suggest a link between neonatal illnesses that are associated with more severe symptoms during childhood, such as CLD, which might cause delayed immunizations or missed WCC in this subset [33].

Our finding that male sex was associated with a slightly lower odds of immunization is similar to the previously reported trend toward lower immunization rates in prematurely born boys that Davis et al [19] reported. The association might also relate to the increased odds of negative outcomes for boys born prematurely [19, 34]. Although boys are less likely than girls to be born at LBW, there seems to be a higher likelihood that they suffer a greater degree of illness [35]. If increased illness contributes to lower immunization rates in LBW infants, then reported associations between male sex and CLD with worse pulmonary outcomes also might figure into lower immunization rates in boys [36].

Regardless of the cause of missed WCC, our results are consistent with those of previous research that linked WCC adherence and immunization completion [19, 22]. Meeting the HEDIS standard for WCC was associated with increased odds of immunization completion, whereas LBW and preterm birth were associated with decreased odds of meeting the HEDIS standard for WCC. This result suggests that a lack of WCC might link LBW with immunization noncompletion. However, we also found that WCC and non-WCC visits were both associated with immunization completion. Previous research has suggested that increased specialist care supplants WCC and leads to immunization noncompletion [17, 37, 38]. Our finding that both WCC and non-WCC visits were associated with immunization completion suggests that replacement of WCC with sick care is unlikely to account for decreased odds of completion in children born at LBW.

Extreme prematurity and LBW often require longer birth hospitalizations and leaves infants at a higher risk of readmission [39], which increases the likelihood of missing WCC appointments and not meeting the HEDIS standard [22, 38]. However, LBW was still significantly associated with decreased odds of completion after accounting for the effects of WCC. This result suggests that missing early WCC as a result of hospitalization does not account completely for the decreased odds of immunization completion. Although our finding that 54% of included children met the HEDIS standard for WCC was higher than previous reported rates of 43%, low rates of completed WCC are still an important target for improving immunization rates [22].

Provider changes negatively affected immunization completion; each change in provider decreased the odds of immunization by 8% in our adjusted analysis. This result might prove an important externally influenced indicator of immunization completion and is particularly relevant to military, low-income, and foster children, who tend to move more frequently.

Although neonatal illness and patterns of healthcare use likely affect immunization completion in infants born at LBW, the relationships seem insufficient to explain decreased immunization completion fully. Provider concerns of decreased immunogenicity, despite research to the contrary, might affect immunization rates, as might other unidentified factors, such as intrauterine growth restriction (IUGR) or being born small for gestational age (SGA) [3, 5, 6, 8, 32, 33, 37, 38, 40–42]. Both IUGR and being born SGA have been linked with more severe outcomes in early childhood, and research suggests that
both factors can affect the mother–infant relationship negatively, which in turn might affect the healthcare the infant receives [43–46].

This study is limited by its reliance on ICD-9 codes and difficulties in tracking immunizations in a mobile population. ICD-9 codes for prematurity and birth weight include codes that indicate specific weeks of gestation and birth weight ranges. However, other codes identify generic LBW or preterm birth. In these cases, it is possible that some LBW or preterm-born infants were misclassified. The use of ICD-9 and procedural codes to identify specific immunization types was also imperfect. When providers used generic procedural codes without an accompanying ICD-9 code of immunization type, those immunizations could not be counted. Similarly, any immunization provided at a pharmacy or free clinic that was not billed to the military health insurance would not be captured. Although these instances are rare, they might have lowered the reported immunization rates. The use of multiple records helped to reduce this problem, but some unverified immunizations likely reduced the immunization-completion rate. Last, although the universal healthcare provided by the military enabled analysis of a number of factors without having to account for the differential impact of healthcare access, our findings might not fully apply to children with less complete care access.

The strengths of this study include the use of a large diverse sample from across the nation and decreased access-to-care bias by inclusion of a population of infants in a free universal healthcare system within the United States. In addition, the use of a large electronic database enabled us to link inpatient and outpatient records to examine multiple factors that might have affected immunizations. Using both EGA and birth weight to determine which was the more impactful variable is also unique to this study and furthers our understanding of caring for newborns at high risk.

CONCLUSIONS

LBW is associated with immunization noncompletion independent of prematurity, neonatal illness, provider changes, WCC completion, parental income, and healthcare utilization. Providers should be particularly vigilant of immunization status in infants with CLD or who were born at any degree of LBW. Our findings suggest that perceived medical fragility by parents or providers might contribute to underimmunization. Subspecialists who provide care to preterm-born infants or infants born at LBW should be aware of the higher likelihood of decreased immunization and seek to routinely review/update immunizations.

In addition, there might be an as-yet-undefined subset of infants born at LBW, such as those born SGA and those with IUGR, who are the source of the current findings. Efforts to maintain consistent access to a medical home and improving adherence to HEDIS standards for WCC, even for infants with extended neonatal hospitalizations, would likely help to increase immunization-completion rates in this population.

Notes

Disclaimer. The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US government.

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