Impact of the Thimerosal Controversy on Hepatitis B Vaccine Coverage of Infants Born to Women of Unknown Hepatitis B Surface Antigen Status in Michigan

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ABSTRACT. Objective. Hepatitis B vaccine is recommended for all infants, and the series may be started during the delivery admission. For infants who are born to women who are positive for hepatitis B surface antigen (HBsAg) or to women whose HBsAg status is unknown, vaccination should be started within 12 hours of birth to prevent perinatal and early childhood hepatitis B virus infection. Because of concerns about mercury exposures from vaccines that contain thimerosal, the United States Public Health Service (USPHS) and the American Academy of Pediatrics (AAP) recommended in July 1999 that the first dose of hepatitis B vaccine be deferred until 2–6 months of age but only for infants who are born to HBsAg-negative women. To assess the impact on birth-dose vaccine coverage for infants who are born to women with unknown HBsAg status, we measured coverage before and after July 1999.

Methods. A sample of Michigan infants who were born to women whose HBsAg status was either unknown or missing were identified by reviewing newborn screening cards for infants who were born during 1) March–April 1999 (before recommendation changes [T1]); 2) July 15–September 15, 1999 (immediately after recommendation changes [T2]); and 3) March–April 2000 (6 months after resumption of pre-1999 practices were recommend [T3]). We verified maternal HBsAg screening and newborn hepatitis B vaccination by reviewing infant and maternal hospital records.

Results. Of 1201 infants who were born to women whose HBsAg status was indicated as unknown or missing on the newborn screening card during the 3 time periods, 216 (18%) were born to women whose status was truly unknown at the time of delivery, as determined by medical record review. During T1, 53% of these 216 infants received hepatitis B vaccine before hospital discharge, compared with 7% of infants who were born during T2 and 57% of infants who were born during T3. During T1, 19% of these infants received hepatitis B vaccine within 12 hours of birth compared with 1% of infants who were born during T2 and 14% of infants who were born during T3.

Conclusions. Hepatitis B vaccine birth-dose coverage for infants who were born to women whose HBsAg status was unknown at the time of delivery was already low in Michigan before the July 1999 USPHS/AAP Joint Statement but decreased significantly during the 2 months after the USPHS/AAP Joint Statement. Abrupt changes in established vaccination recommendations for lower risk children may lead to decreased coverage among higher risk children. Increases in hepatitis B vaccine coverage at birth are necessary to reduce the risk of perinatal infection for infants who are born to women with unknown HBsAg status. Pediatrics 2003;111:e645–e649. URL: http://www.pediatrics.org/cgi/content/full/111/6/e645; infant vaccination, hepatitis B vaccine, thimerosal, vaccine coverage, birth dose, vaccine coverage, vaccine safety.

ABBREVIATIONS. HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; AAP, American Academy of Pediatrics; USPHS, United States Public Health Service; CDC, Centers for Disease Control and Prevention; MDCH, Michigan Department of Community Health; OR, odds ratio; CI, confidence interval.

Screening all pregnant women for hepatitis B surface antigen (HBsAg) and immunizing all infants with hepatitis B vaccine are the cornerstones of efforts to prevent perinatal and early childhood hepatitis B virus (HBV) infection. Vaccination during the delivery admission (birth dose) is recommended for all children who are born to HBsAg-positive women and women whose HBsAg status is unknown and is the preferred schedule for all infants. Hospitals and practitioners who choose to provide the birth dose only to infants who are born to women whose HBsAg status is positive or unknown must ensure the identification of these women and vaccination of their infants within 12 hours of birth. By 1999, many birthing hospitals, recognizing the difficulty of tracking the HBsAg status of pregnant women and vaccinating at-risk infants, established routine policies and practices to initiate hepatitis B vaccination before hospital discharge for all newborn infants. These policies provided a safety net for infants who were born to unidentified HBsAg-positive women because of lapses in testing, communication of test results, or laboratory or transcription error.

On July 8, 1999, the American Academy of Pediatrics (AAP) and the United States Public Health Service (USPHS) jointly recommended reducing infant exposure to thimerosal, a commonly used vaccine preservative that contains mercury. Specifically,
the USPHS/AAP Joint Statement recommended that the first hepatitis B vaccine dose be postponed until 2–6 months of age for infants who are born to HBsAg-negative women; the AAP subsequently recommended that vaccination not begin until 6 months of age. Recommendations for infants who are born to HBsAg-positive women or to women whose HBsAg status was unknown did not change.2,3 By September 1999, preservative-free hepatitis B vaccine was available for newborns in the United States. The Centers for Disease Control and Prevention (CDC) then advocated a return to previous infant hepatitis B vaccination practices, including administering the first dose of hepatitis B vaccine to newborn infants in hospitals that had discontinued the practice.4

Several reports suggested that the change in recommendations led to disruptions in vaccination practices that could potentially have an impact on coverage rates of infants who are born to unscreened and even HBsAg-positive women.5–10 We conducted a study in Michigan to assess the impact of the USPHS/AAP Joint Statement on routine hepatitis B immunization of infants who were born to women whose HBsAg status was unknown. Our primary hypothesis was that these infants were less likely to receive timely immunoprophylaxis after the recommendations changed in July 1999 and that these changes persisted after hepatitis B vaccine that did not contain thimerosal became a preservative became available.

METHODS

Demographic, maternal HBsAg status, and hepatitis B vaccination information was collected on a standardized form from the medical records of Michigan infants born during 3 time intervals. T1 (March 1–April 30, 1999) was used to assess the baseline proportion of infants who were born to women of unknown HBsAg status before the recommendation changes in July 1999; T2 (July 15–September 15, 1999) was the time immediately after the joint statement until the approximate time when preservative-free hepatitis B vaccine first became available; and T3 (March 1–April 30, 2000) was when preservative-free hepatitis B vaccine was widely available.

Infants who were born during the 3 periods were identified by obtaining birth records from the Newborn Screening Division of the Michigan Department of Community Health (MDCH). Michigan newborn screening cards, which have been required by law for all infants who are born in Michigan since 1987, contain a field requesting the HBsAg status of the infant’s mother (“Mother Hepatitis B Surface Antigen Tested? Don’t Know; NO; YES; Date; Result: Positive; Negative”). Of 68,776 total births during these 3 time periods, 9,206 (13%) had maternal HBsAg status recorded as “Don’t Know.” Infants were distributed among the 3 time periods as follows: 2,720 (30%) during T1, 3,297 (36%) during T2, and 3,189 (35%) during T3. To improve efficiency of data collection efforts, we excluded infants who were born at any birthing hospital that reported to MDCH >40% of births as maternal HBsAg status “Don’t Know” or missing or had <15 births for which maternal HBsAg status was reported as “Don’t Know.” Of the 4,179 infants who remained after excluding these hospitals, 1,520 mother-infant pairs (36%) were randomly selected for medical chart review.

The outcome of interest was receipt of a dose of hepatitis B vaccine before the infant was discharged from the hospital. When hour of vaccination was also specified, infants were further classified according to whether they were vaccinated within 12 hours of birth (recommended as optimal practice to prevent perinatal infection). Absence of any indication of HBsAg status on the newborn screening card.

RESULTS

Nineteen of 102 Michigan hospitals that provide obstetric services met the inclusion criteria, and 13 agreed to participate. Of 133,541 births in Michigan in 2000, 41,314 (30.9%) occurred in these 13 hospitals. Of 13 hospitals, 11 are urban areas. Before the USPHS/AAP Joint Statement was released, all 13 reported that they had a policy to offer a birth dose of hepatitis B vaccine to all infants. After the Joint Statement, all 13 hospitals stopped these policies. By the time of the study in 2000–2001, 9 of 13 had resumed their previous policy, and 2 more hospitals reported that they planned to resume. We gained access to 3,335 (89%) of the 3,520 requested mother-infant medical chart pairs. After the completion of data collection, 1201 (79%) birth records could be used for subsequent analyses. The remaining 154 were excluded because some or all of the sections that contained screening and vaccination information were missing from the charts. Of these 1201 births, 216 (18%) were to women whose HBsAg status was not recorded on the chart at the time of hospital discharge. For the remaining 985 infants, maternal HBsAg status was recorded on the chart, despite the “Don’t Know” answer on the infant’s newborn screening card.

The median age of the 216 women of unknown HBsAg status was 26.6 years (range: 14–43 years). None had been reported to the health department as HBsAg positive. Table 1 summarizes other demographic and prenatal care characteristics. Maternal characteristics such as maternal age, race, number of prenatal visits, timing of first prenatal visit, and whether it was the woman’s first delivery did not differ significantly by time period.

The proportion of infants who were born to women with unknown HBsAg status and vaccinated before hospital discharge declined 46% during T2 (95% confidence interval [CI] for decline: 32%–60%). Of 75 infants who were born during T1, 40 (53%) received a dose of hepatitis B vaccine before hospital discharge, compared with 6 (7%) of 81 who were born during T2 (P < .001) and 34 (57%) of 60 infants who were born during T3 (Fig 1).

Four infants who were vaccinated before discharge did not have a time of vaccination recorded. Among infants whose vaccination time was rec-

TABLE 1. Demographic and Prenatal Care Characteristics of 216 Michigan Women With No Recorded HBsAg Screening Result at Time of Delivery, 1999-2000

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85 (39)</td>
</tr>
<tr>
<td>Black</td>
<td>120 (56)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (5)</td>
</tr>
<tr>
<td>First child</td>
<td>52 (24)</td>
</tr>
<tr>
<td>First prenatal visit during first trimester*</td>
<td>33 (35)</td>
</tr>
<tr>
<td>&gt;5 prenatal visits*</td>
<td>32 (40)</td>
</tr>
</tbody>
</table>

* Data unavailable for some women.
corded, the proportion vaccinated within 12 hours of birth (as is recommended) declined 18% (95% CI for decline: 8%–29%). Fourteen (19%) infants who were born during T1 received the vaccine, compared with 1 (1%) who was born during T2 (P < .001). Although only 8 (14%) infants who were born during T3 received the vaccine within 12 hours of birth, this was not significantly different from T1 (Fig 1). When the analysis was restricted to infants who received vaccine, a larger proportion (14 of 39 [36%]) in T1 received vaccine within 12 hours, compared with T2 (1 of 5 [20%]) and T3 (8 of 32 [25%]), but these differences were not statistically significant.

Five infants had a parent(s) who refused vaccine, including 2 who were born during T1, 1 during T2, and 2 during T3. Removing these infants from the analysis did not change the statistical significance of the results.

**DISCUSSION**

Previous studies have shown that after the USPHS/AAP Joint Statement was issued, many hospitals discontinued policies and practices that provided for hepatitis B vaccination of all newborns and that these policies were not reinstated in some hospitals even after preservative-free hepatitis B vaccine became available.5–9 Our study examined whether these policy changes were followed by reduced coverage among infants for whom vaccination recommendations did not change. Our data indicate that a significant decline in administration of the birth dose of hepatitis B vaccine occurred among infants who were born to women of unknown HBsAg status immediately after the USPHS/AAP Joint Statement was released. In Michigan, hepatitis B vaccination of these infants within an appropriate time interval after birth virtually ceased in July through September of 1999, despite specific language in the USPHS/AAP Joint Statement indicating that hepatitis B vaccination practices for these infants should not change. Coverage had returned to the baseline by April 2000; we did not collect data that allowed a determination of how rapidly this occurred. Changes in hepatitis B vaccination coverage during the 3 periods coincided with changes in national recommendations for infants who are born to HBsAg-negative women. This study provides additional evidence that many hospitals and health care providers misinterpreted rapid policy changes associated with evolving, largely theoretical concerns about the safety of thimerosal.

Interpretation of these findings is somewhat limited because of a lack of information about births at hospitals whose patients were not included in the study and about the true HBV infection status of women and infants included in the study. Serologic testing at 9–15 months of age would be necessary to determine the HBV infection status of the infants in our study. No previously collected data exist to compare the characteristics of the overall population of Michigan women with unknown HBsAg status with those whose charts were reviewed. The subset of hospitals in which we reviewed medical records may not have been representative of all Michigan hospitals. We did not review records in hospitals with fewer than 15 births where maternal HBsAg status was reported and those that reported that >40% of women were unscreened. There was no efficient way to identify women whose HBsAg status was unknown when the newborn screening card had missing data or data that were likely to be inaccurate. If these hospitals had lower vaccination coverage during T1 compared with hospitals whose patients were included in the study, then the reduction observed during T2 among study hospitals may not have been statistically significant. However, hospitals that were unable or unwilling to report adequately maternal HBsAg status probably would not have been more likely to provide hepatitis B vaccination to infants who were born to unscreened women during T2.

Case management for infants who are born to HBsAg-positive women is available from the perinatal hepatitis B prevention program in Michigan, but as demonstrated by the inaccuracies found in the maternal HBsAg status field of the newborn screening card in our study, identifying and tracking these women and their infants is difficult. It is interesting that although the number of infants who were born to women whose HBsAg status was truly unknown and identified during T3 was lower than in T1, the number of screening cards with HBsAg status marked as unknown was higher during T3, suggesting that inaccuracies in screening card data worsened during this time period.

Whether our findings reflect a nationwide reduction in first-dose hepatitis B vaccine coverage for infants who are born to women of unknown HBsAg status is uncertain. However, our findings are consistent with findings from hospital surveys that indicate that changes in hepatitis B vaccination policies persisted for at least several months after preservative-free vaccine was widely available and recommendations to resume previous vaccination policies had been made. In late 1999 and early 2000, 6–9 months after the recommendation changes, surveys of all hospitals in Wisconsin,5 Chicago,6 and Colorado7 demonstrated significant decreases in the number of hospitals that offered hepatitis B vaccina-
tion to all newborns and substantial increases in the percentage of hospitals that did not routinely vaccinate infants who were born to HBsAg-positive women. A national survey sample of 773 hospitals in December 1999 indicated similar trends. In Michigan, an unvaccinated infant who was born at a hospital that had suspended its birth-dose policy died from fulminant hepatitis B in December 1999; the infant’s mother erroneously had been reported to the hospital as “hepatitis-negative.” In addition, a similar pattern and magnitude in reduction of coverage for infants who were born to women of unknown HBsAg status was observed in Oregon.

There are several possible explanations for the observed effects on newborn vaccination coverage. First, there may have been confusion about which infants should have vaccination deferred, despite the specific language used in the Joint Statement. In a Colorado survey done in early 2000 of people who identified themselves as being responsible for nursery vaccination policy, 71% learned of the Joint Statement recommendations from colleagues or the news media rather than from the health department or a professional society. The precise language used to indicate which infants should have their vaccination deferred may have been lost in summaries provided by colleagues or the news media. Second, practitioners and hospitals may have considered the theoretical risk from thimerosal exposure to exceed the risk of perinatal or early childhood infection as a result of missed immunoprophylaxis for infants who are born to women of unknown HBsAg status. The rapidity with which the Joint Statement was developed and publicized may have led practitioners and hospitals to conclude that reducing exposure to thimerosal in vaccines was a public health emergency for all infants. Finally, practitioners and other delivery hospital personnel may not have been aware that infants who are born to women of unknown HBsAg status were no longer being routinely immunized. Practitioners may have assumed that prenatal screening could successfully identify all HBsAg-positive women and grown accustomed to the safety net that universal hepatitis B vaccination of newborns provided.

In some settings, women who have not been screened for HBsAg are more likely to be HBsAg positive compared with women who receive prenatal screening, and their infants are less likely to receive appropriate and timely immunoprophylaxis. The CDC provides yearly estimates of the minimum expected number of births to HBsAg-positive women and compares this estimate to the number of pregnant HBsAg-positive women who were reported to the CDC. In 1999, the estimated minimum number of HBsAg-positive women who gave birth was 13,296, but only 9,503 (71%) were identified by perinatal hepatitis B prevention programs (T Malik, personal communication, CDC). A substantial proportion of women who are not identified are also likely unscreened.

For infants who are born to women who are HBsAg positive but whose HBsAg status is unknown at the time of birth, the consequences of missed immunoprophylaxis are potentially serious and long-lasting. The risk of perinatal infection for an infant who is born to an HBsAg-positive woman who is also hepatitis E antigen-positive is as high as 90%. As many as 90% of infants who are infected during the perinatal period develop chronic infection, and of these, up to 25% will die of chronic liver disease during adulthood.

At the time the Joint Statement was issued, no harm from the mercury in thimerosal-containing vaccines had been demonstrated, and there was no consensus about the health risk associated with exposure to the quantities of mercury-containing compounds present in vaccines. In 2001, the Immunization Safety Review Committee of the Institute of Medicine examined the evidence on the relationship between thimerosal in vaccines and neurodevelopmental disorders. The committee concluded that removing thimerosal from childhood vaccines, as part of an overall strategy to reduce mercury exposures for children, was a reasonable goal. The chair of the committee noted that “the hypothesis that thimerosal exposure through the recommended childhood immunization schedule causes neurodevelopmental disorders is not supported by clinical or experimental evidence.”

The unintended impact of the thimerosal controversy on hepatitis B vaccine coverage of infants who are born to women of unknown HBsAg status should serve as another reminder that changes in established recommendations, especially if they occur without timely and extensive communication and education of health care providers, may result in unexpected changes in vaccination practices. Anticipating the need for the public health community to respond to future safety controversies, the Institute of Medicine report also called for “a review and assessment of how public health policy decisions are made under uncertainty” as well as research on how to improve strategies used to communicate rapid changes in vaccine policy. Such strategies might also prove useful for communicating rapid changes in policy necessitated by vaccine shortages or changing disease trends.

Beginning hepatitis B vaccination at birth for all infants is currently the preferred schedule advocated by the AAP, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians. Our data indicate that health care, hospital, and public health professionals should renew efforts to begin hepatitis B vaccination at birth, especially for infants who may be at higher risk of perinatal and early childhood infection, such as those who are born to women whose HBsAg status is unknown. Although hepatitis B vaccine coverage of infants who are born to unscreened women in Michigan returned to the previously low baseline (57%) by discharge, 14% within the first 12 hours of life) by mid-2000, physicians and birthing centers must further increase birth-dose coverage for these infants. Efforts to improve hepatitis B vaccine birth-dose coverage and the quality of data on the newborn screening card in Michigan are under way and include...
providing vaccine and educational resources to hospitals and their staff.

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