Immunization Levels Among Premature and Low-Birth-Weight Infants and Risk Factors for Delayed Up-to-Date Immunization Status

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INFANTS ARE IMMUNOCOMPROMISED compared with older children and adults. Immunoglobulin G (IgG) is transferred transplacentally to the fetus, and intrauterine levels of IgG in the developing infant correlate with gestational age. As a result, premature infants are particularly prone to vaccine-preventable diseases such as pertussis.1-3 Premature infants who contract pertussis are also at increased risk for severe infections, for hypoxic episodes with paroxysmal coughing, and for dying or developing long-term lung damage after infection. To prevent morbidity and mortality due to vaccine-preventable diseases, including pertussis, the Advisory Committee on Infectious Diseases has recommended that premature infants receive immunizations at the same chronological age.

Context Studies have noted that health care professionals may not conform to proper immunization schedules for premature and low-birth-weight infants in the United States. Little is known about the success of current efforts to immunize these high-risk infants.

Objective To describe current immunization practices for premature and low-birth-weight infants and ascertain risk factors for poor immunization status, using large population-based data sources.

Design and Setting Cohort and case-control analyses of immunization data tracked from March 1991 through March 1997 for 3 large health maintenance organizations (HMOs) participating in the Centers for Disease Control and Prevention’s Vaccine Safety Datalink project.

Participants A total of 11,580 low-birth-weight and premature infants were enrolled from birth to age 2 months; 6,832 of these were continuously enrolled from birth to age 24 months. At age 2 months, there were 173,373 full-term, normal-birth-weight infants enrolled as controls; at age 24 months, there were 103,324.

Main Outcome Measures Age-specific immunization status by prematurity and birth weight (<1500 g, 1500-2500 g, born at <38 weeks’ gestation with birth weight of >2500 g, or full-term with normal birth weight) and patient characteristics associated with up-to-date status.

Results At each age, infants weighing less than 1500 g at birth had lower up-to-date immunization levels than other infants. At age 6 months, 52% to 65% of infants weighing less than 1500 g were up-to-date at each of the 3 HMOs compared with 69% to 73% of those weighing 1500 to 2500 g, 66% to 80% of premature infants weighing more than 2500 g, and 65% to 76% of full-term, normal-birth-weight infants. By age 24 months, 78% to 86% of infants weighing less than 1500 g were up-to-date, significantly less than heavier infants, who had levels of 84% to 89%. Well-child preventive care strongly predicted immunization status, while concomitant pulmonary disease did not.

Conclusions Our data suggest that infants born prematurely are vaccinated at levels approaching that of the general population, but levels of vaccination for very low-birth-weight infants lag slightly behind.
LOW-BIRTH-WEIGHT IMMUNIZATION LEVELS

age as recommended for full-term infants. However, a number of studies have noted that health care providers often do not conform to proper immunization schedules for premature infants. Some physicians and some parents of preterm infants mistakenly believe that birth weight, current weight, or the degree of prematurity plays an important role in the decision to initiate immunizations. Consequently, preterm infants often receive their primary immunizations late even though they can mount adequate immune responses when vaccinated at the recommended chronological age.

Because most pediatricians care for only a few premature infants in their practice, educational interventions have been suggested as a means to improve knowledge about immunization recommendations. However, continuing medical education by itself has had notably limited success in providing for sustained improvement in the delivery of preventive care. Furthermore, physicians are often unaware of the immunization status of their own patients, and often overestimate the immunization levels for patients within their own practice.

Research on premature infants has, for the most part, been limited to high-risk subgroups, such as graduates of the neonatal intensive care unit. Since many premature infants are never admitted to an intensive care unit, studies of neonatal intensive care unit graduates may not adequately reflect the immunization status of the larger population of premature infants. As a result, there is a lack of both recent and population-based data from the United States that gauges the adequacy of efforts to immunize premature infants and that covers the full spectrum of gestational age and low birth weight.

To better understand current immunization practices for premature and low-birth-weight infants, we studied such infants using population-based data from 3 large West Coast health maintenance organizations (HMOs). These 3 HMOs contain immunization tracking systems and are part of the Vaccine Safety Datalink (VSD) project, a collaborative study of vaccination and vaccine safety funded and coordinated by the Centers for Disease Control and Prevention that encompasses more than 500,000 children younger than 7 years and contains information on more than 2 million immunizations. Additionally, to identify subgroups of premature or low-birth-weight infants that might benefit from special attention or targeted interventions to improve immunization levels, we used detailed, automated data available at one of the HMOs (Group Health Cooperative of Puget Sound, Seattle, Wash) to assess the relationship between specific patient characteristics and the likelihood of being up-to-date by age, according to the recommended immunization schedule. In particular, we focused on immunization levels among premature infants according to different strata of low birth weight and according to the concomitant presence of pulmonary disease, a common problem among premature infants.

METHODS

Data Source and Population

The VSD project was created in 1991 by the National Immunization Program within the Centers for Disease Control and Prevention. The VSD links medical event information and vaccine history, as well as selected demographic information from the automated clinical databases of Group Health Cooperative (GHC) of Puget Sound, Kaiser Permanente Northwest, Kaiser Permanente Medical Care Program Northern California, and Southern California Kaiser Permanente. Each of the VSD sites in this report (GHC, Kaiser Permanente Northwest, and Kaiser Permanente Medical Care Program Northern California) maintains an immunization tracking system to monitor the immunization status of its members at given ages. At each site these immunization registries are integrated with patient notification and call-back procedures. A detailed description of the VSD project and of the immunization tracking systems in place at each HMO has been published previously. Within each HMO, the study population consisted of children continuously enrolled from birth to age 24 months.

Up-to-Date Immunization Measurement

We used age-specific definitions of up-to-date immunization status as shown in Table 1. The age at which a child was eligible to be counted as up-to-date extended to the end of that age period in months and each separate month was counted as 30.5 days, regardless of exact birth date (for example, a child was up-to-date at 2 months if he/she received the requisite vaccines before age 91 days). To calculate the proportion of children who were up-to-date, we used the number of children continuously enrolled from birth who met the age-specific up-to-date definition, divided by the number of children continuously enrolled from birth who met the definition plus the number of continuously enrolled children who did not meet the age-specific up-to-date definition. At each age point in the analysis, only those children still enrolled were studied.

At age 24 months we measured up-to-date levels using measures similar to that of the Health Plan Employer and Data Information Set (HEDIS), a set of quality-of-care measures. This was calculated as the number of children (in this case, continuously enrolled for at least 732 days) who had had at least 4 doses of diphtheria and tetanus toxoids and pertussis vaccine, 3 doses of oral poliovirus vaccine, 1 dose of measles, mumps, and rubella vaccine, and 4 doses of Haemophilus influenzae type B vaccine with 1 dose administered between 12 and 24 months, divided by the number continuously enrolled for at least 732 days. This measure differs from the standard HEDIS measure in that it includes all children continuously enrolled in HMOs, whereas the HEDIS measure is...
typically applied to employer-insured populations and only more recently has included Medicaid populations within HMOs.19

Finally, in the study of all sites combined, we defined up-to-date at 15 months as receipt of 3 doses of diphtheria and tetanus toxoids and pertussis vaccine (or 3 doses of diphtheria and tetanus toxoids), 2 doses of poliovirus vaccine, 3 doses of *Haemophilus influenzae* type B vaccine, and 1 dose of measles, mumps, and rubella vaccine. In the part of our study that looked at factors affecting up-to-date status at GHC, this was modified slightly to require 3 poliovirus immunizations. We did this because during the study period GHC routinely administered the third dose of poliovirus vaccine at age 6 months.

**Patient Characteristics Associated With Immunization Status**

We used data from the 3 HMOs to classify infants into the following categories of birth weight or prematurity based on discharge *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic codes: less than 1500 g, 1500 to 2500 g, premature infants born at less than 38 weeks with birth weights of more than 2500 g, and full-term, normal-birth-weight infants. In addition, at GHC, the following characteristics were assessed for their influence on up-to-date status: total number of days hospitalized in the first 30 days of life, the number of hospitalizations within the age under observation, and the total number of well-child visits and clinic visits for other reasons. Because the programming for this last variable was time intensive, this characteristic was assessed only for children at age 24 months.

At GHC we also studied immunization levels among premature infants with a history of pulmonary disease. The classification of pulmonary disease included children with hyaline membrane disease or bronchopulmonary dysplasia. Children were classified as having pulmonary disease if they had ever had the diagnosis of either hyaline membrane disease or bronchopulmonary dysplasia at any time between birth and their latest period under observation. Children with pulmonary disease were further stratified into those with at least 1 prescription for β-agonists, theophylline, steroids, and cromolyn sodium, and those who never received such medication.

**Statistical Analysis**

For the analysis of infants at the 3 HMOs, we measured up-to-date levels for premature and low-birth-weight infants at ages 2, 4, 6, 15, 18, and 24 months, and used logistic regression modeling to assess the relationship between different birth-weight categories and immunization status.20 For descriptive purposes, we also assessed immunization levels of full-term, normal-birth-weight infants at various points in the analysis.

Prior to beginning the analysis of the effect of patient characteristics on immunization levels at GHC (as described earlier), we decided to perform significance testing only at ages 6 months and 24 months to reduce the problem of multiple comparisons. We used logistic regression in this part of the analysis to assess the adjusted independent relationship between patient characteristics and immunization status.21

**RESULTS**

**Description of the Study Populations**

There were a total of 11 580 premature and low-birth-weight infants continuously enrolled at the 3 VSD sites through age 2 months. Because not all infants had attained their second birthday at the time of the study, there were

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Immunization Scheduled, mo</th>
<th>Age Evaluated, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis, poliovirus, *</td>
<td>2</td>
<td>91.5</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis, poliovirus, †</td>
<td>4</td>
<td>122</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis, poliovirus, ‡</td>
<td>6</td>
<td>183</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis, poliovirus, ‡</td>
<td>15</td>
<td>457.5</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B, § measles, mumps, and rubella*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis, poliovirus, §</td>
<td>18</td>
<td>549</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B, § measles, mumps, and rubella*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis, poliovirus, §</td>
<td>24</td>
<td>732</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B†, § measles, mumps, and rubella*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One dose.
†Or diphtheria and tetanus toxoids, administered at the same dose schedule.
‡Two doses.
§Three doses.
¶Four doses.
¶One dose may be given initially followed by 3 doses of diphtheria and tetanus toxoids and pertussis or diphtheria and tetanus toxoids.
*One dose should be administered between 1 and 2 years.
6832 premature and low-birth-weight infants at least age 24 months who had been continuously enrolled from birth at the 3 VSD sites. Among the full-term, normal-birth-weight infants, there were a total of 173,373 at age 2 months and 103,324 at age 24 months.

At GHC, there were 694 premature and low-birth-weight infants continuously enrolled through age 2 months. Of this group, slightly more than half were male, 50% had birth weights between 1500 and 2500 g, and 12% had birth weights less than 1500 g. Most of these infants went home relatively soon after birth, and less than 10% had a birth hospital stay of more than 7 days. Among the GHC infants followed up through their second birthday, 35% had been diagnosed as having bronchopulmonary dysplasia and/or hyaline membrane disease.

### Immunization Levels at 3 VSD HMO Sites

At each age in which we assessed up-to-date status, infants with birth weights of less than 1500 g had, with 1 exception, lower up-to-date immunization status than infants with birth weights of 1500 to 2500 g, or premature infants with birth weights of more than 2500 g (Table 2). This finding was consistent among all HMOs.

At age 6 months, between 52% and 65% of infants with birth weights of less than 1500 g were up-to-date at each of the 3 HMO sites, compared with 69% to 73% of those weighing 1500 to 2500 g, and 66% to 80% of premature infants weighing more than 2500 g at birth. Among normal-birth-weight infants, 65% to 76% were up-to-date at 6 months, while 67% to 75% were up-to-date at 18 months. These up-to-date percentages among normal-birth-weight infants were significantly higher than for infants with birth weights of less than 1500 g, but no different from infants with birth weights of 1500 to 2500 g or premature infants with birth weights of more than 2500 g.

When immunization levels were assessed using the HEDIS-like measure at age 24 months, between 78% and 86% of infants weighing less than 1500 g were up-to-date, again significantly less than heavier infants. Among infants with birth weights of 1500 to 2500 g, or premature infants with birth weights of more than 2500 g, up-to-date status had been achieved by 84% to 89%. Among normal-birth-weight infants, 84% to 88% were up-to-date by age 24 months.

### Group Health Cooperative

At GHC, in addition to the findings that infants with birth weights of less than 1500 g were more likely to be lagging in immunization status, we found that male infants were slightly more likely than females to be behind on immunizations at each age, although these differences were not statistically significant (Table 3 and Table 4). Immunization status at 6 and 24 months was not affected by the total number of hospitalizations prior to 6 or 24 months. Infants who were hospitalized for 8 to 14 days in the first month of life were more likely to be up-to-date, a difference that was significant at age 6 months but not at 24 months.

Bronchopulmonary dysplasia or hyaline membrane disease did not affect up-to-date status at 6 and 24 months. In addition, children with bronchopulmonary dysplasia or hyaline membrane disease who were being prescribed medications such as β-agonists had immunization levels at 6 and 24 months (67% and 86% were up-to-date, respectively) similar to children with pulmonary disease who were not taking medication (72% and 91% were up-to-date, respectively) and the overall cohort of premature children (70% and 88% were up-to-date, respectively).

Children with frequent well-child visits were more likely to be up-to-date at age 24 months than children with less than 3 well-child visits. Children with more frequent clinic visits for illness were also more likely to be up-to-date at 24 months, although this difference was not as large as that seen with preventive visits.

### COMMENT

In this population-based study of premature and low-birth-weight infants at 3 large West Coast HMOs, we found that infants born prematurely were vaccinated at levels approaching that of the general population. As early as age 2...
months, infants with birth weights of more than 1500 g had immunization levels indistinguishable from those infants with normal birth weights and gestational ages. This finding was consistent among each of the 3 HMOs.

We also found that very low-birth-weight infants (those with birth weights <1500 g) were less likely, compared with heavier infants, to be up-to-date at each age. Nevertheless, at all 3 HMOs approximately 80% of infants with birth weights of less than 1500 g were up-to-date by age 24 months. While this was significantly less than the other groups of infants, these differences were not nearly as great as they were at earlier ages.

Little is known about the immunization status of low-birth-weight and premature infants in the United States. In a 1995 follow-up study of neonatal intensive care unit graduates, Magoon et al found that between 70% and 88% of preterm infants had at least 1 delay in their immunization schedule, but they did not show overall age-specific immunization levels and their study size was limited to 153 infants. Studies done outside the United States include those by Roper and Day, who showed that infants weighing less than 2000 g had delayed receipt of their first immunization. Contrary to our findings, they found that by age 18 months coverage was almost identical for infants with birth weights of less than 2000 g compared with those with normal birth weights, although in our study the difference was only apparent among infants weighing less than 1500 g.

At GHC, the HMO where we studied the relationship between patient characteristics and up-to-date status, we found that lack of routine well-child care was associated with poorer immunization status. This is consistent with many other studies of children in different settings in which the lack of immunization has also been associated with poorer receipt of other preventive and primary care services. The provision of well-child care to all families is important to ensure that children are immunized on time and that other preventive care is provided as well.

Interestingly, disease severity was not associated with lower immunization levels. Patients with pulmonary disease had immunization levels equal to, or above, the rest of the children under study. One explanation for this finding is that patients with pulmonary problems were more likely to receive nonroutine medical care (P < .001 comparing number of nonroutine medical care visits in first 2 years among children with pulmonary problems [median number of visits, 18] to children without coexisting problems [median number of visits, 12]). These visits most likely provided the opportunity to deliver immunizations in a timely fashion and to bring these infants up-to-date if they were behind.

A potential limitation to our study is that it focuses on infants within HMOs. Each of the HMOs studied here incorporate immunization tracking systems into their delivery systems. The immunization tracking systems provide for automated reminders to be distributed at regularly scheduled intervals to parents or providers when a child, regardless of birth weight or gestational age, falls behind the regular immunization schedule. Immunization registries (such as tracking systems within HMOs or countywide or statewide registries) have been shown to be effective tools for monitoring immunization levels and coverage, and remind and/or feedback systems in genus.
eral have been found to be useful interventions in clinical management.\textsuperscript{15,24} It is important to note that our study shows that, even as early as age 2 months, infants with birth weights of more than 1500 g have immunization levels comparable with the general population. Because the immunization tracking systems’ reminder mechanisms are not activated until older ages (8 and 20 months at GHC, 12 and 18 months at Kaiser Permanente Northwest, and 18 months at Kaiser Permanente Medical Care Program Northern California), it is unlikely that the tracking systems influenced our results for the majority of the low-birth-weight infants. Nevertheless, we believe that it will be important for other researchers to replicate our findings and to compare the immunization status of low-birth-weight infants with normal-birth-weight infants in a variety of other settings, including private-provider offices and inner-city primary care clinics, as well as HMOs that do not incorporate immunization tracking systems into their vaccine delivery systems.

A unique benefit of the current study is our focus on a sample that covered a wide spectrum of infants. Prior studies have focused on high-risk populations, mainly graduates from neonatal intensive care units.\textsuperscript{3,7,10} Because our study encompassed a wider range of less severely affected infants (only 15% spent more than 7 days in the hospital during the first month of life), we were able to gain a better estimate of immunization rates for a population-based sample of low-birth-weight and premature infants.

While these results are encouraging, there is still work to be done for very low-birth-weight infants (<1500 g), especially in the first few months of life. A number of surveys have shown that primary care providers postpone immunizations for infants who have not reached a certain weight (such as 4.5 kg).\textsuperscript{3,8} Specific outreach programs geared toward these very low-birth-weight infants might be necessary to close the immunization gap between this group and the rest of the population. Further assessment of vaccine coverage rates, using the VSD and other data sources, should be performed to gauge the effect of any such intervention programs, and, additionally, to monitor trends over time to ensure that vaccination coverage does not wane.

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\begin{table}[h]
\centering
\caption{Results From Logistic Regression Analysis Showing Association Between Patient Characteristics and Risk for Not Being Up-to-Date} \label{tab:logistic_regression}
\begin{tabular}{|c|c|c|}
\hline
\textbf{Patient Characteristic} & \textbf{6 Months Old} & \textbf{24 Months Old} \\
\hline
\textbf{Sex} & & \\
Female & 1.00 & 1.00 \\
Male & 1.11 (0.78-1.58) & 1.74 (0.93-3.26) \\
\hline
\textbf{Birth weight, g} & & \\
<1500 & 3.47 (1.89-6.36) & 2.10 (0.80-5.51) \\
1500-2500 & 1.47 (0.99-2.17) & 0.76 (0.39-1.46) \\
>2500 & & \\
\hline
\textbf{Days hospitalized, No.*} & & \\
0-7 & 0.74 (0.44-1.25) & 1.00 (0.59-1.72) \\
8-14 & 0.48 (0.27-0.87) & 0.70 (0.39-1.31) \\
15-30 & 0.68 (0.35-1.33) & 1.12 (0.38-3.33) \\
\hline
\textbf{Total hospitalizations†} & & \\
0 & 1.00 & 1.00 \\
1 & 1.21 (0.77-1.91) & 1.06 (0.86-1.32) \\
2 & 0.83 (0.33-2.08) & 1.40 (0.38-5.29) \\
≥2 & 1.90 (0.87-4.12) & 1.77 (0.53-5.91) \\
\hline
\textbf{Pulmonary disease} & & \\
No pulmonary disease & 1.00 & 1.00 \\
Bronchopulmonary dysplasia or hyaline membrane disease without medication & 1.36 (0.71-2.61) & 0.71 (0.21-2.36) \\
Bronchopulmonary dysplasia or hyaline membrane disease with medication & 1.43 (0.70-2.90) & 1.95 (0.31-1.71) \\
\hline
\textbf{Well visits, No.‡} & & \\
0-3 & ... & 1.00 \\
4-7 & 0.59 (0.32-1.07) & 0.37 (0.16-0.88) \\
≥8 & ... & 0.41 (0.16-1.01) \\
\hline
\textbf{Clinic visits (not well), No.‡} & & \\
0-10 & ... & 1.00 \\
11-20 & 0.71 (0.33-1.52) & 0.40 (0.17-0.93) \\
≥20 & ... & \\
\hline
\end{tabular}
\begin{itemize}
\item[*In first 30 days of life.]
\item[†Excludes birth hospitalization.]
\item[‡Ellipses indicate data not available because data collected for children at age 24 months only.]
\end{itemize}
\end{table}


The most beautiful thing we can experience is the mysterious. It is the source of all art and science. —Albert Einstein (1879-1955)