Association Between Administration of Hepatitis B Vaccine at Birth and Completion of the Hepatitis B and 4:3:1:3 Vaccine Series

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A
n estimated 100,000 to 150,000 new hepatitis B virus (HBV) infections occur each year in the United States1 and once infected, infants and children are much more likely to develop chronic HBV infections than are adults.1,2 However, early childhood infections can be prevented through hepatitis B vaccination of infants. The currently licensed hepatitis B vaccines have been shown to be safe, highly efficacious, and to provide long-term protection.1,4

As part of a comprehensive strategy to eliminate HBV transmission from the United States, the Advisory Committee for Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians published recommendations in 1991 and 1992 to vaccinate all infants with 3 doses of hepatitis B vaccine.4,5 The preferred vaccination schedule of the Advisory Committee for Immunization Practices and the American Academy of Pediatrics calls for administering the first dose of hepatitis B vaccine during the newborn period, before the infant is discharged from the hospital; the second dose at 1 to 2 months of age; and the third dose by 6 to 18 months of age.4,5 In the alternate schedule, hepatitis B vaccination is initiated between 1 and 2 months of age. Little is known regarding the prevalence of administration of the first dose of hepatitis B vaccine at birth and how this affects completion of the 3-dose hepatitis B vaccine series as well as receipt of other routinely recommended childhood vaccines. A recent report from a study carried out among children in a large housing development in Chicago, Ill, suggested that initiation of hepatitis B vaccination before the age of 1 month may be associated with increased likeli-

Context The association between infant age at initiation of hepatitis B vaccination and completion of the 3-dose hepatitis B vaccination series is unclear.

Objective To assess the association between administration of the first dose of hepatitis B vaccine within 7 days of birth and completion of the hepatitis B vaccine series and the 4:3:1:3 vaccine series (4 doses of diphtheria-tetanus-pertussis vaccine, 3 doses of polio vaccine, 1 dose of measles-containing vaccine, and 3 doses of Haemophilus influenzae type b vaccine).

Design, Setting, and Participants Analysis of data from the 1998 National Immunization Survey, a random-digit-dialing telephone survey (n = 34,480 completed interviews) of parents of children aged 19 to 35 months from 50 states and 28 selected urban areas in the United States that included a provider record check mail survey.

Main Outcome Measures Percentage of infants who received at least 3 doses of hepatitis B vaccine and percentage who received the 4:3:1:3 vaccine series, by age at receipt of the first dose of hepatitis B vaccine.

Results Overall, 86.9% of children 19 to 35 months of age in 1998 received 3 or more doses of hepatitis B vaccine, and 79.9% completed the 4:3:1:3 vaccine series. Multivariate analysis indicated that, compared with children who received the first hepatitis B vaccine dose within 7 days of birth, odds ratios (ORs) for not completing the 3-dose hepatitis B vaccine series among children who received the first dose at 8 to 41 days, 42 to 91 days, 92 to 182 days, 183 to 273 days, and 274 or more days of age were 2.4 (95% confidence interval [CI], 2.0-3.0), 7.8 (95% CI, 6.5-9.3), 9.6 (95% CI, 7.0-13.3), 18.3 (95% CI, 12.0-28.0), and 46.6 (95% CI, 33.7-64.5), respectively; ORs for not completing the 4:3:1:3 vaccine series among these same groups were 1.0 (95% CI, 0.8-1.1), 1.0 (95% CI, 0.8-1.1), 1.7 (95% CI, 1.3-2.3), 3.8 (95% CI, 2.6-5.6), and 4.0 (95% CI, 2.9-5.5), respectively.

Conclusion Administration of the first dose of hepatitis B vaccine at birth is associated with increased likelihood of completion of the hepatitis B vaccination series.

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hood of hepatitis B vaccine series completion and 4:3:1 (4 doses of diphtheria-tetanus-pertussis [DTP] vaccine, 3 doses of polio vaccine, 1 dose of measles-containing vaccine) series completion by the age of 19 months.\(^8\)

We used data from the 1998 National Immunization Survey (NIS) to determine the distribution of 19- to 35-month-old children in the United States by age at receipt of the first dose of hepatitis B vaccine. We also assessed the relationship between the age at receipt of the first dose and completing the hepatitis B vaccine series and the 4:3:1:3 (4 doses of diphtheria and tetanus toxoids with acellular pertussis vaccine [DTaP]/DTP vaccine, 3 doses of inactivated poliovirus vaccine/oral polio vaccine, 1 dose of measles-containing vaccine, and 3 doses of Haemophilus influenzae type b [Hib] vaccine) series.

**METHODS**

**Survey Design and Collection of Data**

The NIS is conducted quarterly by the Centers for Disease Control and Prevention to obtain national, state, and local area statistics on the vaccination coverage rates for the noninstitutionalized population of children between the ages of 19 and 35 months from 50 states and 28 selected urban areas in the United States. The NIS uses a random-digit-dialing (RDD) survey of households with eligible children followed up with a mail survey of the eligible children's vaccination providers. In 1998, 34,480 completed telephone interviews were obtained in the RDD portion of the NIS.

The RDD portion of the NIS uses a list-assisted sampling frame from which telephone numbers are randomly dialed to contact households. In 1998, approximately 1.8 million telephone numbers were screened to identify households with children who met the age requirements for the survey. After weighting on the basis of independence of sampling within each sampling area, the number of randomly selected telephone numbers sampled within each area on the list-assisted sampling frame, the proportion of numbers on the sampling frame estimated to be eligible households (ie, households with eligible children, and not business telephone numbers), unit nonresponse attributable to incomplete household interviews among eligible households, multiple telephone numbers within eligible households, and noncoverage of households that do not have telephones, the distribution of children who participated in the NIS was similar to that of the distribution of children in the US population between 19 and 35 months of age.\(^9\)

In the RDD portion of the survey, the NIS collects information on demographic characteristics of sampled children along with information describing the socioeconomic conditions in which the children live. In 1998, 83.4% of the respondents in the RDD-sampled households gave verbal informed consent to contact the sampled children's vaccination providers. In the subsequent mail survey of providers, histories were obtained that gave dates on which the sampled children received vaccinations. Among the households giving consent, usable vaccination histories for determining whether a sampled child received recommended vaccinations were obtained for approximately 95% of the vaccination providers. Overall, usable vaccination histories were obtained from providers for approximately 70% of all sampled households that completed the NIS RDD interview. Usable vaccination history refers to “provider-reported vaccination information that was of sufficient quality to be used in deriving estimates based on a set of rules used to compare the provider and household vaccination data.”\(^9\)

Among children who had received at least 1 dose of hepatitis B vaccine, we determined the distribution of children by age at receipt of the first dose (0-7 days [at birth], 8-41 days, 42-91 days, 92-182 days, 183-273 days, and ≥274 days) as well as the relationship between the age at receipt of the first dose of hepatitis B vaccine and the likelihood of completion of the 3-dose hepatitis B vaccine and the 4:3:1:3 vaccine series. To account for the fact that some children (ie, those born prematurely or those who develop minor complications) stay in the hospital several days after birth, we assumed that children who received the first dose of hepatitis B vaccine within 7 days of age received the first dose in the hospital before being discharged. Receipt of the first dose at 8 to 41 days of age constitutes an early immunization visit to the provider as the child is age-eligible for no vaccines other than hepatitis B vaccine during this period. The age of 42 to 91 days is when the first dose of DTaP, Hib, and polio vaccines should be administered to the child; administration of the first dose of hepatitis B vaccine during this time is also appropriate according to recommended guidelines.\(^10\) Children receiving the first dose of hepatitis B vaccine beyond 91 days are late starters for this vaccine.

**Statistical Analysis**

As described elsewhere,\(^11\) sampling weights of children with adequate vaccination provider data were adjusted using response propensities so that this group fairly represented all of the children in the sample. Our analysis proceeded by using children with adequate provider data only along with the adjusted sampling weights.\(^11\)

Estimates of hepatitis B vaccination and 4:3:1:3 vaccination coverage rates and their SEs were calculated with the use of SUDAAN,\(^12\) which is a software package designed for use in the analysis of data from complex survey designs. For hepatitis B vaccination coverage, the outcome measure was having received at least 3 doses of hepatitis B vaccine regardless of the age at receipt of the third dose (no later than 35 months of age as older children are not sampled by the NIS) vs having received only 1 or 2 doses of the vaccine. For 4:3:1:3 vaccine series coverage, the outcome measure was having completed the 4:3:1:3 vaccine series regardless of the age at completion of the series vs not having completed the series among children with at least 1 dose of hepatitis B vaccine. The difference in coverage rates between groups that differed by the age at receipt of the first...
dose of hepatitis B vaccine was assessed using the t test.12

The primary relationships of interest in this analysis are assessing the association of age at receipt of the first dose of hepatitis B with the likelihood of completion of the hepatitis B or the 4:3:1:3 series. These 2 relationships were examined to determine if they were modified by any of the variables suspected to be related to the likelihood of vaccine series completion. The potential predictors included sex of the child (male, female), first-born status of child (no, yes), maternal age group (≤19 years, 20-29 years, ≥30 years), maternal race/ethnicity (white-non-Hispanic, African American-non-Hispanic, Hispanic, American Indian, Asian, other), maternal marital status (never married, married, widowed/divorced/separated/deceased), maternal educational level (<12 years, 12 years, >12 years-noncollege graduate, college graduate), family relocation to a different state since birth of child (yes, no), poverty status (below poverty level, above poverty level but <$75,000 per year income, >$75,000 per year income, unknown), area of current residence (metropolitan statistical area-central city, metropolitan statistical area-suburban, rural), the type of facility in which the child’s vaccination provider has his or her practice (all were public clinics, all were hospitals, all were private provider offices, all were military/other facilities, a mix of 2 or more of the above facility types, unknown), and state hepatitis B entry requirement for day care/Head Start (yes, no). Variables were entered in the multivariate model and 2-way interactions were formed from them in a forward stepwise fashion. Variables were retained in the final model if they affected (by changing the odds ratio [OR]) the relationship of interest.

RESULTS

Overall, 86.9% of children 19 to 35 months of age in 1998 received 3 or more doses of hepatitis B vaccine, and 97.2% children received at least 1 dose of the vaccine. Among children who received at least 1 dose of hepatitis B vaccine, 54.6% (95% confidence interval [CI], 53.5%-55.7%) received their first dose within the first 7 days of birth, and almost all children (approximately 95%) received the first dose within 3 months of age (Table 1). Among children 19 to 35 months of age with at least 1 dose of hepatitis B vaccine, the percentage who received the first dose within the first week of birth varied widely by state (range, 26.2%-82.1%) (Figure).

The percentage of children who completed the 3-dose hepatitis B vaccination series was highest among those who received the first dose of the vaccine at 0 to 7 days (96.3%) and consecutively lower among children who received the first dose at 8 to 41 days, 42 to 91 days, 92 to 182 days, 183 to 273 days, and 274 or more days of age completed the 4:3:1:3 vaccine series (Table 1).

Multivariate analysis indicated that, compared with children who received the first dose of hepatitis B vaccine at 0 to 7 days, the ORs for not completing the hepatitis B vaccine series among children who received the first dose at 8 to 41 days, 42 to 91 days, 92 to 182 days, 183 to 273 days, and 274 or more days of age were 2.4, 7.8, 9.6, 18.3, and 46.6, respectively (Table 2). There was no association between the time of receipt of the first dose of hepatitis B vaccine and the likelihood of not completing the 4:3:1:3 vaccine series among children who received the first dose at 0 to 7 days or at 8 to 41 days or 42 to 91 days of age. However, compared with children who received the first dose of hepatitis B vac-

### Table 1. Age at Receipt of First Dose of Hepatitis B Vaccine and Percentage of Children Completing the Hepatitis B Vaccine Series and the 4:3:1:3 Vaccine Series Among Children 19 to 35 Months of Age Who Received at Least 1 Dose of Hepatitis B Vaccine*

<table>
<thead>
<tr>
<th>Age at Receipt of First Dose of Hepatitis B Vaccine, d</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7</td>
<td>54.6 (53.5-55.7)</td>
</tr>
<tr>
<td>8-41</td>
<td>21.4 (20.5-22.3)</td>
</tr>
<tr>
<td>42-91</td>
<td>17.5 (16.6-18.3)</td>
</tr>
<tr>
<td>92-182</td>
<td>3.0 (2.6-3.5)</td>
</tr>
<tr>
<td>183-273</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>≥274</td>
<td>2.3 (2.0-2.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatitis B Vaccine series</th>
<th>% of children with ≥3 doses (95% CI)</th>
<th>96.3 (95.7-96.8)</th>
<th>91.7 (90.4-92.9)</th>
<th>73.5 (71.7-75.9)</th>
<th>72.5 (66.4-78.7)</th>
<th>56.1 (45.9-66.3)</th>
<th>35.7 (28.5-42.9)</th>
<th>89.4 (88.7-90.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% value†</td>
<td>...</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>...</td>
</tr>
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<table>
<thead>
<tr>
<th>4:3:1:3 Vaccine series</th>
<th>% of children with 4:3:1:3 series up-to-date (95% CI)</th>
<th>81.1 (80.0-82.3)</th>
<th>82.2 (80.3-84.1)</th>
<th>81.1 (78.9-83.3)</th>
<th>68.6 (62.2-75.1)</th>
<th>48.6 (38.3-58.8)</th>
<th>49.6 (41.9-57.4)</th>
<th>79.9 (79.0-80.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% value‡</td>
<td>...</td>
<td>.36</td>
<td>.98</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>...</td>
</tr>
</tbody>
</table>

*Ci indicates confidence interval.
†P value for the t test comparing the percentage of children with 3 or more doses of hepatitis B vaccine in the respective group with that among children who received the first dose of hepatitis B vaccine within 0 to 7 days after birth.
‡P value for the t test comparing the percentage up-to-date with the 4:3:1:3 vaccine series in the respective group with that among children who received the first dose of hepatitis B vaccine within 0 to 7 days after birth.
cine at 0 to 7 days, the ORs for not completing the 4:3:1:3 vaccine series among children who received the first dose at 92 to 182 days, 183 to 273 days, and 274 or more days of age were 1.7, 3.8, and 4.0, respectively.

Among children who had received the first dose of hepatitis B vaccine within 91 days of age, 90% also received the first dose of DTP/DTaP vaccine between 42 to 91 days of age, whereas among children who received the first dose of hepatitis B vaccine after 91 days of age, 33% received the first dose of DTP/DTaP between 42 and 91 days of age.

**COMMENT**

An advantage of administering the first dose of hepatitis B vaccine during the neonatal period, before the child is discharged from the hospital, is initiating the 3-dose hepatitis B vaccination series at the earliest contact with the child and therefore preventing this encounter from becoming a missed opportunity. Administering hepatitis B vaccine to all newborns at birth also ensures that children born to mothers with chronic HBV infection receive prophylaxis against hepatitis B infection. Our assessment of the immunization status of children 19 to 35 months of age in 1998 indicated that administration of the hepatitis B vaccine at birth is becoming incorporated in neonatal care practice in the United States. Receiving the first dose at birth is associated with increased likelihood of completing the 3-dose hepatitis B vaccination series.

Hepatitis B vaccine is the first vaccine for which the recommended schedule options include initiation of vaccination neonatally before the child is discharged from the hospital. Given the previous unfamiliarity of hospital nursery staff with routine vaccination practices, it is encouraging that within a few years of publication of the recommendations, approximately half of newborns currently receive the vaccine at birth. In some states, the vast majority (>70%) of children receive their first dose of hepatitis B vaccine at birth. The state-specific variation in the percentage of children who received the first dose of hepatitis B vaccine at birth is probably partially influenced by the extent of advocacy carried out by state and local health department immunization programs and hepatitis prevention programs.13 The percentage of children receiving hepatitis B vaccination at birth in a state or area also depends on the policies and practices of birthing hospitals serving the respective population. Children born in hospitals that do not have a written policy for offering hepatitis B vaccination to all newborns are several times more likely to not receive the first dose of hepatitis B vaccination before being discharged from the hospital than...
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children born in hospitals with such written policies.13

The significant association between age at administration of the first dose of hepatitis B vaccine and completion of the 3-dose series may reflect clinician concerns about parental resistance to multiple injections during a single visit.14-16 Administering the first dose at birth reduces the number of hepatitis B vaccine injections that need to be administered concurrently with other vaccines during future well-child care visits and therefore may make series completion more acceptable to both providers and parents. In addition, as the only vaccine that can be given to newborns before hospital discharge, initiating hepatitis B vaccination at this age may help emphasize the importance of this vaccine to parents and well-child-care providers.5

It is unclear why the percentage completing the hepatitis B vaccination series was successively lower among children who received the first dose at 8 to 41, 42 to 91, 92 to 182, 183 to 273, and 274 or more days of age. The earliest age at which children are eligible to receive other routinely recommended vaccines (ie, DTaP, Hib, and polio vaccines) is 42 days. Perhaps receipt of the first dose at 8 to 41 days of age indicates that providers and/or parents of these children place more importance on hepatitis B vaccination than parents and/or providers who wait until the child is 42 to 91 days of age. In addition, children receiving the first dose of hepatitis B vaccine at 92 days of age or later are likely to be late starters for other immunizations such as DTaP/DTaP. It is likely that factors other than age at hepatitis B vaccine initiation influenced these children’s likelihood of completing the 4:3:1:3 vaccine series. Also, children who receive their first dose of hepatitis B vaccine at 92 days of age or later were more likely to be late starters for other immunizations including the 4:3:1:3 vaccine series. The fact that the age of administering the first dose of hepatitis B vaccine and likelihood of completing the 4:3:1:3 vaccine series. Several limitations may influence interpretation of these findings. First, the NIS is an RDD telephone survey and does not obtain information from households that do not have telephones. However, the NIS data are weighted to account for children in households without telephones using data from the National Health Interview Survey, which is a face-to-face interview survey among nationally representative sample of noninstitutionalized individuals in the United States. Data are also adjusted to account for household and provider nonresponse. These adjustments help to make NIS coverage estimates nationally representative.

Another limitation is that we may not have controlled for all confounders. Immunization coverage among children can be influenced by many factors, including those related to access to health care, knowledge, attitudes and practices of providers and parents, and sociodemographic characteristics.18-21 In examining the independent association between age at administration of the first dose and completion of the 3-dose hepatitis B vaccine series and the 4:3:1:3 vaccine series, we were unable to adjust for all of these factors. Since we used SUDAAN for multivariate analysis, we also did not have a goodness-of-fit measure. However, in our analysis, we were able to assess several demographic and socioeconomic characteristics, and those that affected the relationship between the time of administering the first dose of hepatitis B vaccine and completing the 3-dose hepatitis B vaccine series or the 4:3:1:3 vaccine series were included in the multivariate models. Even after controlling for these confounders, the ORs for not completing the hepatitis B vaccine series were large with relatively narrow CIs. In addition, if the association between age of administering the first dose and likelihood of completing the hepatitis B vaccine series was entirely due to unidentified confounders that affect the likelihood of receiving vaccines in general, we would expect to see the same relationship between age of administering the first dose of hepatitis B vaccine and likelihood of completing the 4:3:1:3 vaccine series. The fact that the age of administering the first dose of hepatitis B vaccine is not associated with 4:3:1:3 series completion among children who receive the first dose within 91 days of age indicates that such unidentified confounders probably cannot fully account for the association with hepatitis B series completion.

Universal infant hepatitis B vaccination is the most important component of the overall strategy to eliminate HBV transmission from the United States. Maintaining high hepatitis B vaccination coverage levels among US children will protect successive birth cohorts. The likelihood that children receive 3 doses of hepatitis B vaccine is greater among those infants receiving their first dose at birth. Because of this and other advantages, providers should strongly consider a hepatitis B vaccination schedule that initiates vaccination at birth.

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