Jane A. Buxton, MBBS, MHSc, FRCPC, Mei Chong, MSc, Cheryl McIntyre, RN, BScN, Elizabeth Brodkin, MD, Linda McCannell, RN, BScN, Mary Margaret Proudfoot, BN, MSc, Margot Smythe, RN, BScN

# Vaccine timing and post-immunization serology of infants in British Columbia who received hepatitis B vaccine at less than 7 days of age

High-risk infants must be tested after receiving hepatitis B vaccine series to ensure proper follow-up and care.

**ABSTRACT:**

***Background:*** **Vertical transmission of hepatitis B may occur despite postexposure prophylaxis, and 90% of infected infants will progress to chronic infection. In 2005, the BC Centre for Disease Control collaborated with health authorities throughout the province to assess the immunization coverage of children born in 2001.**

***Methods:*** **A random sample of 4631 infants was selected from the client registry data file and linked with the Integrated Public Health Information System to determine vaccine uptake. Where information was incomplete, parents/guardians, health units, and physicians were contacted. Infants who had received hepatitis B vaccine at less than 7 days of age were identified and timing of subsequent hepatitis B vaccine administration was determined. Parents of these infants in two health authorities were recontacted to determine the reason for early vaccination and whether postimmunization testing was performed.**

***Results:*** **Ninety-nine infants received hepatitis B vaccine at less than 7 days of age. All 99 infants received three doses of vaccine; two had received an invalid second dose (less than 28 days after the first). Risk information was available for 46 infants: 16 had a mother and 6 a father or a household contact with hepatitis B infection; 4 were born abroad or were traveling; and 20 (43%) had no identifiable risk factor. It was also determined that 7 of the 22 infants (31%) found to have continued exposure to hepatitis B reported no or uncertain serology.**

***Conclusions:*** **Some infants at high risk of hepatitis B transmission do not receive vaccine in a timely manner. Strategies are needed to increase physician and parent awareness regarding the importance of timely hepatitis B immunization and postimmunization testing, and to implement a protocol involving public health and primary care that ensures serology is performed.**

## Background

Hepatitis B (HB) is a viral infection that can be acquired by vertical transmission. Approximately 90% of infants infected with hepatitis B virus (HBV) will progress to chronic infection, with the possible later development of cirrhosis of the liver or hepatocellular carcinoma.[1] In Canada, all pregnant women should be screened for HBV infection; if a mother is hepatitis B surface antigen (HBsAg)

Dr Buxton is an assistant professor in the Department of Health Care and Epidemiology at the University of British Columbia and a physician epidemiologist at the BC Centre for Disease Control (BCCDC). Ms Chong is a biostatistician at BCCDC. Ms McIntyre is a nurse epidemiologist at BCCDC. Dr Brodkin is a community medicine resident at UBC. Ms McCannell is a program leader in communicable disease for the Richmond Health Service Delivery Area, Vancouver Coastal Health. Ms Proudfoot is the regional coordinator for communicable disease, Northern Health Authority. Ms Smythe is with Vancouver Communicable Disease Control, Vancouver Coastal Health.

positive, and thus infectious, then the infant should receive postexposure prophylaxis at birth.[2,3] Postexposure prophylaxis consists of hepatitis B immune globulin (HBIG) and HB vaccine administered within 12 hours of birth, and subsequent doses of HB vaccine administered at 1 and 6 months of age. Even with complete and timely postexposure prophylaxis, vertical transmission of HBV still occurs in 1% to 2% of infants;[4] rates up to 6.5% have been reported for infants born to mothers with high infectivity—that is, mothers positive for HBe antigen (HBeAg).[5] A recent retrospective review of infants born to mothers with HBV infection over a 7-year period found 2.3% were infected with HBV (oral communication, Ameeta Singh, Provincial Health Office, Edmonton, Alberta).

Infants born to mothers who are at very high risk for HBV infection—that is, intravenous drug users (IDUs) or sex trade workers—but who are HBsAg unknown or negative should also receive HBIG and the first dose of vaccine within 12 hours of birth. Infants with a primary caregiver or household contact (e.g., father or nanny) known to be chronically infected or at high risk of infection with HBV, or with a mother who is high risk but not an IDU or sex trade worker, should receive HB vaccine but not HBIG at birth.

The National Advisory Committee on Immunization and the BC Perinatal Protocol for HBV emphasize that accountability mechanisms should be in place to ensure that every infant born to an HBV-infected mother receives postexposure prophylaxis and is tested for serologic response to the HB vaccine.[2] Serology is recommended for all indications of HB vaccine administration at birth, and should be performed 1 to 6 months after completion of the HB immunization series. Serology will identify infants who have been infected to ensure timely referral and treatment. It will also identify infants who have not mounted an adequate immune response to the vaccine and continue to be at risk.

Of about 40 000 pregnant women who deliver annually in BC, approximately 400 (1%) test positive for HBV on prenatal screening. If 2% of infants born to HBV-positive mothers were infected (despite postexposure prophylaxis), we would expect to identify eight infected infants each year in BC. Fewer infants than this were reported with chronic HBV infection in 2002 (three infants), 2003 (six), and 2004 (two). It is not known if this reflects a true low infection rate or if this lower-than-expected rate is due to lack of routine postimmunization serologic testing, which would identify infected infants. Infants infected at birth are usually asymptomatic. Follow-up procedures for infants with continued HBV exposure vary between and within health authorities. In some health authorities, the requisition for serology is provided to the parents by public health at the time of the third vaccine; in others, follow-up is at the discretion of individual physicians.

The hepatitis B immunization schedule for high-risk infants is 0, 1, and 6 months of age. For normal-risk infants in BC, the universal immunization schedule is 2, 4, and 6 months. The minimum acceptable interval between the first and second dose of HB vaccine is 1 month (28 days).

**Approximately 90% of infants infected with hepatitis B virus (HBV) will progress to chronic infection, with the possible later development of cirrhosis of the liver or hepatocellular carcinoma.**

## Methods

In 2005, the BC Centre for Disease Control (BCCDC) collaborated with the regional health authorities to assess immunization coverage at 2 years of age in a random sample of BC children born between January and December 2001. The aim of this evaluation was to determine the following:

- The reason that infants received HB vaccine at birth.
- If HBIG was administered.
- The timing of subsequent doses of HB vaccine.
- Whether postimmunization serology was performed.

Participants were selected from the client registry data file, chosen for most up-to-date address and telephone contact information, and were restricted to those who also had a record in the Medical Services Plan. A random sample of approximately 300 children

**Table 1.** Age of vaccine receipt of 99 infants who received first dose HB vaccine at less than 7 days.

| | Age first dose (days) | Age second dose (days) | Age third dose (days) |
|---|---|---|---|
| Recommended | 0 | 28 | 182 |
| Mean | <1 | 53 | 204 |
| Median | — | 35 | 188 |
| Range | 0–6 | 26–456 | 65–604 |

**Table 2.** Infants who received HB vaccine at less than 7 days of age in all health authorities.

| Health authority | All infants, random sample | Infants receiving HB vaccine <7 days age (%) |
|---|---|---|
| Vancouver Coastal Health | 922 | 52 (5.6) |
| Northern Health Authority | 796 | 5 (0.6) |
| Vancouver Island Health Authority | 870 | 9 (1.0) |
| Fraser Health Authority | 978 | 23 (2.4) |
| Interior Health Authority | 1065 | 10 (0.9) |
| Provincial total | 4631 | 99 (2.1) |

**Table 3.** Infants who received HB vaccine at less than 7 days of age in health service delivery areas of Vancouver Coastal Health.

| Health service delivery area | All infants in random sample | Infants receiving HB vaccine <7 days age (% ) |
|---|---|---|
| Vancouver | 328 | 19 (5.8) |
| North Shore/Coast Garibaldi | 305 | 4 (1.3) |
| Richmond | 289 | 29 (10.0) |

from each health service delivery area (HSDA) was selected (sample size was based on an estimated 65% point estimate for coverage, with plus or minus 5% error with a 95% confidence interval). The random sample provided an excellent opportunity to explore HB vaccine uptake and postimmunization serology in high-risk infants who received HB vaccine when less than 7 days old.

The integrated Public Health Information System was used to determine vaccine uptake for a total of 4631 infants. Where immunization information was incomplete, the health unit where the child resided was contacted for any paper-based or electronic records. Where records were not available, the health authorities or contracted staff contacted the parent/guardian and the child's physician to obtain immunization information.

A question was added to the coverage survey interview asking if the parent was willing to be contacted again. Infants in the cohort who had received the HB vaccine at less than 7 days of age were identified and the time of administration of subsequent doses of HB vaccine determined. Vancouver Coastal Health and Northern Health authorities agreed to participate in the follow-up of individual infants. A letter to parents was developed explaining the hepatitis B study and allowing parents to refuse to participate. Parents were contacted by telephone and asked a series of standard questions. Staff from the Northern Health Authority and the Richmond HSDA contacted parents directly; researchers at BCCDC contacted parents on behalf of North Shore/Coast Garibaldi HSDA and the Vancouver HSDA.

## Results

Overall, 85.3% of the 4631 participants in the coverage survey had received an acceptable series of HB vaccine at age 2 years. Ninety-nine participants (2%) were identified as receiving HB vaccine at less than 7 days of age; of these, 71 received the vaccine on the day of birth and 15 on the following day. All infants received three doses of vaccine. The timing of the HB vaccine administration is shown in **Table 1**. Two infants received the second dose less than 28 days (27 and 26 days) after the first. Although 64 infants (65%) received the second HB vaccine dose 28 to 40 days after the first, 11 infants (11%) received the second dose at more than 100 days of age. The geographic distribution of all 99 cases is shown in **Table 2**. The geographic distribution of cases within the Vancouver Coastal Health region is shown in **Table 3**.

Infants in the Vancouver Coastal Health and Northern Health authorities accounted for 58% of the infants in the random sample who received a first dose of HB vaccine within 7 days of birth. The reasons for early immunization of the infants who were followed up are shown in **Table 4**; 20 of the 46 infants followed (43%) had no identified HBV contact or risk.

All 16 infants born to mothers identified as HBV-positive received

**Table 4. Reasons reported by parents/guardians for infants receiving hepatitis B vaccine at less than 7 days of age.**

| Reason vaccine given | Infants immunized | Infants tested |
|---|---|---|
| Mother infected | 16 | 9 |
| Household contact/caregiver infected | 6 | 3 |
| Infant adopted from China | 1 | 1 |
| Infant born abroad (Kenya, Korea) | 2 | 0 |
| Infant traveling to Philippines (no other risk) | 1 | 0 |
| Infant born by emergency cesarean section; mother not infected | 1 | 0 |
| No risk factors, physician immunized early | 19 | 0 |
| Parent refused to participate | 2 | — |
| Contact not made | 9 | — |
| Total | 57 | 13 |

HBIG with the first dose of HB vaccine, nine received the first dose on the day of birth (day 0), two on day 1 (which may have been within 12 hours); and one each on day 2 and 3. Two infants who received the second dose of vaccine at more than 100 days after the first dose were reported to have a father with chronic HBV infection.

Seven of the 22 infants (31%) with continued HBV exposure (5 of 16 where the mother was infected, 2 of 6 where a close contact was infected) either did not have postimmunization serology performed or their parents did not know if they had been tested. No infant tested was identified as being infected with HBV.

## Conclusions

This study found that some infants at high risk of hepatitis B transmission do not receive HB vaccine in a timely manner, leaving them at continued risk of infection. Nearly one-third of infants with continued HBV exposure reported no or uncertain postimmunization serology to identify those infected (infection may occur despite complete and timely immunization) and those who have not responded to the vaccine and require further immunization to ensure protection from ongoing exposure.

Two percent of infants in the random sample were identified as receiving hepatitis B vaccine at less than 7 days of age. Overall, 0.95% of pregnant women tested positive for HBV during the 1996 to 2001 fiscal years. Infants whose mothers were at high risk for HBV infection, or whose fathers/primary caregivers had HBV, should also receive vaccine at birth. The number of infants in the sample with HBV-infected mothers was lower than expected. However, infants born to mothers who subsequently moved abroad would have been excluded from this evaluation, as only children residing in BC in 2005, when the survey was conducted, were included.

Vancouver and Richmond have the highest rate in the province for women testing positive for HBV on prenatal screening (written communication, Rob MacDougall, BCCDC laboratory, August 2005). Many infants in Richmond, a health service delivery area with a significant Asian population, received HB vaccine at birth even though they did not have an identified contact. This may be because physicians consider children born to families from endemic countries at high risk.

Two infants received an invalid second dose (i.e., sooner than the recommended minimum of 28 days). Two infants whose fathers were identified as having chronic HBV received the second HB vaccine more than 100 days after the first dose, leaving them unprotected and at risk of infection. In fact, the parents of 7 of the 22 infants (31%) with a mother, father, or other close contact with chronic HBV reported no serology or reported not knowing if serology had been performed. Studies have shown nonresponders to perinatal hepatitis B vaccination respond well to subsequent vaccination.[6] There is a need to improve parents' awareness of the importance of postimmunization testing so that they can ensure infant follow-up, especially as families may change physicians, move to another health authority, or leave the province.

The two different HB infant immunization schedules (high-risk and universal) in BC may be confusing for health care workers. To further complicate matters, there is a mixed system of immunization delivery, with public health delivering about 60% of immunizations and individual physicians about 40%. This proportion varies geographically, with individual physicians (89% GP, 4% pediatrician) administering about 93% of early childhood immunizations in Vancou-

## Hepatitis B vaccine and immune globulin recommendations for high-risk infants

- For infant born to a mother who is known to be hepatitis B surface antigen (HBsAg) positive: **Give hepatitis B immune globulin (HBIG) and hepatitis B (HB) vaccine at birth.**
- For infant born to a mother who is known to be at high risk for hepatitis B infection (intravenous drug user or sex trade worker but whose infectious status at delivery is unknown or negative (possible window period): **Give HBIG and HB vaccine at birth.**
- For infant born to a mother who is not an intravenous drug user or sex trade worker, but who has risk factors for hepatitis B infection and whose infectious status at delivery is unknown or negative (possible window period): **Give HB vaccine at birth.**
- For infant whose father, other primary caregiver, or household contact has chronic hepatitis B infection: **Give HB vaccine at birth.**
- For all high-risk infants who receive HB vaccine at birth: **Give second and third dose of HB vaccine at 1 and 6 months (i.e., vaccine series 0, 1, and 6 months).**

### Postimmunization testing

Postimmunization testing should be performed 1 to 6 months after completion of the HB vaccine series. HBsAg, anti-HBc, and anti-HBs testing should be requested.

- If HBsAg is found, the infant is likely to be a chronic carrier.
- If the infant is negative for HBsAg and anti-HBs, a second series of HB vaccine should be given and serological testing repeated 1 month after the repeat series.
- If anti-HBs ≥10 IU/L, the infant is protected from HBV.
- If anti-HBc is positive before 18 months of age, this may be due to circulating maternal antibodies or cleared infection; anti-HBc testing should be repeated after 18 months of age to determine if past infection occurred.

### Accountability mechanisms

Accountability mechanisms should be in place to ensure that every infant born to an HBV-infected mother receives HBIG and a full course of vaccine, and is tested for serologic response to vaccine.

**Figure.** Hepatitis B vaccine and immune globulin recommendations for high-risk infants

## Babies at high-risk of hepatitis B infection: Information for parents

If you or someone in your household has hepatitis B infection, your baby should receive hepatitis B vaccine at birth and two further doses of vaccine when he or she is 1 month old and 6 months old.

- Your baby must receive these three doses of hepatitis B on time to ensure that he or she is protected.

Your baby should then have a blood test 1 to 6 months after receiving the last of the three doses of hepatitis B vaccine. This test can tell if your baby is protected from hepatitis B infection. Some infants do not respond to the first three doses and need a second course of vaccine to better protect them.

Unfortunately, even when the vaccine is given at the recommended times, a few infants will become infected with hepatitis B. These infants will be referred to a specialist for follow-up and treatment.

- **Your baby must be tested after being vaccinated. This will show whether your baby is protected or infected and will allow further action to be taken if necessary.**

**Patient information.** This note may be freely copied and provided to patients.

ver,[7] and public health administering the majority of infant immunizations in areas outside the Lower Mainland. There is no consistency between and within health authorities as to who orders the serology, and who is responsible for follow-up to ensure that serology has been performed and that appropriate action has been taken.

Ensuring follow-up of high-risk infants receiving HB vaccine at birth presents challenges. The physician who administers the vaccine at birth may not continue with the infant's care in the community, families may move, the infant's first name may not be known at time of hospital discharge, and the infant's last name may differ from the mother's. Physicians may also underestimate the risk of vertical transmission that occurs despite complete and timely immunization and thus not be aware of the importance of postimmunization testing for high-risk infants.

A systematic testing protocol would identify (1) infants who do not mount an immune response and need to receive additional vaccine, and (2) infants who are HBV infected and need timely referral and treatment. To ensure appropriate follow-up, we recommend that strategies be explored to:

- Increase the awareness of physicians and parents regarding timely hepatitis B immunization and the importance of postimmunization testing.
- Implement a systematic protocol involving public health and primary care to ensure serology is performed.

**Of about 40 000 pregnant women who deliver annually in BC, approximately 400 (1%) test positive for HBV on prenatal screening.**

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**Competing interests**

None declared.

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