Impact of Thimerosal-Related Changes in Hepatitis B Vaccine Birth-Dose Recommendations on Childhood Vaccination Coverage

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Context In July 1999, the longstanding preference to begin hepatitis B vaccination of all US infants at birth was temporarily suspended because of concerns about exposure to mercury contained in the vaccine preservative thimerosal. The suspension was lifted in September 1999 when preservative-free hepatitis B vaccine became available.

Objective To determine the effects of changes in recommendations regarding administration of a hepatitis B birth dose on vaccination coverage.

Design, Setting, and Participants Cohort analysis of vaccination status of 41589 US children born before, during, and after the recommendation to suspend the birth dose.

Main Outcome Measures Association between birth cohort and age at receipt of hepatitis B vaccine dose 1, and receipt by 19 months of age of all recommended vaccines.

Results The proportion of US infants who received dose 1 of hepatitis B vaccine at birth declined from 47% among those born 7 to 12 months before the suspension to 11% among those born during the suspension. Birth-dose coverage remained significantly lower in the year after the suspension was lifted (23% in the first 6 months and 33% in months 7-12). Coverage with 3 doses of hepatitis B vaccine by 19 months of age declined from 88% among those born 7 to 12 months before the suspension to 81% among those born during the suspension and 85% among those born in the 6 months after the suspension, but returned to baseline levels for those born 7 to 12 months after the suspension was lifted. These reductions represent 750 000 fewer newborns vaccinated during 2000 compared with 1998, and an excess 182 000 children undervaccinated for hepatitis B at 19 months of age compared with 1998 coverage levels. Coverage with other recommended vaccinations did not decline over this time.

Conclusions Reductions in hepatitis B vaccine birth-dose coverage persisted after recommendations were made to resume previous newborn vaccination practices. Although the recommendation to complete the series by 19 months of age was never changed, infants born between July and December 1999 were less likely to have completed the series by 19 months, compared with infants born during the previous year. The lack of impact on other vaccinations suggests that public confidence in immunization remained strong.

In 1999, the US Food and Drug Administration determined that some newborns could be exposed to levels of ethyl mercury from the vaccine preservative thimerosal that exceeded some federal guidelines for mercury. These

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guidelines were derived from methyl mercury exposure data; no specific guidelines for ethyl mercury existed, and no adverse health effects from ethyl mercury in vaccines had been identified.10,11 However, some authorities expressed concerns about potential health problems and loss of public confidence in vaccination policies unless action was taken immediately.6 As a precautionary measure, the American Academy of Pediatrics (AAP) and the US Public Health Service (USPHS) established the goal of reducing or eliminating thimerosal in pediatric vaccines. On July 9, 1999, the AAP and the USPHS issued a Joint Statement on Thimerosal in Vaccines,7 which advised clinicians to temporarily postpone the first dose of hepatitis B vaccine from birth until 2 to 6 months of age for infants born to HBsAg-negative women. The suspension was suspended for infants born before, during, and after the recommendation changes on vaccination coverage of children born before, during, and after these changes included in multiple NIS survey years.

Figure 1. Month of Birth for Children in the 2001 and 2002 National Immunization Surveys and Birth Cohorts Relative to the Suspension of the Birth Dose of Hepatitis B Vaccine

METHODS

National Immunization Survey

The NIS uses random-digit-dialing to survey households with children aged 19 to 35 months, followed by a mail survey to the children’s vaccination providers to validate vaccination information. Subjects provided verbal consent. Analysis of NIS data is based on households with a completed interview (Council of American Survey Research Organizations [CASRO] response rates: 76.1% in 2001, 74.2% in 2002) and adequate provider data. These strategies include poststratification so that totals match Vital Statistics estimates for each state with respect to maternal education, race/ethnicity, and age group of the child,23,24 accounting for households without telephones by weighting those with interruption in telephone service,25 and using response propensity to adjust for vaccination provider nonresponse.26 Details of the NIS methods, including institutional review board approval for analysis of NIS data, appear elsewhere.23,24

Definitions

Five birth cohorts were defined relative to the period when the hepatitis B birth-dose recommendation was suspended for infants born to HBsAg-negative mothers. The suspension was in effect only for children born July through September 1999. For the current analysis, this timeframe was extended through the end of 1999 to account for time necessary to distribute reformulated vaccine and reinstate birth-dose policies. Thus, children born in July through December 1999 were defined as born “during the suspension” of the birth-dose recommendation for hepati-
Hepatitis B vaccine. Children born in the year before and the year after this suspension period were also studied in 6-month birth intervals. In total, this analysis includes 41,589 children in the 2001 and 2002 NIS who were born July 1, 1998, through December 31, 2000. Figure 1 illustrates the birth months included in these NIS years, as well as the timeline of hepatitis B birth-dose recommendation changes and the definition of birth cohorts used for this analysis.

Age at receipt of the first dose of hepatitis B vaccine was partitioned into 5 mutually exclusive categories based on ACIP recommendations: 1 day, 2 to 7 days, 8 days to 2 months, 3 to 6 months, and not by 6 months. Administration of the first dose within 12 hours of birth is recommended to prevent perinatal transmission of HBV; however, the NIS does not contain information on time of birth or time of vaccination. Therefore, we defined the birth dose as a dose administered on the same date as birth or the following date ("1 day"). To account for infants who remain in the hospital several days after birth but are vaccinated before discharge, a first dose administered after the first day but within 7 days was defined as "2 to 7 days." Vaccination guidelines in effect before and after the thimerosal-related changes called for administration of the first dose of hepatitis B vaccine by age 2 months for all children. During the suspension, the recommended timeframe for administration of the first dose was extended to 6 months of age. Thus, "on-time" vaccination was defined as receipt by 2 months for those born before or after the suspension and receipt by 6 months for those born during the suspension.

To determine the effect of the birth-dose suspension on the overall vaccination program, we examined the association between birth cohort and coverage by 19 months of age for other vaccinations that are routinely recommended during the first 18 months of life. These include 4 doses of diphtheria-tetanus toxoids-acellular pertussis (DTaP) vaccine, 3 doses of poliovirus vaccine, 1 dose of measles-mumps-rubella (MMR) vaccine, 3 doses of Haemophilus influenzae type b (Hib) vaccine, and 1 dose of varicella vaccine, in addition to the 3-dose hepatitis B vaccine series.27,28 Receipt of the 4:3:1:3 series (4 doses of DTaP, 3 doses of poliovirus vaccine, 1 dose of measles-containing vaccine, and 3 doses of Hib) was also examined.

To describe factors associated with hepatitis B vaccination, various characteristics of the child, mother, and immunization providers were evaluated. In the household survey portion of the NIS, parents or caregivers reported race/ethnicity of the child, number of children in the household, and mother's marital status, age, and education level. Poverty status was determined on the basis of household size, composition, and income reported by the survey respondent, as defined by the US Census Bureau.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Birth cohort relative to vaccine suspension</th>
<th>Maternal age, y</th>
<th>Maternal education</th>
<th>No. of vaccination providers</th>
<th>Type of vaccination provider</th>
<th>Urbanicity</th>
<th>Census region</th>
<th>Poverty status</th>
<th>No. of children in household</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-12 mo before†</td>
<td>≤19</td>
<td>&lt;High school</td>
<td>1</td>
<td>Private</td>
<td>Urban</td>
<td>Northeast</td>
<td>At or below</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6 mo before‡</td>
<td>20-29</td>
<td>High school</td>
<td>≥2</td>
<td>Public</td>
<td>Suburban</td>
<td>Midwest</td>
<td>Above</td>
<td>≥2</td>
</tr>
<tr>
<td></td>
<td>During§</td>
<td>≥30</td>
<td>Some college</td>
<td></td>
<td>Other</td>
<td>Rural</td>
<td>South</td>
<td>Below</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo after¶</td>
<td></td>
<td>College graduate</td>
<td></td>
<td></td>
<td></td>
<td>West</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-12 mo after¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

*Data from 2001-2002 National Immunization Surveys. Percentages based on weighted data; sample sizes for provider type and poverty status do not sum to 41,589 due to missing responses. All variables in table were included in the multivariate analysis.

§Children born July 1, 1999, through December 31, 1999.
¶Children born July 1, 2000, through December 31, 2000.
#Confidence interval does not include 1.00 when carried out to more than 1 decimal place.
dose on the first day. First-day coverage decreased to 11% among children born during the suspension. For children born in the 6 months after and in months 7 to 12 after the suspension, first-day coverage was 23% and 33%, respectively ($P < .001$ and $P < .001$ compared with baseline at months 7-12 before the suspension).

Receipt of the first dose on time (ie, by 2 months of age for children born before or after the suspension or by 6 months of age for children born during the suspension) varied by birth cohort (Figure 2). Among children born 7 to 12 months or within 6 months before the suspension, 93% and 92%, respectively, received their first dose of hepatitis B vaccine on time. Among children born in the 6 months after or 7 to 12 months after the suspension, on-time receipt of the first dose decreased to 82% and 89%, respectively ($P < .001$ and $P = .001$ compared with the baseline period). Among children born during the suspension, 89% received their first dose by 6 months. While administration of the first dose at 3 to 6 months of age was considered on time only for children born during the suspension, this practice was more common among those born after the suspension than at baseline ($P < .001$).

Completion of the recommended 3-dose hepatitis B vaccine series by 19 months of age also varied by birth cohort (Table 1). Although 88% of children born 7 to 12 months before the suspension received at least 3 doses by 19 months of age, only 81% of children born during the suspension did ($P < .001$). Compared with the baseline period, coverage with at least 3 doses by 19 months of age remained significantly lower for children born in the 6 months after the suspension (85%, $P = .02$), but was not significantly lower for those born 7 to 12 months after the suspension (87%, $P = .82$).

The percentage of children who had not received any doses of hepatitis B vaccine by 19 months of age was 1.0% and 1.3% among children born 7 to 12 months before and in the 6 months before the suspension, respectively, but increased to 2.0% for children born during the suspension ($P < .001$ compared with baseline) (Table 1). The percentage who did not receive any doses decreased again for children born in the 6 months after and months 7 to 12 after the suspension (1.3%, $P = .23$, and 1.0%, $P = .85$, respectively, compared with baseline).

With more than 4 million infants born in the United States each year, the estimated decline of 7 percentage points in 3-dose hepatitis B vaccination coverage among children born during the 6 months surrounding the suspension and 3 percentage points in the following 6 months represent an excess 182000 children in the United States who were either undervaccinated or unvaccinated against HBV at 19 months of age. Similarly, reductions of 14 to 24 percentage points in birth-dose coverage after the suspension represent approximately 750000 fewer newborns vaccinated during 2000 compared with 1998.

In multivariate analysis, children born during the suspension or in the 12 months after were less likely to receive the birth dose, after controlling for other factors (Table 1). Other significant factors associated with not receiving the birth dose included having a mother who was more than 30 years old, having only 1 provider, having a private provider, living in a suburban area, or living in a household with no other children. Children born during the suspension or in the 6 months after were also significantly less likely to receive 3 doses of hepatitis B vaccine by 19 months of age, after controlling for other factors. However, the other factors associated with undervaccination at 19 months of age differed from those associated with not receiving the birth dose, including having a mother who was 20 to 29 years old or unmarried, having 2 or more vaccination providers, living in an urban area, or living in a family with more than 1 child.

Children born during the suspension were more likely to be unvaccinated (ie, to have received 0 doses of hepatitis B vaccine by 19 months of age) compared with those born 7 to 12 months before the suspension, as were children living in an urban area or in the western region of the United States. Interactions between birth cohort and other factors were examined, but we found none that we believed to be of public health importance.

Coverage by 19 months of age for the recommended doses of DTaP, MMR, and Hib vaccines and the 4:3:1:3 series did not vary significantly by birth cohort (Table 2). Coverage with poliovirus and varicella vaccines increased among the later birth cohorts.

**COMMENT**

This is the first evaluation to our knowledge of how US childhood vaccination coverage was affected by rapid changes in hepatitis B vaccine recommendations related to thimerosal safety concerns. While newborn first-day coverage with hepatitis B vaccine had reached 47% by late 1998, this fell to 22% to 33% in 2000, after the birth-dose suspension was lifted. This reduction represents 750000 fewer newborns vaccinated during 2000 compared with 1998.

Seroprevalence surveys involving many thousands of children would be necessary to determine if increased rates of perinatal and early childhood HBV infection occurred due to reductions in birth-dose hepatitis B vaccination, because HBV infections in infants and young children are usually asymptomatic. Each year, an estimated 20000 HBsAg-positive women give birth in the United States and are at risk of transmitting HBV infection to their infants. Despite the availability of effective testing and prevention methods, an estimated 900 to 1100 infants are infected with HBV in the United States annually. Consequences of these infections may not be apparent for decades. However, studies have shown that 90% of those infected at birth will develop chronic HBV infection and 25% will die of liver disease as adults. While only 5% of HBV infections are acquired during the perinatal period, perinatal infections account for an es-
timated 34% of chronic HBV infections among adults in the United States. 38

In addition to preventing the majority of perinatal infections, providing a birth dose of hepatitis B vaccine to all newborns sets the stage for timely completion of the vaccination series and prevention of HBV infection during childhood. Mathematical models indicate that, without childhood hepatitis B vaccination, an additional 187000 non-perinatal HBV infections would have occurred by age 10 years among children born in 1998 alone. 39 As many as 60% of those infected before 2 years of age, and 25% of those infected between ages 2 and 9 years, develop chronic HBV infection. 36,40 Furthermore, we found that infants who received a birth dose were more likely to have risk factors for not completing the 3-dose series by 19 months of age, suggesting that decreased birth-dose coverage could disproportionately affect infants at high risk for undervaccination.

No changes were made in recommendations for completing the 3-dose hepatitis B vaccine series before 19 months of age. However, in addition to declines in birth-dose coverage, significant reductions in 3-dose coverage occurred among children born within the year (July 1999-June 2000) after the release of the Joint Statement on Thimerosal in Vaccines. These declines occurred after 6 consecutive years of increasing 3-dose hepatitis B vaccine coverage and despite increasing or sustained coverage levels for other vaccines. While it is encouraging that these declines were small and that 3-dose coverage rebounded among children born in the second half of 2000, even the temporary decline in coverage among children born during the suspension and the following 6 months represents an excess 182000 children in the United States who were undervaccinated and potentially unprotected against HBV infection when compared with 1998 coverage levels.

This analysis has several limitations. First, no information is available in the NIS regarding HBsAg status of mothers. This information would allow evaluation of the number of children at risk for perinatal transmission who did not receive the birth dose of hepatitis B vaccine. Furthermore, the number of children born during the suspension or in the year after who were infected with HBV perinatally or during early childhood is unknown because HBV infection in infants and young children is usually asymptomatic and therefore not reported. Second, because no information regarding time of birth or time of vaccination was available, the birth dose was defined as a dose given on the same date as birth or the following date. Thus, some children who were considered to have received the dose during day 1 of life may have received it up to 47 hours after birth. Third, by combining 2 years of survey data, we assume no secular trends in variables used in the weighting methodology. To minimize potential secular trends, only 2 years of data were used, although some children in the 2000 and 2003 NIS were born during our analysis period. Unweighted results were similar to those presented here, providing no evidence of substantial bias caused by the weighting methodology. Fourth, information on infant medical conditions that might cause appropriate delays in administration of the birth dose, such as birth weight less than 2000 g, were not available. However, few infants are born below this weight, and low birth weight was not likely to be more common among cohorts born after the thimerosal controversy than among those born before. 41,42

Despite the published preference by the ACIP and the AAP for initiation of the hepatitis B vaccine series at birth for all infants, and the availability of pediatric hepatitis B vaccines that no longer contain preservatives, increasing birth-dose coverage may be difficult. Challenges in tracking and reimbursement are barriers to giving the birth dose in hospitals, 43 as is a growing preference among pediatricians for multiple-antigen vaccinations, which cannot be given at birth. 44 However, administration of a single-antigen hepatitis B birth dose followed by combination vaccines for subsequent doses is safe and effective. The resulting 4-dose hepatitis

### Table 2. Percentage of Children Who Received Selected Vaccinations by 19 Months of Age, by Birth Cohort

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>7-12 mo Before Suspension, % (95% CI)</th>
<th>6 mo Before Suspension, % (95% CI)</th>
<th>6 mo After Suspension, % (95% CI)</th>
<th>7-12 mo After Suspension, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-12 mo Before Suspension, % (95% CI)</td>
<td>6 mo Before Suspension, % (95% CI)</td>
<td>6 mo After Suspension, % (95% CI)</td>
<td>7-12 mo After Suspension, % (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis B (3)</strong></td>
<td>87.7 (86.3-89.1)</td>
<td>86.3 (85.1-87.4)</td>
<td>81.1 (79.9-82.3)</td>
<td>85.2 (83.9-86.6)</td>
</tr>
<tr>
<td><strong>Diphtheria-tetanus toxoids-acellular pertussis (4)</strong></td>
<td>65.8 (63.9-67.8)</td>
<td>68.9 (67.4-70.3)</td>
<td>67.5 (66.0-68.9)</td>
<td>66.4 (64.7-68.0)</td>
</tr>
<tr>
<td><strong>Poliovirus (3)</strong></td>
<td>79.2 (77.5-80.9)</td>
<td>80.7 (79.4-82.0)</td>
<td>81.5 (80.3-82.6)</td>
<td>82.3 (81.0-83.7)</td>
</tr>
<tr>
<td><strong>Measles-mumps-rubella (1)</strong></td>
<td>85.2 (83.8-86.7)</td>
<td>86.7 (85.7-87.8)</td>
<td>85.5 (84.4-86.6)</td>
<td>86.9 (85.6-88.2)</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae type b (3)</strong></td>
<td>90.4 (89.1-91.7)</td>
<td>91.4 (90.5-92.2)</td>
<td>90.7 (89.8-91.6)</td>
<td>90.2 (89.1-91.4)</td>
</tr>
<tr>
<td><strong>Varicella (1)</strong></td>
<td>65.9 (64.0-67.8)</td>
<td>73.2 (71.8-74.6)</td>
<td>73.6 (72.2-74.9)</td>
<td>77.2 (75.7-78.7)</td>
</tr>
<tr>
<td><strong>Diphtheria-tetanus toxoids-acellular pertussis, 3 poliovirus, 1 measles-containing, 3 Haemophilus influenzae type b</strong></td>
<td>60.4 (58.5-62.4)</td>
<td>63.5 (62.0-65.0)</td>
<td>61.9 (60.4-63.3)</td>
<td>61.8 (60.1-63.5)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Data from 2001-2002 National Immunization Surveys. Percentages based on weighted data.
§Children born July 1, 1999, through December 31, 1999.

*P* Test for differences between birth cohorts.

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tis B vaccine series is recommended by the ACIP, and eligible children can be given all 4 doses using vaccines purchased by the Vaccines for Children Program. Hospitals and birthing centers can restore the safety net provided by the birth dose by (1) reinstating or initiating policies to provide hepatitis B vaccine to all newborns; (2) providing information on the most recent hepatitis B vaccination recommendations to parents and health care workers in newborn nurseries; (3) working with health care professionals and parents to integrate the birth dose into schedules based primarily on combination vaccines; and (4) exploring ways to facilitate information tracking, such as immunization registries.

Although thimerosal-related changes in hepatitis B recommendations were implemented quickly, unintended consequences did result. These included the long-term reduction of birth-dose coverage and reduction in 3-dose coverage for children born in the year after the birth-dose suspension, as described in this analysis, as well as reports of transmission of HBV to unvaccinated children born to HBsAg-positive mothers and greatly reduced birth-dose coverage among infants born to women whose HBsAg status was unknown. The risk to newborns of exposure to the quantities of mercury present in the thimerosal that was previously used in hepatitis B vaccine remains uncertain.

Concerns about thimerosal in vaccines roughly coincided with 2 widely reported vaccine safety-related events. In 1998, Wakefield et al proposed a relationship between MMR and autism that received extensive media attention, although the association was refuted by other investigators. Second, during the period covered by this study, the relationship between rotavirus vaccine and intussusception was confirmed, and the recommendation for use of the vaccine was rescinded in July 1999. Despite media reporting of vaccine-related controversies, 3-dose hepatitis B vaccine coverage rebounded, and no measurable declines occurred in other vaccines in the birth cohorts of this analysis. This suggests that, despite some concerns, public confidence in immunization remained strong.

Effective communication messages are a critical component of rapid changes in vaccination recommendations. Careful assessment of the communication strategies used during and after the suspension of the birth dose of hepatitis B vaccine may provide insights for developing general strategies for disseminating rapid changes in vaccine recommendations, whether due to safety concerns, shortages, or changes in disease incidence.

Author Contributions: As principal investigator, Ms Luman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Luman, Fiore, Strine, Barker. Analysis and interpretation of data: Luman, Fiore. Drafting of the manuscript: Luman, Fiore, Strine. Critical revision of the manuscript for important intellectual content: Luman, Fiore, Barker. Statistical expertise: Luman. Supervision: Barker.

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Role of the Sponsor: This study, including design and conduct, data collection, analysis and interpretation of the data, and manuscript preparation, review, and approval was conducted under the auspices of HHS/CDC. The CDC gave final approval of the manuscript.

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HEPATITIS B VACCINE BIRTH-DOSE RECOMMENDATIONS AND COVERAGE


The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds.

—John Maynard Keynes (1883-1946)