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Prevention of Vertical Transmission of Hepatitis B

An Observational Study

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Background: For mothers with chronic hepatitis B virus (HBV) infection, the Centers for Disease Control and Prevention recommends immunoprophylaxis to decrease perinatal transmission. However, its effectiveness and risk factors for failure have not been well-studied in community practice.

Objective: To investigate the effectiveness of a contemporary immunoprophylaxis protocol.

Design: Observational study.

Setting: An HBV perinatal immunoprophylaxis program within Kaiser Permanente Northern California.

Patients: 4446 infants born to 3253 HBV-positive mothers between 1997 and 2010.

Measurements: Adherence to immunoprophylaxis, follow-up testing rates, maternal risk factors for HBV transmission, and transmission rates.

Results: The infant infection rate was 0.75 per 100 births from 1997 to 2010 (Poisson 95% CI, 0.48 to 1.10). Rates per 100 births were 3.37 (CI, 2.08 to 5.14) for e antigen–positive mothers and 0.04 (CI, 0.001 to 0.24) for e antigen–negative mothers. Among mothers with viral load testing, the lowest level associated with transmission was 6.32×10^7 IU/mL. Infection rates per 100 births were 3.61 (CI, 0.75 to 10.56) among the 83 births to mothers with viral loads of 5×10^7 IU/mL or greater and 0 among the 831 births to mothers with viral loads less than 5×10^7 IU/mL, regardless of e antigen status.

Limitations: Testing for HBV immunity and infection was less complete in earlier years. Viral load testing was only consistently available starting in 2007.

Conclusion: Prenatal HBV screening followed by postnatal prophylaxis is highly effective in preventing vertical transmission of HBV. A negative e antigen status or a viral load less than 5×10^7 IU/mL (90.9% of women tested) identifies women at extremely low risk for transmission after immunoprophylaxis who are unlikely to benefit from further interventions.

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Hepatitis B virus (HBV) infection remains globally endemic, with approximately 350 million chronically infected patients worldwide and an estimated 800 000 to 1.4 million carriers in the United States (1, 2). Hepatitis B virus carrier status is a major risk factor for future illness (3); approximately 25% of HBV-infected children will eventually die of complications from chronic liver disease or liver cancer (1, 2). Because 35% to 50% of carriers are believed to be infected by perinatal exposure to blood or blood-contaminated fluids (4), the prevention of vertical transmission from mother to child plays a vital role in decreasing disease prevalence. Approximately 24 000 HBV-infected women give birth annually in the United States (5), which makes their offspring an important at-risk population.

Perinatal HBV transmission can be reduced by using tests for hepatitis B surface antigen (HBsAg) to identify HBV-infected pregnant women and providing hepatitis B immunoglobulin (HBIg) and hepatitis B vaccine to their infants soon after birth (2). The U.S. Preventive Services Task Force strongly recommends HBV screening of pregnant women at their first prenatal visit and immunization for all newborns. The Centers for Disease Control and Prevention recommends that infants of HBV-positive mothers receive HBIg and vaccine within 12 hours of birth and 2 additional vaccine doses at ages 1 to 2 months and 6 months (1).

Studies have evaluated the efficacy of prophylaxis programs to prevent HBV vertical transmission under controlled settings. However, their effectiveness in clinical practice and risk factors for failure despite timely immunoprophylaxis are not well-defined. Most previous effectiveness studies were small (<200 patients); were often done in countries with varying prophylaxis protocols; had low adherence; had limited follow-up testing on infants; or lacked data on maternal risk factors, such as e antigen status, viral load, and use of other antiviral medications (6–11). The availability of comprehensive data from many patients would permit identification of higher-risk populations who may benefit from additional prophylaxis measures, such as late-pregnancy antiviral treatment, and, conversely, populations who are unlikely to benefit or may even experience relative harms from treatment, such as development of viral resistance due to short-term medication use.

We conducted an observational study to investigate the effectiveness of a contemporary immunoprophylaxis protocol administered in an integrated health services delivery organization as well as to evaluate adherence, follow-up testing, transmission rates, and maternal risk factors for transmission.

METHODS

Study Population and Hepatitis B Tracking

This study was conducted within Kaiser Permanente Northern California (KPNC), an integrated health services delivery organization that has approximately 3.3 million members and delivers more than 36 000 infants annually. Its membership demographics approximate the underlying census population of northern California (12). The Regional Perinatal Screening Hepatitis B program ("tracking program") was started in 1988 to identify and help treat prenatal hepatitis B carriers and their exposed infants to decrease the risk for vertical transmission. Screening efforts identify pregnant carriers, and tracking efforts follow infants to ensure proper immunization and follow-up testing. Our study included births from 1997 through 2010 at KPNC facilities.

Case Identification and Testing

Pregnant women receiving prenatal care or delivering at KPNC facilities are tested for HBsAg as part of a prenatal screening panel; if their results are positive, a hepatitis B e antigen test is automatically done. Starting in 2006, regional guidelines advised providers to order HBV DNA, e antigen, and liver function tests for HBsAg-positive pregnant patients and refer those with a viral load of 200 000 IU/mL or greater to a gastroenterologist. This level was chosen, in the absence of definitive data, because high viral loads may be associated with an increased risk for transmission. Because viral load testing in HBsAg-positive women became routine at KPNC facilities during 2007, results relating to maternal viral load include deliveries from 1 July 2007 through 31 December 2010.

Postnatal Tracking

Pregnant HBsAg-positive women due to deliver within 4 months are identified by using an electronic search of KPNC data systems followed by manual record review. The tracking program follows infants to verify appropriate administration of HBIg and hepatitis B vaccine doses. Electronic reminders are sent to pediatric providers before the first scheduled infant check-up and when serologic tests are due. The HBIg is considered on time if administered within 12 hours of birth. Hepatitis B vaccines are considered to have been delivered on time if they meet these criteria: birth dose at age 12 hours or younger, second dose at age 24 to 67 days, and third dose at age 164 to 214 days. We also considered an alternate definition whereby the third dose was on time if it was administered within 245 days (8 months) of birth.

Serologic testing for hepatitis B surface antibody and HBsAg is recommended by KPNC to occur at least 4 weeks after receipt of the final hepatitis B vaccine dose (generally at the next well-child check-up), from age 9 to 15 months. Before 2006, serologic testing for hepatitis B was recommended but not tracked. In March 2006, the program initiated testing of HBsAg status and immunity for all new infants and made efforts to retrospectively follow all untested children born to HBsAg-positive mothers since 1997.

Context

The Centers for Disease Control and Prevention recommends that pregnant women be screened for hepatitis B and that infants of hepatitis B–positive mothers receive immunoprophylaxis. The effectiveness of this intervention at the community level is unknown.

Contribution

In a Kaiser Permanente integrated health system, a centralized program of prenatal screening and neonatal immunoprophylaxis resulted in no transmission of hepatitis B to infants whose mothers were e antigen–negative or –positive with a viral load less than 5×10^7 IU/mL.

Caution

A centralized approach may be difficult to implement in many prenatal care settings.

Implication

A community-based intervention was effective in preventing neonatal hepatitis B infection.

—The Editors

Statistical Analysis

Analyses were done using SAS, version 9.1 (SAS Institute, Cary, North Carolina), and Stata, version 10.1 (StataCorp, College Station, Texas). The primary outcomes of interest included rates of infant immunization; rates of testing mothers for e antigen and viral load; and infant infection rate, which was defined as the number of HBsAg-positive infants among those with on-time administration of HBIg and vaccines (per 100 children tested). Infants who left KPNC coverage were excluded from analyses for vaccinations or testing due after their departure. Demographic comparisons between the screening program population and the KPNC maternal and neonatal populations (**Table 1**) were done using *t* tests for continuous variables (age) and 2-sample tests of proportion for categorical variables (race or ethnicity and sex). A chi-square test was used to test the association between maternal e antigen status and testing of children for HBsAg. Ninety-five percent CIs for HBV infection rates were calculated assuming a Poisson distribution (*ci . . . , poisson* command in Stata). When relative risk estimates (incidence rate ratios) were presented, Poisson regression was used to evaluate the association between potential risk factors and incidence of HBV infection in children (*poisson* command in Stata).

The study protocol was approved by the Kaiser Permanente Institutional Review Board.

Role of the Funding Source

The funding sources had no role in the design and conduct of the study; collection, management, analysis,

Table 1. **Demographic Characteristics of HBsAg-Positive Mothers, Their Children, and All Births at KPNC Facilities, 1997–2010***

Characteristic	HBsAg-Positive Mothers	Children	All Births at KPNC Facilities†
Race/ethnicity			
Non-Hispanic white	179 (5.5)	332 (7.2)	193 970 (40.7)‡
Hispanic	99 (3.0)	149 (3.4)	121 931 (25.6)‡
African American	127 (3.9)	181 (4.1)	36 798 (7.7)
Asian/Pacific Islander	2607 (80.1)	3254 (73.2)	83 166 (17.5)‡
American Indian	7 (0.2)	8 (0.2)	1409 (0.3)
Multiracial/other	132 (4.1)	208 (4.7)	22 766 (4.8)
Unknown	102 (3.1)	324 (7.3)	16 059 (3.4)‡
Total	3253 (100)	4446 (100)	476 099 (100)
Maternal age			
Mean (SD), *y*	31.0 (5.3)	–	29.2 (6.0)‡
<20 y	62 (1.4)	–	28 846 (6.0)
20–24 y	435 (9.8)	–	79 499 (16.7)
25–29 y	1206 (27.1)	–	134 444 (28.3)
30–39 y	1587 (35.7)	–	137 117 (28.9)
35–39 y	935 (21.0)	–	76 048 (16.0)
≥40 y	221 (5.0)	–	18 857 (4.0)
Total	4446 (100)	–	474 811 (100)
Sex			
Male	–	2159 (48.6)	232 284 (48.8)
Female	–	2287 (51.4)	243 748 (51.2)
Total	–	4446 (100)	476 032 (100)

HBsAg = hepatitis B surface antigen; KPNC = Kaiser Permanente Northern California.
* Data are numbers (percentages) unless otherwise indicated.
† Excludes the 4446 births in the HBsAg-positive population. Among infants born at KPNC, 1288 were missing maternal age and 67 had unknown/other sex.
‡ $P < 0.001$ using *t* test for continuous variable (i.e., age) and 2-sample tests of proportion for categorical variables (i.e., race/ethnicity and sex).

and interpretation of the data; or preparation of the manuscript.

RESULTS

Study Population

Between 1997 and 2010, the tracking program followed 4446 infants born within KPNC to 3253 HBsAg-positive mothers, with an average of 318 births per year (range, 261 to 381); this was approximately 9.25 births to HBsAg-positive mothers per 1000 total births within KPNC. Compared with the overall KPNC population, mothers who were HBsAg-positive were older and their children were more likely to be of Asian or Pacific Islander ethnicity and less likely to be white (non-Hispanic or Hispanic) or of an unknown race or ethnicity (**Table 1**).

Rates of Immunization

The rate of timely immunization increased between 1997 and 2010 (**Table 2**), and 87% of children received HBIg and all 3 hepatitis B vaccine doses on time from 2006 to 2010 under the strictest criteria of 12 hours, 67 days, and 214 days. **Figure 1** shows annual immunization compliance with various timing criteria.

Serologic Testing for HBV Immunity

A prospective program of postvaccination testing began in 2006. At the same time, a retroactive testing program was implemented to follow up on children born before 2006. Among children remaining in KPNC membership at least 2 months after completion of the vaccination series, 79% of those born in 1997 to 2000 and 94% of those born in 2006 to 2010 had follow-up testing for hepatitis B surface antibody (immunity) (**Table 3**). Of the children tested, 67% of the 1997 to 2000 group had immunity on the first test and 91% had immunity on any test (initially or after additional vaccination). For the 2006 to 2010 group, 98% had immunity on the first test and 99% had immunity on any test (**Table 3**).

Testing Mothers for e Antigen and Viral Load and Children for HBsAg

Among all 4446 infants born from 1997 to 2010 to HBsAg-positive women, 3872 (87%) mothers were tested for e antigen within 1 year before or after childbirth; of these, 94% were tested before delivery. Of the mothers who gave birth between 1 July 2007 through 2010 to a total of 1185 infants, 1100 (93%) were tested for viral load and 1008 (85%) were tested for both e antigen and viral load. When we included the period before routine viral load testing (1997 to 2010), 1290 mothers (29%) were tested for viral load and 1183 (27%) were tested for both e antigen and viral load.

Among all births, 3966 infants (89%) retained KPNC membership through the postvaccination testing period. Among these, follow-up testing for HBsAg was completed for 3353 (85%) of all infants, 2945 (85%) of the 3473 infants with maternal e antigen testing, and 837 (93%) of the 904 infants with both maternal viral load and e antigen testing (after 1 July 2007).

HBV Infection Rate

Among all children, 0.75% (25 of 3353 tested) were HBsAg-positive as of January 2012 (**Table 4**); thus, the overall infection rate was 0.75 per 100 births (95% CI, 0.48 to 1.10). The overall testing rates increased over time (**Table 2**), and there was a decrease in infection rates over this period (unadjusted Poisson incidence rate ratio per year, 0.90 [CI, 0.82 to 1.00]) (**Figure 2**).

Of the 25 children with HBV infection, all received HBIg and vaccines within or close to the recommended intervals. All 25 had HBIg and the first vaccine dose within 12 hours of birth; 19 had the second dose within 24 to 62 days of birth, and the other 6 received it within 70 days of birth. Most HBV-infected children (22 of 25) also received the third dose within the recommended 164 to 214 days; the remaining 3 received their third dose between 219 and 237 days (and received their second dose on time).

By e Antigen Status

Among the 624 tested children born to 481 e antigen–positive mothers, the overall infection rate was 3.37 per

100 births (CI, 2.08 to 5.14). Among 2317 children born to the 1823 e antigen–negative mothers, only 1 infant (with an unknown viral load) was infected (0.04 per 100 births [CI, 0.001 to 0.24]), although this child received HBIg and was appropriately vaccinated (**Figure 2**). The relative risk for transmission for maternal e antigen–positive status was an incidence rate ratio of 79.72 (CI, 10.61 to 598.70), after adjustment for sex, race of the infant, and maternal age. Testing of children for HBsAg was not related to maternal e antigen status ($P = 0.32$ [data not shown]). In a supplemental analysis including maternal e antigen and adverse birth outcomes as predictors, only e antigen was associated with hepatitis B transmission; however, power was limited due to the relatively small number of births with low birth weight ($n = 153$), preterm delivery ($n = 220$), and small size for gestational age ($n = 177$).

By Viral Load and e Antigen Status

Among the 835 women with viral load and e antigen results (July 2007 onward), 3 infants of women with a viral load of 5×10^7 IU/mL or greater (3 of 76 [4.0%]) tested positive for HBsAg (3.95 per 100 births [CI, 0.81 to 11.53]). The mothers of these 3 infants were e antigen–positive. All 3 infants received their HBIg and vaccines approximately within the recommended time frame, except for 1 child who received the second vaccine dose at 70 days. The maternal viral loads for the 3 infected children were 2.77×10^8 IU/mL, greater than 1.1×10^8 IU/mL (limit of that assay), and 6.32×10^7 IU/mL.

The distribution of infants by different cutoffs of maternal viral load and e antigen status is described in **Table 5**. No episodes of transmission occurred among the 671 children of e antigen–negative mothers with a viral load less than 5×10^7 IU/mL (80.4% of population) or among the 88 children of e antigen–positive mothers with a viral load less than 5×10^7 IU/mL (10.5% of population) (**Table 5**). Together, these groups comprised 90.9% of the population. Whether children received serologic testing was unrelated to maternal viral load ($P = 0.77$ [data not shown]).

Other Therapies for Hepatitis B

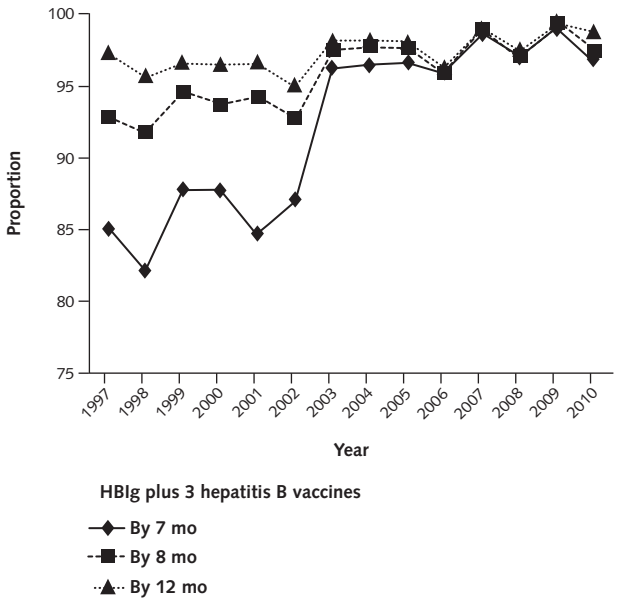
Among the 1100 women with viral load testing (July 2007 onward), 115 (10%) had 1 or more prescriptions filled for an oral antiviral medication against HBV before delivery, including 39% of mothers who had a viral load of 200 000 IU/mL or greater (the cutoff for recommended referral to a gastroenterologist) and 4% who had a viral load less than 200 000 IU/mL. Lamivudine was the most commonly used agent, followed by tenofovir.

Table 2. **Timing and Completeness of Prophylaxis Among Children Born to HBsAg-Positive Mothers, 1997–2010**

Variable	1997–2000, *n* (%)	2001–2005, *n* (%)	2006–2010, *n* (%)	Total, *n* (%)
Total births	1152 (100)	1616 (100)	1678 (100)	4446 (100)
Age at HBIg				
<12 h	1120 (97.2)	1574 (97.4)	1649 (98.3)	4343 (97.7)
12 to <24 h	20 (1.7)	33 (2.0)	23 (1.4)	76 (1.7)
≥24 h	11 (1.0)	8 (0.5)	5 (0.3)	24 (0.5)
Missing or declined vaccine	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)
Age at first dose of hepatitis B vaccine				
<12 h	1121 (97.3)	1587 (98.2)	1659 (98.9)	4367 (98.2)
12 to <24 h	23 (2.0)	24 (1.5)	16 (1.0)	63 (1.4)
≥24 h	8 (0.7)	4 (0.3)	2 (0.1)	14 (0.3)
Missing or declined vaccine	0 (0)	1 (0.1)	1 (0.1)	2 (0.04)
Age at second dose of hepatitis B vaccine*				
<24 d	2 (0.2)	0 (0)	0 (0)	2 (0.04)
24–67 d	1079 (94.9)	1492 (94.1)	1498 (93.0)	4069 (93.9)
68–92 d	51 (4.5)	87 (5.5)	105 (6.5)	243 (5.6)
>92 d	5 (0.5)	7 (0.4)	6 (0.4)	18 (0.4)
Missing or declined vaccine	0 (0)	0 (0)	2 (0.1)	2 (0.04)
Total	1137 (100)	1568 (100)	1611 (100)	4334 (100)
Age at third dose of hepatitis B vaccine†				
<164 d	12 (1.1)	3 (0.2)	7 (0.5)	22 (0.5)
164–214 d	909 (84.5)	1356 (91.8)	1432 (93.8)	3697 (90.6)
215–245 d	97 (9.0)	92 (6.2)	67 (4.4)	256 (6.3)
>245 d	58 (5.4)	26 (1.8)	20 (1.3)	104 (2.6)
Total	1076 (100)	1477 (100)	1526 (100)	4079 (100)

HBIg = hepatitis B immunoglobulin; HBsAg = hepatitis B surface antigen.
* Target at 1–2 mo. Excludes 110 (2.5%) infants who left Kaiser Permanente Northern California integrated health system before the end of the 2-mo interval.
† Target at 6 mo. Excludes 365 (8.2%) infants who left Kaiser Permanente Northern California integrated health system before the end of the 6-mo interval. The visit was considered completed at 6 mo until the start of the seventh month (214 d) and completed at 7 mo until the start of the eighth month (245 d).

Figure 1. **Proportion of infants receiving HBIg within 12 h after birth plus 3 hepatitis B vaccines within 7, 8, and 12 mo, 1997–2010.**



An individual hepatitis B vaccination may or may not have been on time. In 2001, the program coordinators began calling the infants' providers before the 6-mo appointment to remind them to administer the final vaccine and postvaccination serologic tests. This policy probably caused the increase in the proportion of infants who received HBIg and all 3 vaccine doses by month 7 between 2001 and 2003. HBIg = hepatitis B immunoglobulin.

Among the mothers of the 3 infected children born between July 2007 and 2010, 1 did not have prenatal antiviral prescriptions (viral load $>1.1 \times 10^8$ IU/mL) and 2 began antiviral therapy in the week before delivery (6 days and 2 days before delivery for mothers with viral loads of 6.32×10^7 IU/mL and 2.77×10^8 IU/mL, respectively).

Table 4. **Infections Among Children Tested for HBsAg: Overall Infection Rate and by Maternal e Antigen Status***

Variable	Infected/Tested Children, *n/N (%)*	
	Born From 1997 to 2010	Born From July 2007 to December 2010
All children tested	25/3353 (0.8)	3/981 (0.3)
By maternal e antigen status†		
Negative	1/2317 (0.04)	0/722 (0)
Positive	21/624 (3.4)	3/169 (1.8)
Total with maternal e antigen–positive status	22/2941 (0.7)	3/891 (3.4)

HBsAg = hepatitis B surface antigen.
* Infections represent the number of children in each category who tested positive for e antigen divided by the total number of children tested for e antigen.
† Four results labeled "borderline" for maternal e antigen status were excluded from these totals.

Discussion

Our study shows that immunoprophylaxis with HBIg and hepatitis B immunization is effective at preventing perinatal transmission of HBV. Risk factors for transmission include maternal e antigen–positive status and higher viral load, although a precise cut point is difficult to assign because of the low overall infection rate. Among mothers who were e antigen–negative or were e antigen–positive with a viral load less than 5×10^7 IU/mL, few of whom were receiving antiviral therapies, there were no episodes of vertical transmission. The lowest recorded viral load in a mother–child transmission pair was 6.32×10^7 IU/mL for an e antigen–positive mother. Thus, a viral load less than 5×10^7 IU/mL, below which no patient experienced transmission, represented a cutoff supported by the current data; 90.9% of all mothers in our study were in this category.

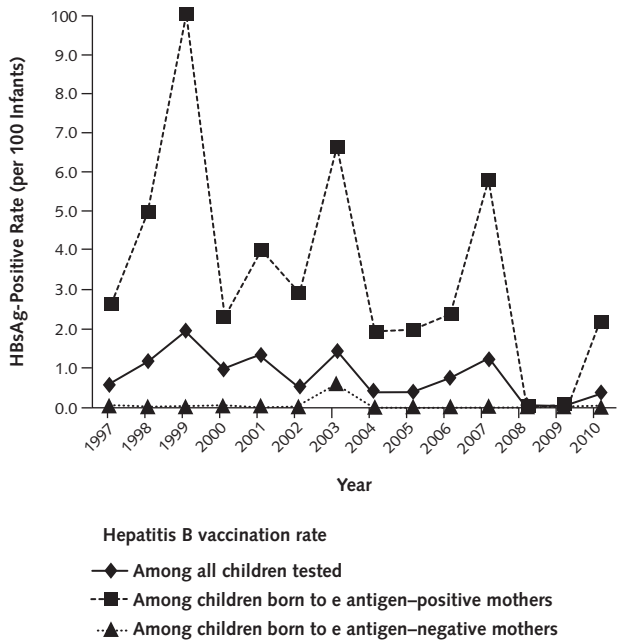
Our study provides data on neonatal transmission of hepatitis B in the era of contemporary management and therapy. Estimates of vertical HBV transmission rates from the 1970s, before immunoprophylaxis was available, indi-

Table 3. **Timing and Completeness of Testing for Immunity and Infection Among Children Born to HBsAg-Positive Mothers, 1997–2010**

Variable	Total	1997–2000	2001–2005	2006–2010
HBV immunity*				
Tested, *n (%)*	3540 (89)	811 (79)	1305 (91)	1424 (94)
Positive at first test, *n (%)*	3132 (88)	545 (67)	1196 (92)	1391 (98)
Ever positive, *n (%)*	3420 (97)	737 (91)	1273 (98)	1410 (99)
Median age at first test (IQR), *mo*	11 (10–16)	21 (11–109)	11 (10–16)	10 (9–12)
HBV infection*†				
Tested, *n (%)*	3353 (85)	715 (70)	1235 (86)	1403 (93)
Rate (95% CI)‡	0.75 (0.48–1.10)	1.12 (0.48–2.21)	0.81 (0.39–1.49)	0.50 (0.20–1.03)
Median age at first test (IQR), *mo*	12 (10–17)	37 (11–113)	12 (10–18)	10 (9–12)

HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IQR = interquartile range.
* Immunity status determined by the presence of hepatitis B surface antibody. Excludes 480 (10.8%) infants who left the Kaiser Permanente Northern California integrated health system before the end of the postimmunization testing interval.
† Infection status determined by the presence of hepatitis B antigen.
‡ Rates per 100 children tested; 95% CIs calculated assuming a Poisson distribution.

Figure 2. **HBV-positive rate among all children tested (n = 3353) and by maternal e antigen testing status (624 positive and 2317 negative).**



HBsAg = hepatitis B surface antigen.

cated that approximately 40% of infants born to HBV-infected mothers developed chronic HBV infection, and transmission rates were 90% among e antigen–positive mothers (11). Although the Centers for Disease Control and Prevention has prophylaxis guidelines, little information exists about their effectiveness in the United States (13). A meta-analysis of research trials suggested that immunoprophylaxis (HBIg and 3 doses of hepatitis B vaccine) may decrease neonatal transmission rates by 92% (relative risk, 0.08 [CI, 0.03 to 0.17]) compared with no immunoprophylaxis (14). A study of 2356 children in Taiwan, where universal HBV screening and 3 doses of hepatitis B vaccine were recommended, found transmission rates of 0.29% among children of e antigen–negative mothers and 9.26% among children of e antigen–positive mothers (substantially higher than our finding). The study had high rates of follow-up but no detailed information on vaccine administration and viral load. The HBIg costs in that study were covered only for infants of e antigen–positive mothers, and HBIg was administered within 12 hours of birth less frequently (15) than in our study. In another community-based study in the United States, among infants followed by the national Perinatal Hepatitis B Prevention Program, the average proportion completing the recommended immunization series decreased from 86% in 1994 to 78% in 2008; however, relatively few infants (49.3%) had follow-up serologic testing, precluding complete analyses of effectiveness (13). A more recent community-based study from the Enhanced Perinatal Hepatitis B Case Management Projects reported a testing rate of 77% (15).

Our results suggest that an organized program with high rates of prenatal screening, detection, and immunoprophylaxis can effectively prevent vertical transmission of hepatitis B. By 2010, most HBsAg-positive mothers in our study received prenatal testing for e antigen status and HBV viral load, nearly all of the infants of infected mothers received HBIg and all 3 hepatitis B vaccine doses within the recommended time frames, and most children received follow-up testing for HBV immune status and infection.

Maternal antiviral therapy in addition to infant immunoprophylaxis has been advised for some pregnant women with hepatitis B, although data supporting its use and identifying which populations are the most likely to benefit are scant (16). A case–control study of infants in Taiwan born between 1972 and 1980, before the use of immunoprophylaxis, reported an increased risk for transmission among mothers with higher maternal viral loads (17). A study of HBsAg-positive pregnant women in Australia identified 4 cases of transmission among 138 infants tested for HBsAg (2.9%) after immunoprophylaxis; the mothers all had HBV DNA levels greater than 1×10^8 IU/mL (18).

Our study has 2 important clinical implications. First, there was essentially no postprophylaxis transmission for mothers who were e antigen–negative or for mothers who were e antigen–positive with a viral load less than 5×10^7 IU/mL. Prenatal treatments, such as oral antiviral agents,

Table 5. **Infections Among Children Tested for HBsAg, by Maternal e Antigen Status and Viral Load***

Variable	Infected/Tested Children, *n/N (%)*		
	Low Viral Load	High Viral Load	Total
Viral load <200 000 or ≥200 000 IU/mL			
Maternal e antigen status			
Negative	0/652 (0)	0/20 (0)	0/672 (0)
Positive	0 (36)	3/127 (2.4)	3/163 (1.8)
Total tested	0/688 (0)	3/147 (2.0)	3/835 (0.4)
Viral load <5 × 10^7 or ≥5 × 10^7 IU/mL			
Maternal e antigen status			
Negative	0/671 (0)	0/1 (0)	0/672 (0)
Positive	0/88 (0)	3/75 (4)	3/163 (1.8)
Total tested	0/759 (0)	3/76 (3.9)	3/835 (0.4)

HBsAg = hepatitis B surface antigen.
* Infections represent the number of children in each category who tested positive for e antigen divided by the total number of children tested for e antigen. Among 3966 infants who retained membership in Kaiser Permanente Northern California through the postvaccination testing period, follow-up testing for HBsAg was completed for 3353 (85%) of all infants, 2945 (85%) of 3473 infants with maternal e antigen testing, and 837 (93%) of 904 infants with both maternal viral load and e antigen testing (after 1 July 2007). Differences between the aforementioned numbers and those presented in the table are due to infant exclusion because of results labeled "borderline" for maternal e antigen status.

are unlikely to be of additional benefit in this population and may cause harm, even if used only for short periods, by inducing viral resistance or posttreatment hepatitis flares (19). Second, there was a detectable but low risk for transmission after prophylaxis among children of mothers who were e antigen–positive with a viral load of 5×10^7 IU/mL or greater.

This study has several limitations. First, testing for HBV immunity and infection was less complete and timely in earlier years than in later years of the study (**Table 2**). The longer opportunity for infection after birth could explain higher failure rates among these older children; however, this is probably not a complete explanation because a higher proportion of these children was also initially antibody-negative and required a booster or second series of immunizations. Second, because DNA testing has been widely used only in recent years, we were able to analyze data stratified by DNA viral load levels for only a subset of patients. However, this subset still represents one of the largest populations with viral load data reported to date, which enabled us to analyze infection rates stratified by maternal viral load. This information has been lacking in large U.S. studies. Third, most women did not receive antiviral therapy, which permitted an evaluation of the effectiveness of immunoprophylaxis alone. Finally, the results were measured in an organized screening and tracking program, which may be difficult to implement in some settings. The National Perinatal Hepatitis B Prevention Program, for example, found that lower rates of timely immunization and testing occur in some settings (13). Nonetheless, the increasing use of electronic data systems suggests similar programs could be created. The high rates of immunization and infant testing enabled us to evaluate the true effectiveness of a prophylaxis program.

In summary, our study shows that, with high rates of adherence, immunoprophylaxis administered according to current Centers for Disease Control and Prevention guidelines is highly effective for preventing perinatal transmission of HBV from HBsAg-positive mothers, particularly for those who are e antigen–negative or have a viral load less than 5×10^7 IU/mL. Such women are unlikely to benefit from additional interventions to decrease vertical transmission. Mothers who were e antigen–positive or had a viral load of 5×10^7 IU/mL or greater had low but detectable transmission rates. Future studies to evaluate the effectiveness of additional prophylaxis measures, such as late-pregnancy antiviral treatment, are warranted among these high-risk women.

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