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Prevention of Vertical Transmission of Hepatitis B: An Observation Study

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Abstract

Background—For mothers with chronic hepatitis B virus (HBV) infection, the US Centers for Disease Control recommend 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—HBV perinatal immunoprophylaxis program within Kaiser Permanente Northern California, an integrated health services delivery organization.

Patients—4,446 infants born to 3,253 HBV positive mothers, between 1997–2010.

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Measurements—Compliance with 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 for 1997-2010 (Poisson 95% confidence interval (CI): 0.48-1.10). Rates were 3.37 per 100 (95% CI 2.08-5.14) for e-antigen positive mothers; and 0.04 (95% CI 0.001-0.24) for e-antigen negative mothers. Among mothers with viral load testing, the lowest level associated with transmission was 63,200,000 IU/ml. Infection rates per 100 were 3.61 (95% CI 0.75-10.56) among the 83 births to mothers with viral loads $\geq 50,000,000$ IU/mL and 0.00 among the 831 births to mothers with viral loads $<50,000,000$ IU/mL, regardless of e-antigen status.

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

Conclusion—Pre-natal HBV screening followed by post-natal prophylaxis is highly effective in preventing vertical transmission of HBV. A negative e-antigen status or a viral load of $<50,000,000$ IU/mL (90.9% of women tested) identifies women at extremely low risk of transmission after immunoprophylaxis who are unlikely to benefit from further interventions.

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INTRODUCTION

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

Perinatal HBV transmission can be reduced by identifying HBV-infected pregnant women using tests for hepatitis B surface antigen (HBsAg) and providing hepatitis B immunoglobulin (HBIG) and hepatitis B (HepB) 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 US Centers for Disease Control and Prevention (CDC) recommends that infants of HBV-positive mothers receive HBIG and HepB vaccination within 12 hours of birth, and 2 additional HepB vaccinations at ages 1-2 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 (N<200 patients), often occurred in countries with varying prophylaxis protocols, had low compliance, 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 anti-viral medications.(6-11) The availability of comprehensive data from large numbers of 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 harm from treatment, such as the 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 within an integrated health services delivery organization, including evaluation of compliance, 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. KPNC has approximately 3.3 million members and delivers over 36,000 infants annually. KPNC membership demographics approximate the underlying census population of Northern California.(12) The KPNC Regional Perinatal Hepatitis B Tracking program (hereafter “the tracking program”) was started in 1988 to identify and help manage prenatal hepatitis B carriers and their exposed infants to decrease risk of vertical transmission. Screening efforts identify pregnant carriers, and tracking efforts follow infants to ensure proper immunization and follow-up testing. The present study included births from 1997 through 2010 at KPNC facilities.

Case Identification and Testing

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

Post-Natal Tracking

Pregnant HBsAg+ women due to deliver within 4 months are identified 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 HepB vaccinations. Electronic reminders are sent to pediatric providers prior to the first scheduled infant check-up and when serology tests are due. HBIG were considered “on time” if administered within 12 hours of birth. HepB vaccines were considered “on time” using the following parameters: birth dose: 12 hours of age; second dose: 24 to 67 days of age; and third dose: 164 to 214

days of age. We also considered an alternate definition, whereby the third dose was “on time” if it was administered within 245 days (8 months) of birth.

KPNC serologic testing for hepatitis B surface antibody and hepatitis B surface antigen is recommended to occur at 4 weeks after receipt of the final HepB vaccination (generally at the next well-child check-up), from 9 to 15 months of age. Prior to 2006, testing for hepatitis B serology was recommended but not tracked. In March of 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+ mothers since 1997.

Statistical Methods

Analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC) and Stata version 10.1 (StataCorp, College Station, TX). The main outcomes of interest included: rates of infant immunization (%); rates of testing mothers for e-antigen and viral load (%); and infant infection rate, defined as number of infants with HBsAg positivity among those with on time administration of HBIG and vaccinations (per 100 children tested). Infants who left KPNC coverage were excluded from analyses for vaccinations or testing due after their departure from membership. Demographic comparisons between the screening program population and the KPNC maternal and neonatal populations (Table 1) were performed using t-tests for continuous variables (i.e. age), two-sample tests of proportion for categorical variables (i.e. race/ethnicity, sex), and chi-square test for association between testing of children for HBsAg and maternal e-antigen status. Ninety-five percent confidence intervals (CI) for HBV infection rates were calculated assuming a Poisson distribution (Stata command *ci...*, *poisson*). Where relative risk estimates [i.e. incidence rate ratios (IRR)] are presented, Poisson regression was used to evaluate the association between potential risk factors and incidence of HBV infection in children (Stata command *poisson*). The study protocol was approved by the Kaiser Permanente Institutional Review Board.

RESULTS

Study population

Between 1997 and 2010, the program followed 4,446 infants born within KPNC to 3,253 HBsAg+ mothers, with an average of 318 births per year (range: 261-381); this was approximately 9.25 births to HBsAg+ mothers per 1,000 total births at KPNC. Compared with the overall KPNC population, mothers who were HBsAg+ were older, and their children were more likely to be Asian/Pacific Islanders and less likely to be White (non-Hispanic or Hispanic) or of an unknown race/ethnicity (Table 1).

Rates of immunization

The rate of timely immunization increased between 1997-2010 (Table 2a) and, using the most strict criteria of 12-hours, 67 days, and 214 days, 87% of children received HBIG and all 3 HepB vaccinations “on time” in 2006-2010 (Figure 1).

Serologic testing for HBV immunity

A prospective program of post-vaccination testing began in 2006; at the same time, a retroactive testing program was implemented to follow up on children born pre-2006. Among children remaining in KPNC membership at least 2 months past completion of the vaccination series, 79% of those born in 1997-2000 and 94% of those born 2006-2010 had follow-up testing for hepatitis B surface antibody (i.e., immunity) (Table 2b). Of children tested, 67% born 1997-2000 demonstrated immunity on the first test, and 91% demonstrated immunity on any test (i.e., initially or following additional vaccination). For the period 2006-2010, 98% demonstrated immunity on the first test and 99% demonstrated immunity on any test (Table 2b).

Testing mothers for e-antigen/viral load and children for HBsAg

Among all 4,446 infants born to HBsAg+ women (1997-2010), 3,872 (87%) of mothers were tested for e-antigen within one year before or after the delivery; among them, 94% were tested prior to delivery. For mothers of the 1,185 children born July 1, 2007 through 2010, 1,100 (93%) were tested for viral load and 1,008 (85%) were tested for both e-antigen and viral load. Including the period prior to routine viral load testing (i.e., 1997-2010), 1,290 (29%) of mothers were tested for viral load and 1,183 (27%) for both e-antigen and viral load.

Among all births, 3,966 infants (89%) retained KPNC membership through the post-vaccination testing period; among these, follow-up testing for HBsAg was completed for 3,353 (85%) of all infants, for 2,945 (85%) of 3,473 infants with maternal e-antigen testing, and for 837 (93%) of 904 infants with both maternal viral load and e-antigen testing (after July 1, 2007).

HBV infection rate

Among all children, 0.75% (25/3,353 tested) were positive for HBsAg as of January 2012 (Table 3a); thus, the overall infection rate was 0.75 per 100 (95%CI: 0.48-1.10). The overall testing rates increased over time (Table 2a), and there was a decrease in infection rates over this period [unadjusted Poisson IRR per year = 0.90, 95%CI (0.82-1.00)] (Figure 2).

Of the 25 children with HBV infection, all had their HBIG and vaccinations within or close to the recommended intervals. All 25 had HBIG and the first vaccination within 12-hours of birth; 19 had the second vaccination within 24-62 days of birth and the 6 who were outside of this range received it within 70 days of birth. The majority (22/25) of the HBV-infected children also received the third vaccination within the recommended 164-214 days; the remaining three received their third vaccination between 219 and 237 days (and had their second vaccination on time).

HBV infection rate 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 (95%CI: 2.08-5.14). Among 2,317 children born to the 1,823 e-antigen-negative mothers, only 1 infant was infected (viral load unknown), even though this child received HBIG and was appropriately vaccinated (0.04 per 100; 95%CI: 0.001-0.24).

(Figure 2). The relative risk of transmission for maternal e-antigen positive status was IRR=79.72, 95%CI (10.61-598.70), after adjustment for sex, race of the infant, and maternal age. Testing of children for HBsAg was not related to maternal e-antigen status (chi-square $p=0.32$, data not shown). In a multivariate analysis which included e-antigen pre-term delivery, low birthweight, and small for gestational age, only e-antigen was a predictor of hepatitis B transmission; however, the small number of outcomes in these subgroups provided limited power for these sub-analyses.

HBV infection rate 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 viral load $>50,000,000$ IU/ml (3/76=3.95%) tested positive for HBsAg (3.95 per 100, 95%CI: 0.81, 11.53); all 3 mothers were e-antigen positive. All 3 children received their HBIG and vaccinations approximately within the recommended time frame, except that 1 child received the second vaccination at 70 days. The maternal viral loads for the 3 infected children were 277,000,000, $>110,000,000$ (limit of that assay), and 63,200,000 IU/ml.

The distributions of infants by different cut-offs of maternal viral load and e-antigen status are described in Table 3b. There were no episodes of transmission among the 671 children of e-antigen negative mothers with a viral load of $<50,000,000$ IU/ml (80.4% of population) or among the 88 children of e-antigen positive mothers with a viral load of $<50,000,000$ IU/ml (10.5% of population) (Table 3b); together, these groups included 90.9% of the population. Whether children received serologic testing was unrelated to maternal viral load (chi-square $p=0.77$, data not shown).

Other therapies for hepatitis B

Among the 1,100 women with viral load testing (July 2007 onward), 115 (10%) had 1 or more prescriptions filled for an oral antiviral medication against HBV prior to delivery, including 39% of mothers who had a viral load $>200,000$ IU/ml (the cut-off for recommended referral to a gastroenterologist) and 4% of mothers who had a viral load of $<200,000$ IU/ml., Lamivudine was the most commonly used agent, followed by Tenofovir.

Among the 3 infected children born July 2007-2010, 1 mother did not have prenatal antiviral prescriptions (viral load $>110,000,000$ IU/ml), and 2 mothers began antiviral therapy in the week before delivery (6 days and 2 days prior to delivery for mothers with viral loads of 63,200,000 and 277,000,000, respectively).

DISCUSSION

The present study demonstrates that immunoprophylaxis with HBIG and hepatitis B immunization is very effective at preventing perinatal transmission of HBV. Risk factors for transmission include maternal positive e-antigen status and higher viral load, although a precise cut point is difficult to assign, given the low overall infection rate. Among mothers who were e-antigen negative or who were e-antigen positive with a viral load $<50,000,000$ IU/mL, few of whom were on anti-viral therapies, there was no episode of vertical transmission. The lowest recorded viral load in a mother-child transmission pair was

63,200,000 IU/mL for an e-antigen positive mother; thus, a viral load <50,000,000 IU/ml represented a cut-off supported by the current data, below which no patient experience transmission and which represented 90.9% of all mothers.

The current study provides data on neonatal transmission of hepatitis B within the era of contemporary management and therapy. Estimates of vertical HBV transmission rates from the 1970s, before immunoprophylaxis was available, indicated 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 CDC has prophylaxis guidelines, little information exists regarding their effectiveness in the US.(13) A meta-analysis of research trials suggested that immunoprophylaxis (HBIG and 3 doses of HepB vaccine) may decrease neonatal transmission rates by 92% (RR=0.08, 95% CI: 0.03-0.17) compared with no immunoprophylaxis.(14) A study of 2,356 children in Taiwan, where universal HBV screening and 3 doses of HepB vaccine was 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. HBIG costs in that study were covered only for infants of e-antigen positive mothers and there was a lower frequency of HBIG administration within 12 hours of birth¹⁵ compared with the present study. In another community-based study within the US, 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 program can effectively prevent vertical transmission of hepatitis B. By 2010, the majority of HBsAg+ mothers in the current study received prenatal testing for e-antigen status and HBV viral load, nearly all of infants of infected mothers received HBIG and all 3 HepB vaccinations 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 1972-1980, prior to the use of immunoprophylaxis, reported an increased risk of transmission among mothers with higher maternal viral loads.(17) A study of HBsAg+ 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 >100,000,000 IU.(18)

There are two important clinical implications of our study. First, there was essentially no post-prophylaxis transmission for mothers who were e-antigen negative, or for mothers who were e-antigen positive with a viral load <50,000,000 IU/ml. Prenatal treatments such as

oral antiviral agents are unlikely to be of additional benefit in this population and may cause harm, even if used only for short periods of time, by inducing viral resistance or post-treatment hepatitis flares.(19) Second, there was a detectable but very low risk of transmission after prophylaxis among children of mothers who were e-antigen positive with a viral load $\geq 50,000,000$ IU/ml.

This study has several limitations. First, testing for HBV immunity and infection was somewhat less complete and timely in earlier years than during the later years of the study (Table 2). The longer opportunity for post-birth infection could explain higher failure rates among these older children; however, this is unlikely to be a complete explanation since a higher proportion of these older children were also initially antibody-negative and required a booster or second series of immunizations. Second, since DNA testing was widely utilized only in more 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, enabling us to analyze infection rates stratified by maternal viral load, information that has been lacking in large US studies. Third, because the majority of women did not receive anti-viral therapy, it permitted an evaluation of the effectiveness of immunoprophylaxis alone. Lastly, the results were measured within 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 much 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 testing of the infants enabled us to evaluate the true effectiveness of a prophylaxis program.

In summary, we demonstrate that, with high rates of adherence, immunoprophylaxis using current CDC guidelines is highly effective for preventing perinatal transmission of HBV from HBsAg+ mothers, particularly for mothers who are negative for e-antigen or who have a viral load of $<50,000,000$ IU/ml. These populations of women are unlikely to benefit from additional interventions to decrease vertical transmission. Mothers who were e-antigen positive and/or had a viral load $\geq 50,000,000$ IU/ml had very 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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Figure 1. Proportion of births receiving HBIG within 12 hours plus 3 HepB vaccines within 7, 8 and 12 months*, KPNC 1997-2010

Abbreviation: HBIG- *hepatitis B immunoglobulin*; HepB-*hepatitis B*

* This refers to having received the HBIG and 3 HepB vaccinations within the specified time period; an individual HepB vaccination may or may not have been “on time”.

** In 2001, the Program Coordinators began calling the infant’s provider prior to the 6 month appointment to remind them to administer the final vaccine and post vaccine serology. This policy likely has resulted in increase in the proportion of infants who received HBIG and all 3 vaccinations by month 7 between 2001 and 2003.

Figure 2. HBV+ rate among all children tested (n=3,353) and by maternal e-antigen (HBeAg) testing status (n=624 HBeAg+, n=2,317 HBeAg-)

Abbreviation: HBsAg+- hepatitis B surface antigen positive status; HBeAg- hepatitis B e-antigen status

Table 1

Demographic characteristics of HBsAg+ mothers and their children and all KPNC births*, 1997-2010.

	HBsAg+ Mothers n (%)	Children n (%)	All KPNC births* n (%)
Race/ethnicity			
NH White	179 (5.5)	322 (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/PI	2,607 (80.1)	3,254 (73.2)	83,166 (17.5) **
Native American	7 (0.2)	8 (0.2)	1,409 (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	3,253 (100)	4,446 (100)	476,099 (100)
Maternal age (years)			
mean (SD)	31.0 (5.3)		29.2 (6.0) **
<20	62 (1.4)		28,846 (6.0)
20-24	435 (9.8)		79,499 (16.7)
25-29	1,206 (27.1)		134,444 (28.3)
30-34	1,587 (35.7)		137,117 (28.9)
35-39	935 (21.0)		76,048 (16.0)
40+	221 (5.0)		18,857 (4.0)
Total	4,446 (100)		474,811 (100)
Sex			
Female		2,159 (48.6)	232,284 (48.8)
Male		2,287 (51.4)	243,748 (51.2)
Total		4,446 (100)	476,032 (100)

Abbreviations: HBsAg=Hepatitis B surface antigen; KPNC=Kaiser Permanente Northern California; NH=Non-Hispanic; PI=Pacific Islander; SD=standard deviation

* Excluding the 4,446 births in the HBsAg+ population. Among KPNC infants, 1,288 were missing maternal age, and 67 had unknown/'other' sex.

** p<0.001 using t-test for continuous variable (i.e. age) and two-sample tests of proportion for categorical variables (i.e. race/ethnicity and sex).

Table 2

Timing and completeness of prophylaxis and testing for immunity and infection among children born to HBsAg+ mothers, 1997-2010.

2a. Prophylaxis				
	Total n (%)	1997-2000 n (%)	2001-2005 n (%)	2006-2010 n (%)
At Birth				
Total	4,446 (100)	1,152 (100)	1,616 (100)	1,678 (100)
HBIG				
<12 hours	4,343 (97.7)	1,120 (97.2)	1,574 (97.4)	1,649 (98.3)
12 to <24 hours	76 (1.7)	20 (1.7)	33 (2.0)	23 (1.4)
24 hours	24 (0.5)	11 (1.0)	8 (0.5)	5 (0.3)
Missing/Refused	3 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
1st HepB Vaccine				
<12 hours	4,367 (98.2)	1,121 (97.3)	1,587 (98.2)	1,659 (98.9)
12 to <24 hours	63 (1.4)	23 (2.0)	24 (1.5)	16 (1.0)
24 hours	14 (0.3)	8 (0.7)	4 (0.3)	2 (0.1)
Missing/Refused	2 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
2nd HepB Vaccine (target 1-2 mo) *				
<24 days	2 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
24 to 67 days	4,069 (93.9)	1,079 (94.9)	1,492 (94.1)	1,498 (93.0)
68 to 92 days	243 (5.6)	51 (4.5)	87 (5.5)	105 (6.5)
>92 days	18 (0.4)	5 (0.5)	7 (0.4)	6 (0.4)
Missing/Refused	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Total	4,334 (100)	1,137 (100)	1,586 (100)	1,611 (100)
3rd HepB Vaccine (target 6 mo) **				
<164 days	22 (0.5)	12 (1.1)	3 (0.2)	7 (0.5)
164 to 214 days	3,697 (90.6)	909 (84.5)	1,356 (91.8)	1,432 (93.8)
215 to 245 days	256 (6.3)	97 (9.0)	92 (6.2)	67 (4.4)
>245 days	104 (2.6)	58 (5.4)	26 (1.8)	20 (1.3)
Total	4,079 (100)	1,076 (100)	1,477 (100)	1,526 (100)
2b. Testing for immunity and infection				
	Total n (%)	1997-2000 n (%)	2001-2005 n (%)	2006-2010 n (%)
HBV Immunity (HBsAb) ***				
N (%) tested	3,540 (89)	811 (79)	1,305 (91)	1,424 (94)
N (%) positive at 1 st test	3,132 (88)	545 (67)	1,196 (92)	1,391 (98)
N (%) ever positive	3,420 (97)	737 (91)	1,273 (98)	1,410 (99)
Median age tested (IQR) [†]	11 (10-16)	21 (11-109)	11 (10-16)	10 (9-12)
HBV Infection (HBsAg) ***				
N (%) tested ^{**}	3,353 (85)	715 (70)	1,235 (86)	1,403 (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 tested (IQR) [‡]	12 (10-17)	37 (11-113)	12 (10-18)	10 (9-12)

* Excluding n=110 (2.5%) who left KP before 2-month interval was complete

** Excluding n=365 (8.2%) who left KP before 6-month interval was complete. Visit was considered completed “at 6 months” until start of 7th month (214 days), and completed “at 7 months” until start of 8th month (245 days).

*** Excluding n=480 (10.8%) who left KP before post-immunization testing interval was complete

[‡] Age, in months, represents age first tested.

[‡] Rate per 100 children tested; 95% confidence intervals calculated assuming a Poisson distribution Recommended time frame for each immunization is indicated by italics (i.e., <12 hours)

Abbreviations: HBIG = hepatitis B immunoglobulin; HBV = hepatitis B; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; IQR = interquartile range, i.e. 25th to 75th percentile; CI = confidence interval

Table 3

Infections* among children tested for HBV surface antigen, overall and by maternal e-antigen status** and viral load***.

3a. Overall infection rate and by e-antigen status

	Total (infected/tested (%))
<u>Births 1997-2010</u>	
All children tested	25 / 3,353 (0.75%)
By maternal e-antigen status**	
e-Antigen –	1 / 2,317 (0.04%)
e-Antigen +	21 / 624 (3.4%)
Total with maternal e-antigen	22 / 2,941 (0.7%)
<u>Births July 2007 to December 2010</u>	
All children tested	3/ 981(0.31%)
By maternal e-antigen status**	
e-Antigen –	0 / 722 (0%)
e-Antigen +	3/ 169 (1.8%)
Total with maternal e-antigen	3/ 891 (3.4%)

Table 3b By maternal e-antigen* and viral load (July 2007 to December 2010)**

	Low viral load (infected/tested (%))	High viral load (infected/tested (%))	Total (infected/tested (%))
	<200,000 IU/mL	200,000 IU/mL	
e-Antigen –	0 / 652 (0%)	0 / 20 (0%)	0 / 672 (0%)
e-Antigen +	0 / 36(0%)	3 / 127 (2.4%)	3 / 163 (1.8%)
Total tested	0 / 688 (0%)	3 / 147 (2.0%)	3 / 835 (0.36%)
	<50,000,000 IU/mL	50,000,000 IU/mL	
e-Antigen –	0 / 671 (0%)	0 / 1 (0.0%)	0 / 672 (0%)
e-Antigen +	0 / 88(0%)	3 / 75(4.0%)	3 / 163 (1.8%)
Total tested	0 / 759 (0%)	3 / 76 (3.9%)	3 / 835 (0.36%)

* Infections represent the number of children in any given category who tested antigen positive divided by the number of children tested for antigen. Each cell shows the number of children infected, the number of children tested, and the percent of children infected.

** A small number of “borderline” maternal e-antigen status results (n=4) were excluded from these totals.

*** Among 3,966 infants who retained KPNC membership through the post-vaccination testing period, follow-up testing for HBsAg was completed for 3,353 (85%) of all infants, for 2,945 (85%) of 3,473 infants with maternal e-antigen testing, and for 837 (93%) of 904 infants with both maternal viral load and e-antigen testing (after July 1, 2007). (Note: Differences between numbers listed here and those presented in the table are due to infants excluded due to borderline maternal e-antigen status result.