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 750000 fewer newborns vaccinated during 2000 compared with 1998, and an excess 182000 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.

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PREVENTING PERINATAL AND early childhood infections by providing hepatitis B vaccine to infants beginning at birth is safe, effective, and an important component of the comprehensive strategy to eliminate hepatitis B virus (HBV) transmission in the United States. In 1991, the Advisory Committee on Immunization Practices (ACIP) recommended that all children receive 3 doses of hepatitis B vaccine by 19 months of age. The first dose should be administered within 12 hours of birth to infants whose mothers are hepatitis B surface antigen (HBsAg)–positive or of unknown HBsAg status; vaccination at birth of children of HBsAg-negative mothers is preferred but should not be delayed beyond the age of 2 months.[1] In practice, routine vaccination of all infants at birth serves as a safety net, providing immunoprophylaxis to infants born to women with unsuspected HBV infection or HBsAg-positive women whose status is incorrectly recorded or interpreted as negative. Infants who receive hepatitis B vaccine at birth are also more likely to complete the 3-dose hepatitis B vaccine series on time[2] and may be more likely to receive other recommended vaccinations on time, although findings have not been consistent.[2,3]

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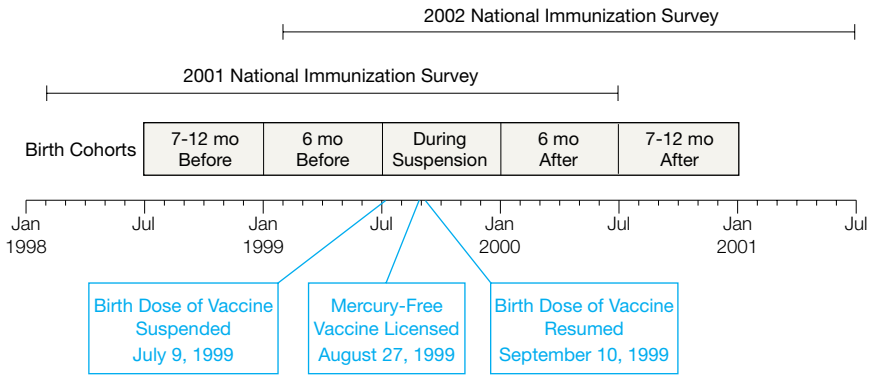
Figure 1. Month of Birth for Children in the 2001 and 2002 National Immunization Surveys and Birth Cohorts Relative to the Suspension of the Birth Dose of Hepatitis B Vaccine



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.[4,5] 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. After licensure of hepatitis B vaccines that did not contain thimerosal as a preservative, recommendations to resume previous birth-dose practices were issued on September 10, 1999.[8] Supplies sufficient to vaccinate all newborns with preservative-free vaccine were available shortly thereafter.[9] Hospital surveys conducted in late 1999 and early 2000 indicated that routine hepatitis B vaccination of newborns did not immediately resume after preservative-free vaccine became widely available, and thimerosal-related vaccination recommendations were sometimes misinterpreted or improperly implemented.[10-14] However, the impact of the recommendation changes on vaccination coverage has not been evaluated.

Data on vaccination coverage among children aged 19 to 35 months in the United States are obtained annually from the National Immunization Survey (NIS). Coverage with 3 doses of hepatitis B vaccine increased each survey year from 1994 to 2000 (37%, 68%, 82%, 84%, 87%, 88%, and 90% respectively).[15-21] In 2001, however, coverage decreased slightly to 89%[22] ($P=.004$ compared with 2000). The percentage of children receiving dose 1 within 1 day of birth also increased from 43.4% in the 1999 NIS to 46.2% in the 2000 NIS, and then declined to 34.7% in the 2001 NIS ($P<.001$ compared with 2000). However, the full effects of the thimerosal-related recommendation changes are likely to be obscured in previously published results because each year's NIS data include children born during a 28-month period, with children who were born before, during, and after these changes included in multiple NIS survey years.

We conducted a birth cohort analysis using the 2001 and 2002 NIS surveys. This approach allowed us to compare vaccination coverage of children born before, during, and after the release of the Joint Statement on Thimerosal in Vaccines and subsequent recommendation changes. We evaluated both the immediate and residual impact of the suspension of the birth dose of hepatitis B vaccine on vaccination coverage.

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 vaccination history (70.4% in 2001, 67.6% in 2002). The NIS uses a variety of weighting strategies to reduce bias and to ensure that all children in the United States are represented by children with 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 propensities 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-

tis 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.

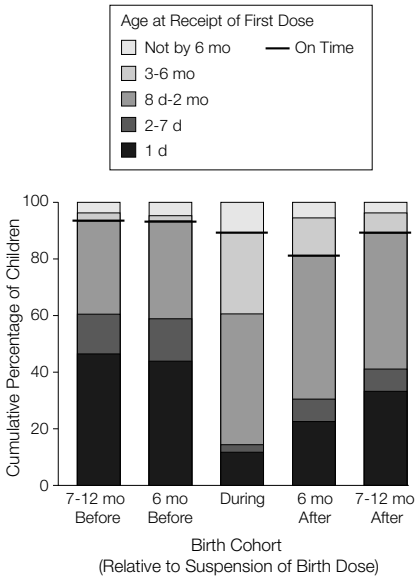
To describe factors associated with hepatitis B vaccination, various characteristics of the child, mother, and immunization providers were evaluated. In the household survey portion of the NIS, parents or caregivers reported race/ethnicity of the child, number of children in the household, and mother's 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.[29] Urbanicity (urban, suburban, and rural) was determined by respondents' telephone area code/exchange.[30] Census region was based on respondents' state of residence, as defined by the US Census Bureau.[31] Health care facility type (public, private, or other/mixed) was reported by the immunization providers. The number of providers was based on the number of usable vaccination records submitted for the child.

Analysis

Estimates of coverage rates, odds ratios, and standard errors were calculated using SUDAAN, version 8.0,[32] and χ^2 tests were conducted to assess the associations between birth cohort, age at receipt of the first dose of hepatitis B vaccine, and receipt of vaccinations by 19 months of age. The level of significance was set a priori at .05. Children born in months 7 to 12 before the suspension of the birth-dose recommendation were considered baseline for comparisons. Adjustments were not made for multiple comparisons because the a priori hypothesis was that there would be differences in coverage rates between those born before the suspension and those born during and after the suspension. Multivariate logistic regression models were constructed to evaluate the effect of birth cohort, along with sociodemographic factors, on receipt of the birth dose and undervaccination for hepatitis B vaccine at 19 months of age.

The magnitude of the public health impact of the changes in vaccination practices was estimated by applying the coverage estimates to the US infant population. We compared the number of infants in the United States who were unvaccinated or incompletely vaccinated against HBV during the suspension and in the year after to what would have been expected had late 1998 coverage levels been maintained.

Figure 2. Age at Receipt of First Dose of Hepatitis B Vaccine by Birth Cohort, 2001 and 2002 National Immunization Surveys



Comparison of cumulative percentage of children who were vaccinated on time and by each age cutoff. The thick black horizontal line represents children who received their first dose of hepatitis B vaccine on time (ie, by 2 months for those born before or after the suspension, by 6 months for those born during the suspension).

RESULTS

The percentage of children who received a dose of hepatitis B vaccine on the day of birth or the day after birth ("1 day") varied substantially by cohort (FIGURE 2 and TABLE 1). In the year before the suspension, more than 40% of children received a hepatitis B vaccine

Table 1. Factors Associated With Receipt of Hepatitis B Vaccine: Birth Dose, 3 Doses by 19 Months of Age, and 1 or More Doses by 19 Months of Age*

Factor	Unweighted Sample Size	Birth Dose		3 Doses by 19 mo of Age		≥1 Doses by 19 mo of Age	
		Bivariate, % (95% CI)	Multivariate, OR (95% CI)	Bivariate, % (95% CI)	Multivariate, OR (95% CI)	Bivariate,% (95% CI)	Multivariate, OR (95% CI)
Birth cohort relative to vaccine suspension							
7-12 mo before†	5968	46.6 (44.7-48.6)	Reference	87.7 (86.3-89.1)	Reference	99.0 (98.6-99.4)	Reference
6 mo before‡	9666	43.6 (42.1-45.1)	0.9 (0.8-1.0)	86.3 (85.1-87.4)	0.8 (0.7-1.0)#	98.7 (98.4-99.0)	0.8 (0.5-1.2)
During§	11 458	11.2 (10.3-12.1)	0.1 (0.1-0.2)	81.1 (79.9-82.3)	0.6 (0.5-0.7)	98.0 (97.6-98.5)	0.6 (0.4-0.9)
6 mo after‖	9224	22.6 (21.3-23.9)	0.3 (0.3-0.4)	85.2 (83.9-86.6)	0.8 (0.6-0.9)	98.7 (98.4-99.0)	0.8 (0.5-1.4)
7-12 mo after¶	5273	32.8 (30.7-34.9)	0.6 (0.5-0.6)	87.5 (85.9-89.0)	0.9 (0.8-1.1)	99.0 (98.5-99.4)	1.0 (0.5-1.9)
Race of child							
White	24 947	28.4 (27.6-29.2)	Reference	85.8 (85.1-86.5)	Reference	98.6 (98.3-98.8)	Reference
Black	6070	30.6 (28.6-32.6)	1.0 (0.9-1.2)	81.6 (80.0-83.3)	0.9 (0.8-1.1)	98.6 (98.1-99.1)	0.9 (0.6-1.4)
Hispanic	8214	28.8 (27.2-30.4)	1.0 (0.9-1.1)	84.8 (83.4-86.2)	1.1 (1.0-1.3)	98.7 (98.3-99.1)	1.2 (0.8-1.9)
Other	2358	26.3 (23.5-29.1)	0.9 (0.8-1.1)	85.2 (82.3-88.0)	0.9 (0.7-1.2)	98.5 (97.7-99.3)	1.0 (0.5-1.8)
Maternal age, y							
≤19	1209	31.4 (27.3-35.5)	1.2 (1.0-1.6)	85.5 (81.9-89.2)	0.9 (0.6-1.2)	99.4 (99.0-99.8)	1.5 (0.7-3.2)
20-29	17 681	31.1 (30.0-32.1)	1.2 (1.1-1.3)	83.2 (82.2-84.2)	0.8 (0.8-0.9)	98.7 (98.4-98.9)	1.1 (0.8-1.4)
≥30	22 699	26.5 (25.6-27.4)	Reference	86.4 (85.7-87.1)	Reference	98.5 (98.2-98.7)	Reference
Maternal education							
<High school	5262	29.8 (27.9-31.7)	1.1 (0.9-1.2)	83.5 (81.8-85.1)	0.9 (0.8-1.1)	98.8 (98.4-99.2)	1.7 (1.0-3.0)
High school	12 330	30.4 (29.2-31.6)	1.1 (1.0-1.2)	84.0 (82.9-85.1)	0.9 (0.8-1.0)	98.8 (98.5-99.1)	1.6 (1.1-2.3)
Some college	7391	29.6 (27.9-31.2)	1.1 (1.0-1.3)#	83.7 (82.2-85.1)	0.9 (0.7-1.0)#	98.6 (98.1-99.0)	1.3 (0.8-1.9)
College graduate	16 606	25.9 (24.9-26.8)	Reference	87.3 (86.5-88.2)	Reference	98.2 (97.9-98.5)	Reference
Maternal marital status							
Married	30 417	27.5 (26.7-28.3)	1.0 (0.9-1.1)	86.0 (85.3-86.6)	1.2 (1.1-1.4)	98.5 (98.2-98.7)	0.9 (0.6-1.2)
Not married	11 172	31.7 (30.3-33.1)	Reference	82.3 (81.1-83.6)	Reference	98.9 (98.7-99.2)	Reference
No. of vaccination providers							
1	29 815	26.6 (25.8-27.3)	0.7 (0.7-0.8)	85.3 (84.7-86.0)	1.1 (1.0-1.3)#	98.6 (98.3-98.8)	1.2 (0.8-1.6)
≥2	11 774	33.8 (32.5-35.2)	Reference	84.0 (82.9-85.1)	Reference	98.7 (98.3-99.0)	Reference
Type of vaccination provider							
Private	20 618	26.0 (25.1-26.8)	Reference	85.7 (85.0-86.5)	Reference	98.5 (98.2-98.7)	Reference
Public	5141	33.6 (31.7-35.4)	1.3 (1.2-1.5)	83.0 (81.3-84.8)	0.9 (0.8-1.1)	99.2 (98.8-99.5)	1.6 (0.9-2.7)
Other	9825	31.9 (30.5-33.3)	1.1 (1.0-1.2)#	84.3 (83.2-85.4)	1.0 (0.9-1.1)	98.5 (98.1-98.9)	1.1 (0.8-1.6)
Urbanicity							
Urban	18 154	29.8 (28.6-30.9)	0.9 (0.8-1.0)	83.4 (82.4-84.4)	0.8 (0.7-1.0)#	98.3 (98.0-98.6)	0.7 (0.5-1.0)#
Suburban	14 662	26.1 (25.1-27.1)	0.8 (0.7-0.9)	86.0 (85.1-86.8)	1.0 (0.8-1.1)	98.7 (98.4-99.0)	1.1 (0.7-1.5)
Rural	8773	33.2 (31.7-34.7)	Reference	85.4 (84.1-86.6)	Reference	98.9 (98.6-99.2)	Reference
Census region							
Northeast	6958	26.2 (24.6-27.7)	1.0 (0.9-1.2)	85.6 (84.2-87.0)	1.2 (1.0-1.4)#	98.2 (97.8-98.7)	1.1 (0.8-1.7)
Midwest	9612	30.6 (29.3-31.9)	1.2 (1.0-1.3)#	85.6 (84.6-86.7)	1.2 (1.0-1.4)#	98.8 (98.5-99.1)	1.7 (1.1-2.5)
South	15 407	29.9 (28.7-31.1)	1.1 (1.0-1.2)	84.9 (83.9-85.9)	1.2 (1.0-1.3)#	99.0 (98.7-99.2)	1.7 (1.2-2.5)
West	9612	27.0 (25.6-28.4)	Reference	83.9 (82.5-85.3)	Reference	98.1 (97.6-98.6)	Reference
Poverty status							
At or below	6274	30.8 (29.2-32.5)	1.0 (0.9-1.1)	82.1 (80.6-83.6)	1.0 (0.8-1.1)	98.7 (98.3-99.1)	0.8 (0.5-1.2)
Above	25 852	28.1 (27.3-28.9)	Reference	85.6 (84.9-86.3)	Reference	98.6 (98.4-98.8)	Reference
No. of children in household							
1	11 661	27.6 (26.3-28.8)	0.9 (0.8-1.0)#	87.8 (86.7-88.8)	1.4 (1.3-1.6)	98.7 (98.4-99.0)	1.1 (0.8-1.5)
≥2	29 928	29.1 (28.3-29.9)	Reference	83.9 (83.2-84.6)	Reference	98.5 (98.3-98.7)	Reference

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, 1998, through December 31, 1998.
‡Children born January 1, 1999, through June 30, 1999.
§Children born July 1, 1999, through December 31, 1999.
‖Children born January 1, 2000, through June 30, 2000.
¶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,[33] 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 182 000 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 750 000 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 750 000 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 20 000 HBsAg-positive women give birth in the United States[34] 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.[35] 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.[36,37] While only 5% of HBV infections are acquired during the perinatal period, perinatal infections account for an es-

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

Type of Vaccine (No. of Doses Received by 19 mo of Age)	7-12 mo Before Suspension, % (95% CI)†	6 mo Before Suspension, % (95% CI)‡	During Suspension, % (95% CI)§	6 mo After Suspension, % (95% CI)‖	7-12 mo After Suspension, % (95% CI)¶	*P* Value#
Hepatitis B (3)	87.7 (86.3-89.1)	86.3 (85.1-87.4)	81.1 (79.9-82.3)	85.2 (83.9-86.6)	87.5 (85.9-89.0)	<.01
Diphtheria-tetanus toxoids-acellular pertussis (4)	65.8 (63.9-67.8)	68.9 (67.4-70.3)	67.5 (66.0-68.9)	66.4 (64.7-68.0)	66.0 (63.8-68.1)	.06
Poliovirus (3)	79.2 (77.5-80.9)	80.7 (79.4-82.0)	81.5 (80.3-82.6)	82.3 (81.0-83.7)	82.7 (81.1-84.4)	.02
Measles-mumps-rubella (1)	85.2 (83.8-86.7)	86.7 (85.7-87.8)	85.5 (84.4-86.6)	86.9 (85.6-88.2)	86.9 (85.3-88.5)	.22
Haemophilus influenzae type b (3)	90.4 (89.1-91.7)	91.4 (90.5-92.2)	90.7 (89.8-91.6)	90.2 (89.1-91.4)	91.2 (89.8-92.6)	.54
Varicella (1)	65.9 (64.0-67.8)	73.2 (71.8-74.6)	73.6 (72.2-74.9)	77.2 (75.7-78.7)	78.5 (76.7-80.4)	<.01
4:3:1:3 series (4 diphtheria-tetanus toxoids-acellular pertussis, 3 poliovirus, 1 measles-containing, 3 *Haemophilus influenzae* type b)	60.4 (58.5-62.4)	63.5 (62.0-65.0)	61.9 (60.4-63.3)	61.8 (60.1-63.5)	60.8 (58.6-63.0)	.12

Abbreviation: CI, confidence interval.
*Data from 2001-2002 National Immunization Surveys. Percentages based on weighted data.
†Children born July 1, 1998, through December 31, 1998.
‡Children born January 1, 1999, through June 30, 1999.
§Children born July 1, 1999, through December 31, 1999.
‖Children born January 1, 2000, through June 30, 2000.
¶Children born July 1, 2000, through December 31, 2000.
#χ^2 Test for differences between birth cohorts.

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 18700 nonperinatal 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 hepati-

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.[45] 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[10] and greatly reduced birth-dose coverage among infants born to women whose HBsAg status was unknown.[46] 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.[47-50]

Concerns about thimerosal in vaccines roughly coincided with 2 widely reported vaccine safety-related events. In 1998, Wakefield et al[51] proposed a relationship between MMR and autism that received extensive media attention, although the association was refuted by other investigators.[52] 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.[53,54] 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.

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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.
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REFERENCES

1. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep.* 1991;40(RR-13):1-25.
2. Yusuf HR, Daniels D, Smith P, Coronado V, Rodewald L. Association between administration of hepatitis B vaccine at birth and completion of the hepatitis B and 4:3:1:3 vaccine series. *JAMA.* 2000;284:978-983.
3. Lauderdale DS, Oram RJ, Goldstein KP, Daum RS. Hepatitis B vaccination among children in inner-city public housing, 1991-1997. *JAMA.* 1999;282:1725-1730.
4. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics.* 2001;107:1147-1154.
5. Stratton K, Gable A, McCormick MC, eds. *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders.* Washington, DC: National Academy Press; 2001.
6. Freed GL, Andreae MC, Cowan AE, Katz SL. The process of public policy formulation: the case of thimerosal in vaccines. *Pediatrics.* 2002;109:1153-1159.
7. Centers for Disease Control and Prevention. Notice to readers: thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR Morb Mortal Wkly Rep.* 1999;48:563-565.
8. Centers for Disease Control and Prevention. Notice to readers: availability of hepatitis B vaccine that does not contain thimerosal as a preservative. *MMWR Morb Mortal Wkly Rep.* 1999;48:780-782.
9. Centers for Disease Control and Prevention. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. *MMWR Morb Mortal Wkly Rep.* 1999;48:996-998.
10. Centers for Disease Control and Prevention. Impact of the 1999 AAP/USPHS joint statement on thimerosal in vaccines on infant hepatitis B vaccination practices. *MMWR Morb Mortal Wkly Rep.* 2001;50:94-97.
11. Oram RJ, Daum RS, Seal JB, Lauderdale DS. Impact of recommendations to suspend the birth dose of hepatitis B virus vaccine. *JAMA.* 2001;285:1874-1879.
12. Clark SJ, Cabana MD, Malik T, Yusuf H, Freed GL. Hepatitis B vaccination practices in hospital newborn nurseries before and after changes in vaccination recommendations. *Arch Pediatr Adolesc Med.* 2001;155:915-920.
13. Hurie MB, Saari TN, Davis JP. Impact of the joint statement by the American Academy of Pediatrics/US Public Health Service on thimerosal in vaccines on hospital infant hepatitis B vaccination practices. *Pediatrics.* 2001;107:755-758.
14. Brayden RM, Pearson KA, Jones JS, Renfrew BL, Berman S. Effect of thimerosal recommendations on hospitals' neonatal hepatitis B vaccination policies. *J Pediatr.* 2001;138:752-755.
15. State and national vaccination coverage levels among children aged 19-35 months—United States, April-December 1994. *MMWR Morb Mortal Wkly Rep.* 1995;44:613, 619, 621-623.
16. Centers for Disease Control and Prevention. National, state and urban area vaccination coverage levels among children aged 19-35 months—United States, January-December 1995. *MMWR Morb Mortal Wkly Rep.* 1997;46:176-182.
17. Centers for Disease Control and Prevention. Vaccination coverage by race/ethnicity and poverty status—United States, 1996. *MMWR Morb Mortal Wkly Rep.* 1997;46:963-968.
18. Centers for Disease Control and Prevention. National, state and urban area vaccination coverage levels among children aged 19-35 months—United States, 1997. *MMWR Morb Mortal Wkly Rep.* 1998;47:547-554.
19. Centers for Disease Control and Prevention. Notice to readers: national vaccination coverage levels among children aged 19-35 months—United States, 1998. *MMWR Morb Mortal Wkly Rep.* 1999;48:829-830.
20. Centers for Disease Control and Prevention. National, state and urban area vaccination coverage levels among children aged 19-35 months—United States, January-December 1999. *MMWR Morb Mortal Wkly Rep.* 2000;49:585-589.
21. Centers for Disease Control and Prevention. National, state and urban area vaccination coverage levels among children aged 19-35 months—United States, 2000. *MMWR Morb Mortal Wkly Rep.* 2001;50:637-641.
22. Barker L, Luman E, Zhao Z, Smith P, Linkins R, Santoli J, Rodewald L, McCauley M. National, state, and urban area vaccination coverage levels among children aged 19-35 months—United States, 2001. *MMWR Morb Mortal Wkly Rep.* 2002;51:664-666.
23. Smith PJ, Battaglia MP, Huggins VJ, et al. Overview of the sampling design and statistical methods used in the National Immunization Survey. *Am J Prev Med.* 2001;20(suppl 4):17-24.
24. Zell E, Ezzati-Rice TM, Battaglia M, Wright R. National Immunization Survey: the methodology of a vaccination surveillance system. *Public Health Rep.* 2000;115:65-77.
25. Frankel MR, Srinath KP, Hoaglin DC, et al. Ad-

justments for non-telephone bias in random-digit-dialling surveys. *Stat Med.* 2003;22:1611-1626.
26. Smith PJ, Rao JNK, Battaglia MP, et al. *Compensating for Provider Nonresponse Using Response Propensities to Form Adjustment Cells: The National Immunization Survey.* Hyattsville, Md: National Center for Health Statistics; 2001. Vital and Health Statistics Series 2, No. 133.
27. Centers for Disease Control and Prevention. Recommended Childhood Immunization Schedule—United States, January-June 1996. *MMWR Morb Mortal Wkly Rep.* 1996;44:940-943.
28. Centers for Disease Control and Prevention. Recommended Childhood Immunization Schedule—United States, 2001. *MMWR Morb Mortal Wkly Rep.* 2001;50:7-10, 19.
29. Dalaker J. *Poverty in the United States, 1998.* Washington, DC: US Government Printing Office; 1999. Current Population Report, Series P60-207.
30. Stokley S, Smith PJ, Klevens RM, Battaglia MP. Vaccination status of children living in rural areas in the United States: are they protected? *Am J Prev Med.* 2001;20(suppl 4):55-60.
31. US Census Bureau. *Census 2000 Basics.* Washington, DC: US Government Printing Office; 2002.
32. Research Triangle Institute. *SUDAAN User's Manual, Release 8.0.* Research Triangle Park, NC: Research Triangle Institute; 2001.
33. Centers for Disease Control and Prevention. *Vital Statistics of the United States, 1999, Volume 1, Natality.* Hyattsville, Md: National Center for Health Statistics; 2001.
34. Centers for Disease Control and Prevention. *Hepatitis Surveillance Report.* Atlanta, Ga: Centers for Disease Control and Prevention; 1996. No. 56.
35. Centers for Disease Control and Prevention. *Guidelines for Viral Hepatitis Surveillance and Case Management.* Atlanta, Ga: Centers for Disease Control and Prevention; 2002.
36. McMahon BJ, Alward WLM, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis.* 1985;151:599-603.
37. Beasley RP, Hwang L-Y. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. *Viral Hepatitis and Liver Disease.* New York, NY: Grune & Stratton; 1984:209-224.
38. Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization: an economic analysis of current recommendations. *JAMA.* 1995;274:1201-1208.
39. Armstrong GL, Mast EE, Wojczynski M, Margolis HS. Childhood hepatitis B virus infections in the United States before hepatitis B immunization. *Pediatrics.* 2001;108:1123-1128.
40. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. *Proc R Soc Lond B Biol Sci.* 1993;253:197-201.
41. Ventura SJ, Martin JA, Curtin SC, Menacker F, Hamilton BE. Births: final data for 1999. *Natl Vital Stat Rep.* 2001;49:1-100.
42. Martin JA, Hamilton BE, Ventura SJ. Menacker F, Park MM. Births: final data for 2000. *Natl Vital Stat Rep.* 2002;50:1-101.
43. Cabana MD, Aiken KD, Davis MM, et al. Effect of state vaccine-financing strategy on hepatitis B immunization in hospital nurseries. *Ambul Pediatr.* 2002;2:367-374.
44. Cooper A, Yusuf H, Rodewald L, Malik T, Pollard R, Pickering L. Attitudes, practices, and preferences of pediatricians regarding initiation of hepatitis B immunization at birth. *Pediatrics.* 2001;108:e98.
45. Centers for Disease Control and Prevention. Notice to readers: FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (PEDIARIX) for use in infants. *MMWR Morb Mortal Wkly Rep.* 2003;52:203-204.
46. Biroscak BJ, Fiore AE, Fasano N, et al. Impact of the thimerosal controversy on hepatitis B vaccine coverage of infants born to women of unknown hepatitis B surface antigen status in Michigan. *Pediatrics.* 2003;111:e645-e649.
47. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics.* 2003;112:604-606.
48. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury—current exposures and clinical manifestations. *N Engl J Med.* 2003;349:1731-1737.
49. Pichichero ME, Cernichiari E, Lopricato J, Treanor J. Mercury concentrations and metabolism in infants reciving vaccines containing thimerosal: a descriptive study. *Lancet.* 2002;360:1737-1741.
50. Verstraeten T, Davis RL, DeStefano F, et al. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics.* 2003;112:1039-1048.
51. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet.* 1998;351:637-641.
52. DeStefano F, Thompson WW. MMR vaccine and autism: an update of the scientific evidence. *Expert Rev Vaccines.* 2004;3:19-22.
53. Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR Morb Mortal Wkly Rep.* 1999;48:577-581.
54. Centers for Disease Control and Prevention. Withdrawal of rotavirus vaccine recommendation. *MMWR Morb Mortal Wkly Rep.* 1999;48:1007.

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)