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1.0 INTRODUCTION

In British Columbia (BC), all cases of hepatitis B virus (HBV) that have not yet been entered into an electronic public health information system require documentation, geographical attribution and consideration for follow-up care. This guideline aims to meet the needs of BC health care professionals who are following-up individuals with newly identified HBV infection.

To meet the needs of the Regional Health Authorities (RHA's) and the communities they serve, this document presents information in a flexible way, to encourage client engagement with the health care system. Follow-up may occur by public health personnel or primary care providers.

1.1 Authority

Infection with Hepatitis B virus is a reportable condition under the Public Health Act (2008) and Schedule A of the Health Act Communicable Disease Regulation.

BC Public Health Act (2008) is available at:
http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_08028_01

Schedule A is available at: http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/12_4_83

1.2 Rationale for HBV Follow Up

Follow up of newly identified HBV infections can contribute to positive outcomes for the individual, their partners, their families and the community. Clients who test positive for HBV can be engaged into care to provide information about:

- transmission prevention
- follow-up clinical care (i.e., serology, imaging)
- treatment options
- education around lifestyle and diet
- immunizations
- screening for sexually transmitted infections

This is a key moment in which appropriate counselling can be offered for alcohol and substance use, including harm reduction services, which can include overdose prevention and naloxone training, and opioid agonist therapy.

1.3 Goals

To support public health personnel and primary care providers with information to engage individuals to reduce harms and adverse sequelae related to HBV. Using principles of health equity (e.g., trauma informed practice and cultural safety), to:

1. Provide universal immunization of all:
    - Infants
    - Individuals born 1980 or later
2. Provide targeted immunization of all:
    - Individuals who are at risk of becoming infected with HBV
    - Close, non-immune contacts of persons who are infected with HBV
3. Eliminate perinatal infection through:
    - Universal screening of all pregnant women for HBsAg prior to delivery
    - Screening for HBV DNA for pregnant women who are HBsAg and/or HBeAg positive
    - Consideration of antiviral prophylaxis if mother has a viral load >200,000 IU/mL
    - Follow–up of infants born to mothers who are HBsAg positive to ensure immunized infants are protected, and infants infected with HBV have been identified and engaged into care
4. Provide post-exposure immunoprophylaxis as indicated for persons at risk of infection
5. Consider HBV screening of immigrants from endemic countries.
6. Educate and counsel infected individuals and their contacts about:
    - Coinfection with human immunodeficiency virus (HIV) and other types of hepatitis
    - Immunization for hepatitis A and other vaccines where appropriate
    - Transmission prevention
    - Liver health (e.g., alcohol)
    - Reducing harms associated with illicit drug use (IDU), by connecting individuals with HBV with harm reduction prevention and support resources. This can include information on distribution sites for harm reduction supplies, supervised consumption sites, detoxification, mental health and substance use services, outreach programs, and opioid agonist therapy such as methadone maintenance therapy or buprenorphine/naloxone (e.g., Suboxone) therapy.

2.0 DEFINITIONS

Alanine aminotransferase (ALT) - Enzyme produced by the liver. Increased levels indicate inflammation of the liver, but do not always correlate with the severity of the disease process.

Anamnestic response – In response to being exposed to an antigen, the rapid reappearance of antibody in the blood an individual who had previously developed a primary immune response. This reflects ones immune memory, which is able to provide long term protection.

Anti-viral therapy -

- **Interferon (IFN)** – a type of cytokine with antiviral and immunomodulatory properties
- **Nucleos(t)ide Analogue (NA)** – oral antiviral treatment

Attribution – Refers to the geographic area (e.g., RHA) for surveillance reporting purposes.

Case Definitions – defined here for the purpose of surveillance reporting of acute, chronic and unspecified HBV infections (refer to Section 7.0)

Case Definitions	Criteria
Acute hepatitis B infection*	**Confirmed case** Hepatitis B surface antigen (HBsAg) and immunoglobulin M antibody to hepatitis B core antigen (anti-HBc IgM) positive in the context of compatible clinical history or probable exposure **OR** Clearance of HBsAg in a person who has prior HBsAg positive documentation within the last 6 months in the context of a compatible clinical history or probable exposure
	Probable case (not yet confirmed) Acute clinical illness in a person who is epidemiologically linked to a confirmed case
Chronic hepatitis B infection*	HBsAg positive for more than 6 months **OR** Detection of HBsAg in the documented absence of anti-HBc IgM **OR** Detection of HBV DNA for more than 6 months
	Note: In the absence of prior lab testing in BC, documentation received from other jurisdictions should be confirmed. When a client who has immigrated to BC from a HBV endemic country presents with a HBsAg positive result and has no history of acute symptoms, there is a high likelihood that this individual has a chronic HBV infection.
Undetermined hepatitis B infection	Does not fit the criteria for either an acute case or a chronic infection **AND** HBsAg positive **OR** detection of HBV DNA
	Note: This may be the case with occult HBV infection

***** Even with positive HBsAg and anti-HBc IgM results, a compatible clinical history or probable exposure is necessary. Clients with chronic HBV infection can experience a rise in anti-HBc IgM related to reactivation.

Contact
A susceptible individual who has had exposure to potentially infectious blood or body fluids of an HBV infected person. The incubation period for HBV is 45 to 160 days, with an average of 90 days.

Documentation – Recording of results and follow-up care provided to those testing for HBV. Guidelines may vary by RHA and agency.

Exposure –

- **Percutaneous Exposure -** Contact through the skin with blood of an HBV infected person, for example, through needlestick or other sharps injury, tattooing, body piercing, electrolysis, or acupuncture.

- **Perinatal Exposure –** Contact through vertical transmission from mother to infant during the perinatal period. The likelihood of transmission significantly increases when the hepatitis B surface antigen (HBsAg) positive mother is HBV DNA > 200 000 IU/mL

- **Permucosal Exposure -** Contact through the mucous membrane lining body cavities of an HBV infected person, for example, through a lesion of the eyes, nose, mouth, vagina, rectum or urethra with blood or body fluid

Flare or acute exacerbation of hepatitis B – Individuals with chronic HBV infection can present with intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value. This clinical presentation can mimic that of acute HBV infection (1).

Hepatitis B Immune Globulin (HBIg) – Passive immunoprophylaxis used in combination with hepatitis B vaccine to prevent mother-to-infant transmission and in certain other post-exposure scenarios. Prepared as a solution of hepatitis B Ig for intra-muscular administration. Waning anti-HBs levels can be detected up to 6 months later (2).

Horizontal transmission – Transmission via close person-to-person contact (e.g., household contacts). HBV somehow enters the bloodstream via extended, frequent contact with small cuts or skin rashes (3).

Iatrogenic – Unintentional and unfavourable response to a medical treatment or procedure caused by a healthcare provider.

Immunocompromised - Where the immune response is attenuated and functions at less than normal capacity due to the administration of immunosuppressive therapy, malnutrition or disease processes. Those who have HIV infection and CD4+ cell count ≤ 200 cells/mm^3, chronic kidney disease, or who have been on long-term immune suppressants may not be able to mount a normal antibody response to HBV and should be vaccinated. Immunocompromised individuals with chronic HBV infection can experience reactivation and/or flares. Those with agammaglobulinemia are unable to make their own antibodies.

Liver fibrosis - An accumulation of extracellular matrix proteins that are produced in excess, inefficiently broken down, or both. Normal liver cells are replaced with fibrous tissue and this leads to disruption of the normal liver function. Main causes include chronic HBV or HCV infection, excessive alcohol intake (>2-3 drinks/day) and non-alcoholic steatohepatitis (NASH), which is associated with obesity, diabetes or metabolic syndrome. Autoimmune hepatitis can also lead to chronic liver inflammation. Symptoms may not be present unless there is severe damage to liver function (4).

May be classified according to a histologic scoring system, such as METAVIR (5) :

- F0 = no fibrosis
- F1 = portal fibrosis without septa
- F2 = portal fibrosis with few septa
- F3 = numerous septa without cirrhosis
- F4 = cirrhosis

  - **Cirrhosis** - Progression of fibrosis to scarring and disruption of normally functioning structures in the liver. The presence of extensive 'bridging fibrosis' (fibrosis forming bridges between portal-vascular structures) on liver histology can confirm this diagnosis. It can be predicted by non-invasive investigations, such as by Fibroscan®. Advanced cirrhosis is supported by marked coagulopathy, portal hypertension, ascites and liver failure (5).

The gold standard for determining the severity of liver damage is liver biopsy.

Non-invasive alternative tools to measure liver fibrosis:

- **Fibroscan® (Transient Elastography)** - Ultrasound method used to detect advanced fibrosis and cirrhosis. A transducer probe mounted on a vibrator transmits vibrations toward the liver. The velocities of the pulse echos that follow the vibrations directly correlate with liver stiffness. These results can be correlated with the METAVIR scoring system. Results can be influenced by hepatic inflammation, obesity (less reliable results in BMI ≥ 25-28 kg/m^2), ascites, narrow intercostal spaces, and increased central venous pressure (4, 5).
- **Aspartate Aminotransferase-to-Platelet ratio index (APRI)** - An indirect method used to predict significant and severe fibrosis or cirrhosis. For the upper limit of a normal AST level, most labs use 40 IU/L. APRI score > 1.5 indicates significant fibrosis or cirrhosis, and APRI < 0.7 indicates no significant fibrosis (5)

$$\textbf{APRI} = \frac{\dfrac{\text{AST level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

For an online calculator, see www.hepatitisc.uw.edu/page/clinical-calculators/apri

- **FIB-4** - An indirect method used to help with liver fibrosis staging. FIB-4 < 1.45 indicates no significant fibrosis, and FIB-4 > 3.25 is predictive of advanced fibrosis or cirrhosis (5).

$$\textbf{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

For an online calculator, see www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

Non-responder – After one complete primary hepatitis B series, when someone has anti-HBs < 10 IU/L measured at 1 to 6 months post-vaccination

- **2-series non-responder –** After 2 complete hepatitis B series, when someone has anti-HBs < 10 IU/L measured at 1 to 6 months post-vaccination. Individual is considered susceptible to HBV and will require prophylaxis in post-exposure scenarios.

Number needed to treat (NNT) – in the context of post-exposure prophylaxis, the number of people needed to treat with hepatitis B vaccine and HBIg after exposure, in order to prevent one case of HBV infection over a certain time period. This estimate can help provide an indication as to the clinical effectiveness of a particular intervention or treatment.

Occult Blood infection (OBI) - Characterized by a positive HBV DNA (low viral replication) and presence of anti-HBc Total alone, or anti-HBc Total and anti-HBs in the absence of HBsAg (6)

Post-exposure prophylaxis (PEP) – Hepatitis B vaccine and HBIg can provide susceptible individuals with protection from HBV infection after exposure to HBV in certain scenarios, when given within a certain timeframe. An assessment of the type of transmission event, and if available, the immunization histories and post-vaccination serologic testing of the source and exposed persons, will help guide the decision as to whether or not PEP is indicated.

Reactivation – Increase in HBV replication in an individual with HBsAg-positive chronic HBV infection or resolved HBV infection. HBeAg-negative chronic hepatitis can reactivate following HBeAg seroconversion. Can occur spontaneously or after initiation of immune suppressing therapy (e.g. rituximab, HIV-related immunosuppression), corticosteroid therapy, immune modulation therapy, solid organ transplant or organ transplant recipients (7).

Susceptibility – A person is considered susceptible to HBV if they have **no** history of a protective antibody level following administration of a complete hepatitis B vaccine series (i.e., anti-HBs level less than 10 IU/L upon completion of vaccine series) OR no history of a test result indicating immunity from prior HBV infection (i.e., HBsAg nonreactive, anti-HBcTotal reactive and anti-HBs ≥ 10 IU/L)

Window period – duration of time between infection and laboratory detection of infection

3.0 HEPATITIS B VIRUS

Hepatitis B is a small double stranded DNA virus from the *Hepadnaviridae* family that can cause chronic liver disease (8). HBV is a blood-borne virus that is highly transmissible via perinatal, percutaneous or sexual exposure to a HBV infected person's blood and/or body fluids. Household contacts are also at risk of infection.

3.1 Clinical Description

HBV infection is most commonly acquired through sexual contact, injection drug use (IDU), and perinatal exposure from mother to infant. The likelihood of progression to chronic HBV infection is inversely related to the age at the time of infection (9). Around 95% of acute HBV infections acquired by immune competent adults will resolve within 6 months and provide lasting immunity, while 10-90% of infants born to mothers testing HBsAg reactive will acquire HBV infection, depending upon the mother's HBV DNA viral load (10-14). The incubation period for HBV is 45 to 160 days, with an average of 90 days.

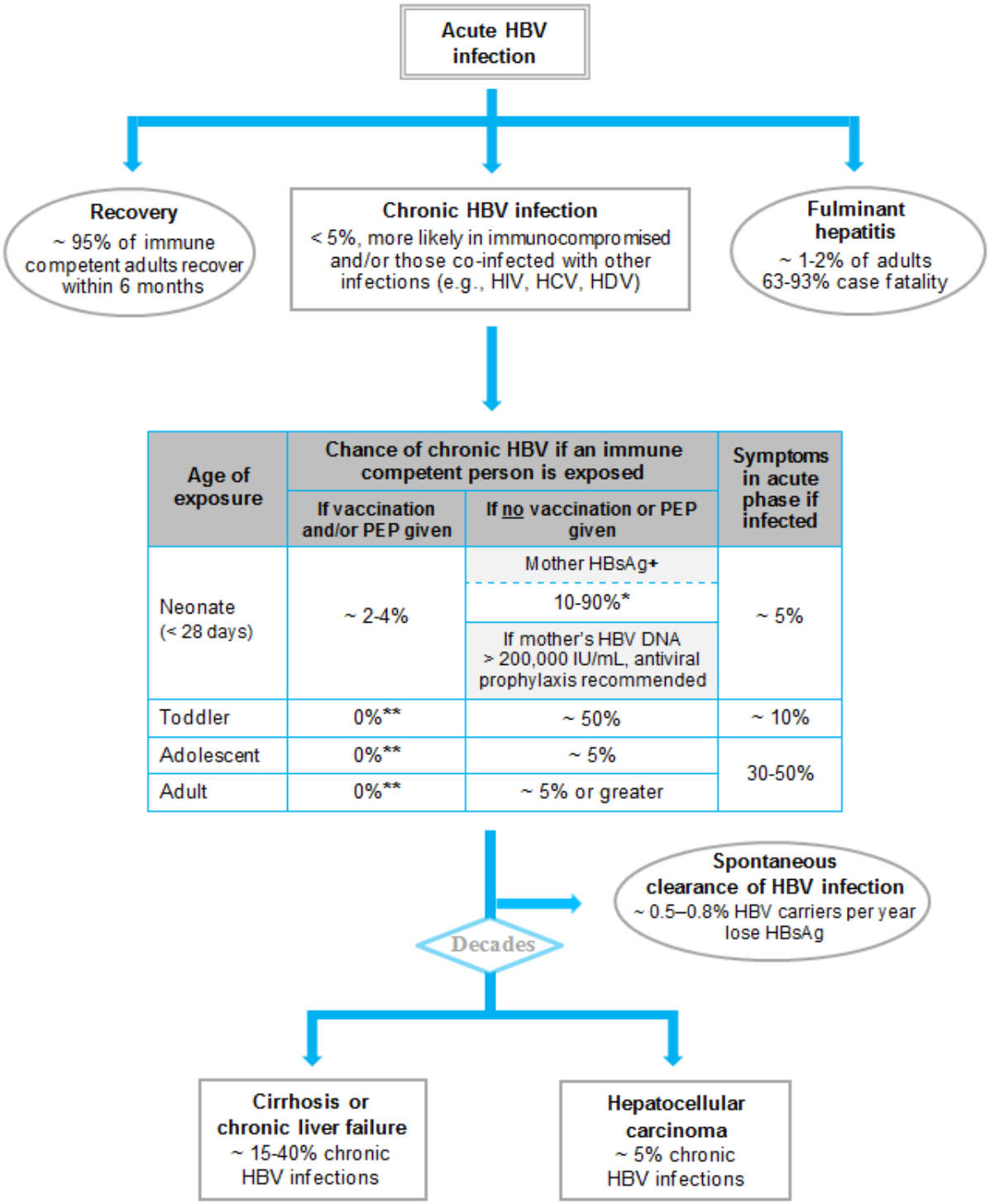
Less than 10% of children and 30–50% of adults with acute HBV infection have symptoms (refer to Table 3-1) (10, 15). Severity ranges from asymptomatic cases detectable only by serology and liver function tests, to fatal cases of acute hepatic necrosis that have an insidious onset of clinical illness. More likely to occur in older adults and those with prior liver damage, around 1-2% of adults with acute HBV infection will progress to fulminant hepatitis, of which there is a 63-93% case fatality rate (2, 10). Fulminant hepatitis may present as fatigue, jaundice, encephalopathy, ascites and worsening lab results. Individuals with chronic HBV infection who are withdrawing from immunosuppressive therapy, can also experience flares that could lead to fulminant hepatitis.

Chronic HBV infection is a leading cause of liver cancer and liver transplantation in Canada (16). Chronic HBV infection is most often asymptomatic, and this can lead to low rates of testing, diagnosis and reporting (17).

Table 3-1: Symptoms of acute HBV infection (2, 7, 10, 15, 18)

Acute Phase	Symptoms
Viral Replication Phase	• Asymptomatic • Abnormal liver chemistry • Serologic HBV markers present
Prodromal Phase (3-10 days)	• Anorexia • Vague right upper quadrant abdominal discomfort • Nausea and vomiting • Fatigue • Malaise • Arthralgia & arthritis • Myalgia • Rash & pruritus • Fever (may be absent or mild) • Headache
Icteric Phase (1-3 weeks)	• Dark urine • Light or gray stools • Jaundice • Hepatomegaly • Splenomegaly (less common)
Convalescent Phase	• Symptoms and jaundice resolve, although malaise and fatigue may persist for months • Liver enzymes return to normal

Figure 3-1: Pathogenesis of hepatitis B infection (7, 10-14)



Age of exposure	Chance of chronic HBV if an immune competent person is exposed		Symptoms in acute phase if infected
	If vaccination and/or PEP given	If no vaccination or PEP given	
Neonate (< 28 days)	~ 2-4%	Mother HBsAg+ 10-90%* If mother's HBV DNA > 200,000 IU/mL, antiviral prophylaxis recommended	~ 5%
Toddler	0%**	~ 50%	~ 10%
Adolescent	0%**	~ 5%	30-50%
Adult	0%**	~ 5% or greater	

* Consider mother's HBeAg and HBV DNA status. Risk to the infant is lower if the mother is HBeAg negative and HBV DNA is < 200, 000 IU/mL. Refer to Section 5.3 and Section 8.3.

** Those who have responded to prior vaccine or PEP

3.2 Chronic HBV Infection

Differentiating between acute HBV infection and an acute exacerbation of a chronic HBV infection, can be difficult, given the similarity in clinical presentation and serological markers. Individuals with acute HBV infection are likely to have had more recent exposures (e.g., sexual exposure), and to be symptomatic. Individuals with chronic HBV infection tend to have histories such as prior blood transfusions and/or family history in HBV endemic areas (i.e., perinatal infection or acquisition in childhood through horizontal transmission). While anti-HBc IgM is used to differentiate between acute and chronic HBV case definitions, it can be present in both acute and chronic HBV clinical scenarios (8, 19).

The phases of chronic HBV infection (refer to Figure 3-2) can vary widely from inactive, with very low levels of HBV DNA virus, to active, with very high or fluctuating levels of HBV DNA virus and liver enzyme levels. Progression through the different phases is not static and can be unpredictable. An individual's chronic hepatitis B status depends on evaluation of serial serology results and histological activity of the liver in the context of the presenting clinical scenario.

Practitioner Alert!

All individuals with chronic HBV infection are potentially infectious, regardless of clinical phase

The concepts of occult blood infection, reactivation and flares are important in understanding the nature of chronic HBV infection, testing, and ongoing transmission concerns. Risk for hepatocellular carcinoma (HCC) and cirrhosis increase during phases of active hepatitis, reactivation and hepatic flares (15).

3.2.1 HBV Occult Blood Infection

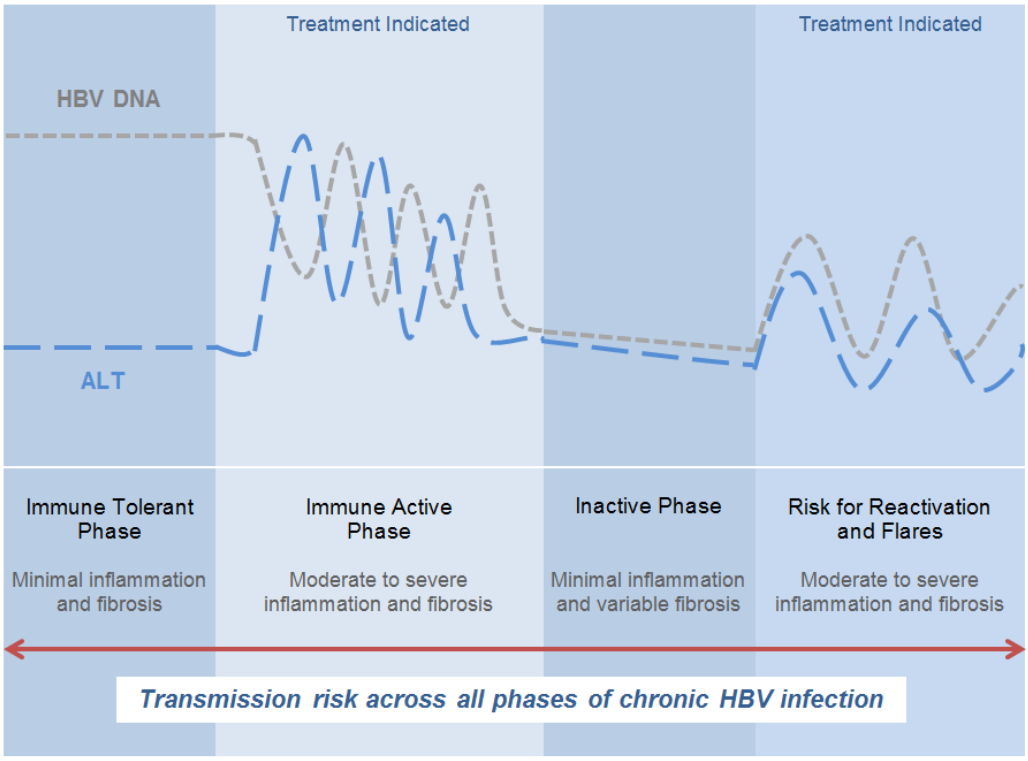
Occult Blood Infection (OBI) can be seen in around 10% of HBsAg-negative/anti-HBc Total-positive individuals, where low levels of HBV DNA can be transiently detected even after successful HBsAg seroclearance. Infectivity is unclear, however liver disease can still progress in the absence of HBsAg (20-22).

3.2.2 HBV Reactivation

HBV reactivation is the reappearance of active necroinflammatory liver disease after being in an inactive chronic HBV phase or having had a resolved HBV infection (HBsAg loss), and is usually reflected by fluctuating ALT and HBV DNA levels (refer to Figure 3-2) (1). Rates have been reported as high as 50% for HBsAg-positive individuals on chemotherapy for lymphoma and 25% for anti-HBc Total positive individuals on rituximab, compared to an overall spontaneous reactivation rate of 10-20% in inactive carriers (23, 24).

Reactivation can be prevented in the context of immunosuppressive therapy by screening for all three HBV screening markers in all individuals, and HBV DNA levels in those with a prior history of HBV infection, before starting immunosuppressive therapy. Prophylactic antiviral treatment can help to decrease HBV reactivation and related hepatitis by 79-100% in certain cases of immunosuppressive therapy (25). Early monitoring of HBV DNA in those with a prior history of HBV infection will also help to detect reactivation in the context of OBI (26).

Figure 3-2: Natural history of chronic HBV infection (15, 24, 27, 28)



3.2.3 HBV Flares

HBV flares describe intermittent elevation of aminotransferase activity to greater than 10 times the upper limit of normal and more than 2 times the baseline value in an individual with chronic HBV infection (1). They can occur spontaneously, but are more often seen in the context of immunosuppression, chemotherapy, immune restoration (e.g., HBV/HIV coinfection) and during or upon completion of antiviral therapy. Symptoms can be absent or can vary from acute hepatitis to hepatic failure. Urgent antiviral therapy is required when HBV flares present in the context of cirrhosis (29).

Practitioner Alert!

HBV reactivation or flares can occur in individuals with inactive chronic HBV infection or with HBsAg loss (OBI), if they become immune suppressed, during or upon completion of immunosuppressive therapy, or experience immune restoration.

3.3 Hepatitis B and Coinfection

Coinfection with HIV, hepatitis A (HAV), hepatitis C (HCV) or hepatitis D (HDV) can result in more severe and progressive liver disease. This can include higher rates of cirrhosis, HCC and mortality. Coinfection is important to consider when evaluating an individual for HBV, as there are similar transmission pathways, and the clinical features for the hepatitis viruses are similar (7, 8).

3.3.1 Coinfection with Hepatitis C Virus (HCV)

HCV appears to play a role in interfering with HBV replication, as HBsAg clearance is 2.5 times higher, compared with HBV monoinfection, and HBV DNA levels are often low or undetectable (6, 30). While 25% of individuals with HCV infection will clear the HCV virus, 42% of those with HBV/HCV coinfection at baseline will clear the HCV infection (31, 32). Moderate to severe reactivation of HBV infection has been reported when direct-acting antivirals are used for HCV treatment (1, 7, 30, 33).

3.3.2 Coinfection with Hepatitis D Virus (HDV)

HDV requires active HBV infection in order to fully assemble and propagate infection, and is transmitted through blood and sexual contact. It occurs more frequently in immigrant populations originating from endemic countries. In North America, HDV is uncommon and transmission occurs most frequently in the context of IDU. Horizontal transmission is more common in endemic countries, and perinatal transmission is rare (7, 34). In BC, there were 2 cases of HDV infection in 2015, and 4 cases in 2016.

When HBV and HDV infection occur simultaneously, the majority of adults will clear both infections, but 5% will go on to have chronic infections. A superinfection occurs when an individual with pre-existing chronic HBV infection acquires a HDV infection at a later date. The incubation period for HDV superinfection is 2-8 weeks. Up to 90% of HBV/HDV superinfections will progress to chronic HDV infection and can lead to acute liver failure. HBV/HDV coinfections are very difficult to treat, and can lead more quickly to severe liver disease with greater likelihood of fulminant infection (7, 34).

Immunization of household and sexual contacts against HBV is crucial in preventing HDV infections. For individuals with chronic HBV infection, consider screening for HDV if there is a history of IDU, high-risk sexual behaviours, hemodialysis, advanced liver disease, or immigration from a high-prevalence region (34).

For HDV testing information, refer to Appendix A.

3.3.3 Coinfection with HIV

Around 9.8% of individuals with HIV infection in Canada are also coinfected with HBV (35) . Compared with HBV monoinfection, coinfection with HIV increases progression of cirrhosis, HCC and liver-related mortality, and can increase HBV DNA levels (36, 37). Initiation of antiretroviral therapy (ART) in the context of advanced HIV disease and HBV coinfection could lead to flares and immune reconstitution syndrome. If ART is stopped and the agents used had anti-HBV activity, HBV reactivation and flares could occur (7, 38).

Individuals with HIV infection should be offered HBV screening at baseline, and those with isolated anti-HBc Total results should have HBV DNA testing to rule out OBI (39). Individuals with HIV infection, who are nonresponders to 2-series of HBV vaccine, should be screened yearly for HBV (7).

Refer to the BC Centre for Excellence in HIV/AIDS Primary Care Guidelines for the Management of HIV/AIDS in British Columbia for further information on clinical care recommendations.

Refer to the BC Communicable Disease Control Manual, Chapter 2: Immunization, Part 2-Immunization of Special Populations for further recommendations on HIV infection and vaccinations.

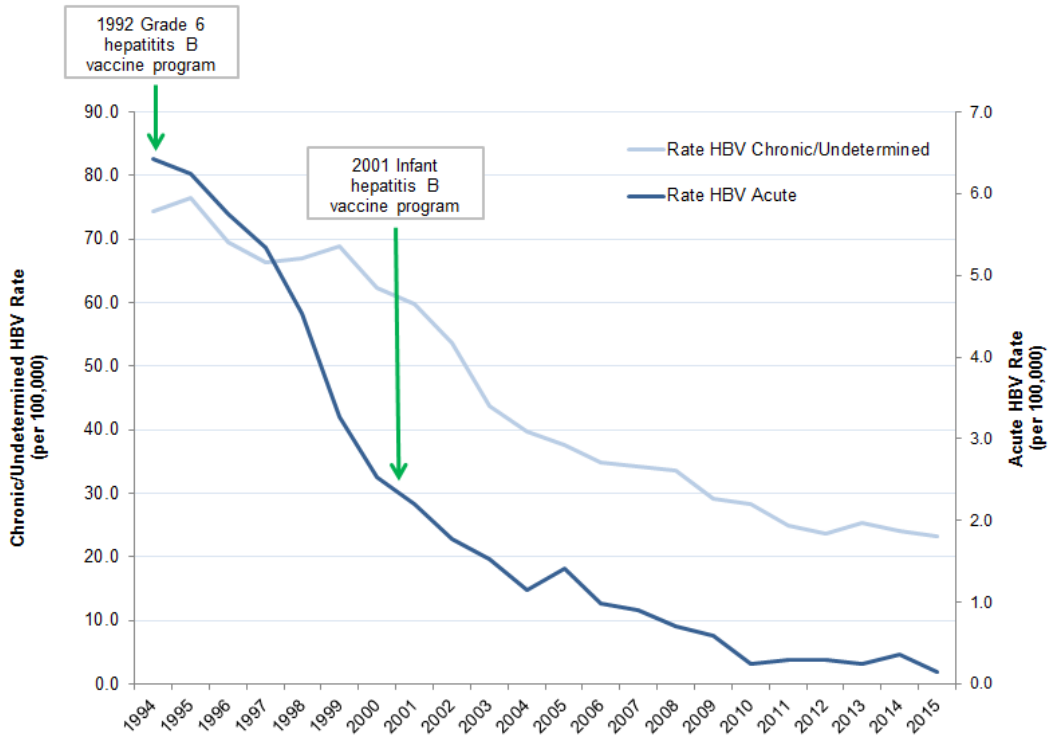
3.4 Epidemiology

For a complete up to date report, see the most recent BCCDC Annual Summary of Reportable Diseases.

With the introduction of a grade 6 hepatitis B immunization program and a catch up program for grade 12 students (1980 birth cohort) in 1992, and the implementation of a universal infant program in 2001, BC has seen a 99% reduction in acute HBV infections from 1992 to 2015. The incidence of acute HBV in BC has remained < 1 per 100,000 since 2007, well below the national average of > 5 per 100,000. There have only been 6 to 14 new cases of acute HBV infections reported per year from 2010 to 2015.

Between 1990 and 2015, 46,502 individuals were diagnosed with acute or chronic/undetermined HBV infection in BC. Since the early 1990s, annual rates of newly diagnosed cases of HBV reported in BC have declined (see Figure 3-3). The rate of reported acute HBV infection has been similar across health regions with very few case detections in recent years: Vancouver Coastal Health Authority (VCHA) at 3 to 8 cases per year, followed by Fraser Health Authority (FHA) at 1 to 5 cases per year.

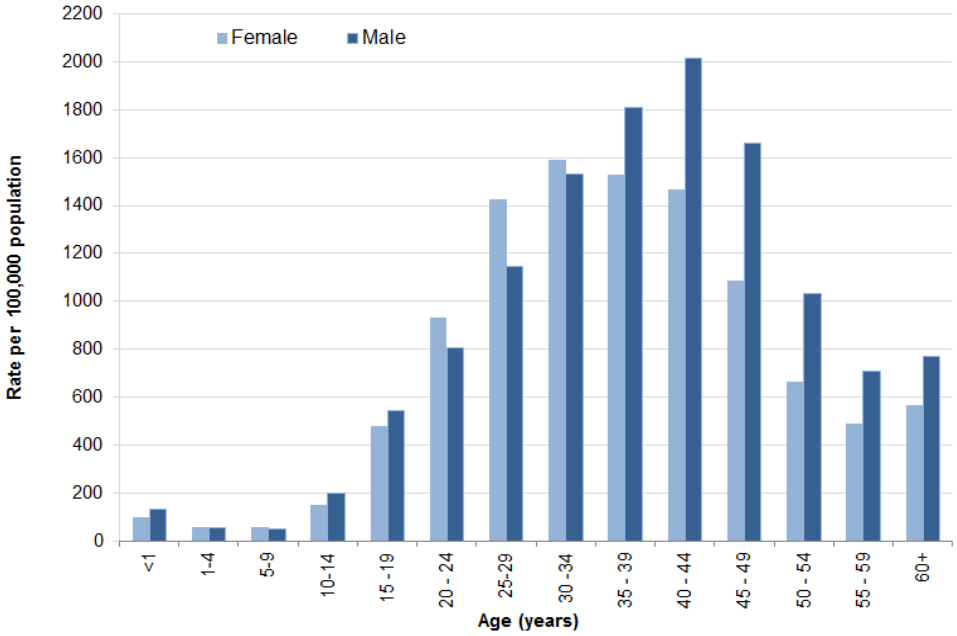
Figure 3-3: Annual acute and chronic/undetermined HBV infection rates per 100,000 BC population from 1990 to 2015



Amongst individuals diagnosed with chronic/undetermined HBV infection, rates have declined from a peak of 76.5/100,000 people in 1995 to 23.3/100,000 people in 2015. These trends may reflect changing immigration patterns and increased global hepatitis B vaccination programs. The rate of chronic HBV was highest in VCHA (2013: 41.5/100,000 population), followed by FHA (14.2/100,000 population), while the rate was similar across other health regions.

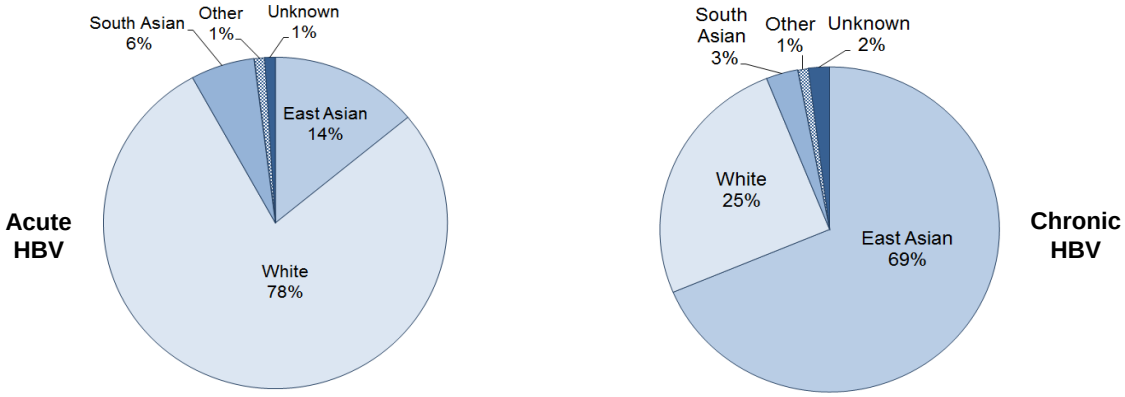
Chronic/undetermined HBV rate by age and sex suggests earlier diagnosis among women with peak age of 25-29 years while among males peak age was 35-39 years. Earlier diagnosis among women may be related to increased health care system access by women compared with men, as well as recommendations for universal prenatal HBsAg testing in BC (Figure 3-4).

Figure 3-4: Chronic/undetermined HBV rates in BC by age group, from 1990-2015



Preliminary analysis of local ethnicity data from 1990-2015 suggests that 78% of individuals diagnosed with acute HBV infection in BC were of Caucasian ancestry, while 14% were of East Asian ancestry. In contrast, 69% of individuals diagnosed with chronic/undetermined HBV infection were of East Asian ancestry and 25% of Caucasian ancestry (Figure 3-5). This underscores the importance of HBV screening among immigrants from East Asian countries, given that chronic HBV infection is treatable.

Figure 3-5: Percentage of acute and chronic/undetermined HBV cases by ethnicity in BC, 1990-2015



Analyses of the BC Hepatitis Testers Cohort (BC-HTC) has shown that from 1992 to 2013, compared to individuals diagnosed with chronic HBV infection, a higher proportion of individuals diagnosed with acute HBV infection engaged in illicit drug use (IDU) (16% vs. 2.3%) and problematic alcohol use (15% vs. 2.4%), had a major mental illness (12% vs. 3.5%), and showed a higher rate of HIV (9.1% vs 2.05%) and HCV co-infection (35.7% vs. 6.3%). For certain high risk groups, a syndemic, coordinated approach to prevention and care for individuals with acute HBV infection is needed, as transmission routes for HBV, HCV and HIV infection are similar. Given the small number of acute HBV cases seen each year, a focus on engaging and treating people with chronic HBV infection is important to address the potential for forward transmission of HBV infection.

3.5 Risk Factors and Screening Indications

An effective screening approach allows for the identification and timely follow-up of those requiring treatment and ongoing care to prevent cirrhosis and HCC, as well as susceptible contacts requiring vaccination. Given the success of BC's universal vaccination programs and low incidence and prevalence rates of HBV, screening of asymptomatic, non-pregnant adolescents and adults at low risk for HBV infection is not considered to be beneficial (40, 41). The decision to screen for chronic infection or immunity should consider risk factors, risk for future exposure, and prior testing and vaccination history.

In Canada, the most commonly identified risk factors associated with acute HBV infection are riskier sexual activities and IDU, while 70% of chronic cases are seen in individuals immigrating from high HBV prevalence areas (15). For around 30% of HBV infections, no risk factors can be identified (15). In BC, where HBV prevalence is low, routine screening is not recommended. Refer to Table 3-2 for a summary of risk factors associated with acute and chronic HBV infection.

HBV screening should be routinely done in certain clinical scenarios (1, 15, 42):

- Pregnancy (first trimester)
- HIV or HCV infection
- Immune suppressing therapy (risk of hepatic flares or reactivation of chronic HBV infection)
- Immune compromised (more likely to develop chronic infection after acute infection)
- Contacts to acute or chronic HBV infection
- Findings suggestive of chronic liver disease (refer to Table 3-1):
  - Abnormal liver biochemistry (often the only finding)
  - Hepatomegaly, splenomegaly and jaundice (late findings)
  - Thrombocytopenia
- Findings suggestive of acute hepatitis
- Diagnosis of HCC
- Prior diagnosis of other liver disease
- Exposure at a young age, where immediate or extended family immigrated from, or where a child visited, an endemic area

Many immigrants and refugees from regions of high HBV endemicity are likely to have been previously exposed through household contact or other travels. While Canadian Immigration Canada recommends screening adults and children from countries where chronic HBV prevalence rates are greater than 2%, this is not a part of the routine immigration medical (1, 42). Refer to the WHO International Travel and Health interactive map for updated global HBV prevalence rates: http://apps.who.int/ithmap/.

3.5.1 Chronic Kidney Disease

Chronic hemodialysis presents individuals with increased risk for the acquisition of HBV infection via repeated opportunities for nosocomial transmission. In addition, individuals with chronic kidney disease are immunosuppressed due to renal failure and related therapy. Anti-HBs levels tend to decrease whether related to vaccination or natural resolved infection (43).

Refer to the BC Provincial Renal Agency Hepatitis B Guidelines for initial and annual HBV screening and follow-up recommendations (www.bcrenalagency.ca/health-professionals/clinical-resources/hemodialysis).

Refer to the BC Immunization Manual, Part 2-Immunization of Special Populations and Part 4-Biological Products, for recommended screening and vaccinations for all predialysis, hemodialysis and peritoneal dialysis.

Table 3-2: Risk factors for HBV infection (7, 10, 14, 15, 44, 45)

	Activity	Comments
More commonly associated with acute HBV infection	Exposure to a HBsAg positive person	• Percutaneous • Sexual or household contact
	Riskier sexual activities	Unprotected sex and/or multiple sexual partners
	Illicit drug use	Greatest risk in those who have ever shared drug preparation or injecting equipment. Transmission can occur when sharing non-injection drug use equipment, as the integrity of the mucosa can be compromised or ulcerated (e.g., snorting can irritate nasal mucosa, smoking crack pipes can damage oral mucosa)
	Shared or contaminated materials used for personal services, alternative health care or personal hygiene	Particularly in unregulated premises where unsterile equipment or improper technique is used for activities that have the potential to break the skin (e.g., tattooing, piercing, glucometers, toothbrushes, nail clippers)
	Incarceration	High level of needle sharing in persons who inject drugs (PWID) and unsterile tattooing practices
	Travel or residence	In an area of intermediate or high HBV prevalence (refer to (42))
	Accidental needle stick injury	Percutaneous exposure, without PEP: • If source is HBsAg positive or negative, and exposed person has been vaccinated: virtually zero % chance of seroconversion • If source is HBeAg positive and exposed person has ***not*** been vaccinated: 30% chance of seroconversion • If source is HBeAg negative and exposed person has ***not*** been previously vaccinated: 5-10% chance of seroconversion
	Institutionalization	Particularly in institutions for the developmentally challenged
More commonly associated with chronic HBV infection	Perinatal transmission	Unimmunized neonates of HBsAg positive mothers have a 10-90% chance of acquiring HBV infection Risk increases when HBV DNA ≥ 200,000 IU/mL, which is an indication for anti-viral prophylaxis in 3rd trimester to reduce the risk of transmission to the infant
	Potential iatrogenic exposures	Medical care received where basic infection control practices are not followed and where the blood supply is not tested
		In Canada, increased risk if a transfusion recipient or had medical procedure prior to 1970
	Exposure at a young age	Where the child visited, or the family immigrated from a high HBV prevalence area
	Family history	Hepatitis B or hepatocellular carcinoma (HCC)

3.6 Transmission

HBV is thought to be 50-100 times more infectious than HIV, and more infectious than HCV as well (15, 46, 47). Blood contains the highest HBV titre of all bodily fluids and is the most important vehicle for transmission whereas lower levels are found in other body fluids. In unvaccinated individuals, the risk of sexual or needle stick transmission is increased if HBV DNA > 1000-2000 IU/mL (7, 48).

HBV can most efficiently be transmitted through perinatal, percutaneous and sexual contact, less so by permucosal contact. All individuals with acute and chronic HBV infection, regardless of which phase, should be considered potentially infectious.

In areas of high HBV endemicity, transmission occurs mainly through perinatal and horizontal transmission. In more industrialized areas, where the occurrence of new HBV infection is low, IDU and high-risk sexual activities are the most common means of transmission. Areas of low HBV prevalence are seeing more individuals with chronic HBV infection via immigration, who require monitoring and treatment, and identification of contacts who are in need of screening for past infection or immunization (49).

Table 3-3: Relative risk of transmission (3, 44-46)

Higher risk	Lower risk	Extremely low risk unless blood is present
• Blood • Serous fluid (e.g., cerebrospinal, synovial, pleural, peritoneal, pericardial, amniotic, inflammatory exudates)	• Semen and vaginal fluids (sexual transmission)	• Saliva* • Feces • Nasal secretions • Sputum • Sweat • Tears • Urine • Vomitus

* HBV transmission via **casual** mucosal contact to saliva that is not visibly contaminated with blood is uncommon. Although HBV has been detected in saliva, reports involving HBV transmission when a HBV-infected person bites (i.e., percutaneous) another person have involved bloody saliva. Blood was more likely the means of transmission, not the saliva (3, 50-52).

Breastfeeding is considered to be safe. If nipples are cracked or bleeding, transmission is plausible; however, given that neonates born to HBsAg positive mothers should be receiving prophylaxis immediately after birth (HBIg, a complete hepatitis B vaccine series, and follow-up post-vaccination serology), this is unlikely (3, 51).

HBV is **not** spread by casual contact such as kissing, hugging, sneezing or coughing, or via sharing food, water, eating utensils or drinking glasses. (3, 51).

Chronic HBV infection is highly stigmatized in some communities. Clear education around risk of transmission, and providing opportunities to address any concerns or fears about HBV transmission, can be crucial to help ensure successful future follow-up and outcomes for some clients. Refer to Section 8.4 for further case management strategies to address HBV stigma.

4.0 LABORATORY AND TESTING INFORMATION

HBV serology is done at the BCCDC Public Health Laboratory (PHL) and in private and hospital laboratories. Serum from outside laboratories should be sent to BCCDC PHL if they are not able to perform confirmatory testing or identify false positive results. Outside laboratories have been requested to state “provisional reactive” on any results sent to physicians and health authorities prior to confirmatory testing.

Refer to the BCCDC Public Health Laboratory Guide and website for information on requisitions, testing, and sample collection and processing instructions.

Consider offering an HIV test whenever HBV is tested for or diagnosed, as there can be similar risk factors and means of transmission (53).

4.1 Hepatitis B Serology Testing

There are several HBV markers to consider when testing for HBV infection that vary according to the natural progression of the disease and immunization status. The decision as to which HBV markers to order for initial screening depends upon the indication for screening.

Table 4-1: Hepatitis B Serology testing (15, 54)

HBV serologic marker	Term	Clinical correlation
HBsAg	Hepatitis B surface antigen	• Detection of acute or chronic HBV infection
Anti-HBs	Antibody to HBsAg	• Immunity due to vaccination (may decline to undetectable levels over time) ***or*** past infection
Anti-HBc Total (IgM + IgG)	Total antibody to core antigen	• Identifies prior infection with HBV • Not present after immunization • May be falsely positive in areas of low HBV prevalence
Anti-HBc IgM	IgM class antibody to hepatitis B core antigen	• Appears early in acute infection, lasting > 6 months • Often present during chronic HBV infection (flares, reactivation) • Requires clinical correlation for interpretation
HBeAg	Hepatitis B e antigen	• Indicates viral replication and correlates with higher HBV DNA • Identifies infected individuals at higher risk for transmitting HBV • Not required for routine diagnosis
Anti-HBe	Antibody to HBeAg	• Indicates recovery from acute infection • Identifies infected individuals at lower risk for transmitting HBV • Not required for routine diagnosis
HBV DNA	Hepatitis B DNA viral load	• Indicates the magnitude of HBV replication and risk of disease progression • Useful for therapeutic monitoring of chronic HBV infection • Predictor of cirrhosis and HCC development

Figure 4-1: Acute HBV infection with recovery (15, 28, 55-57)

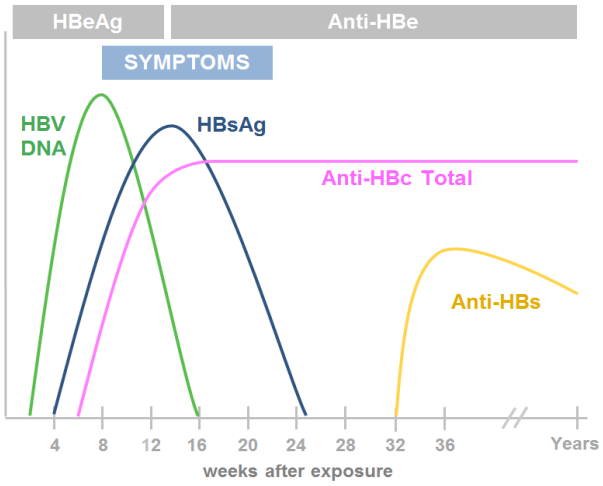
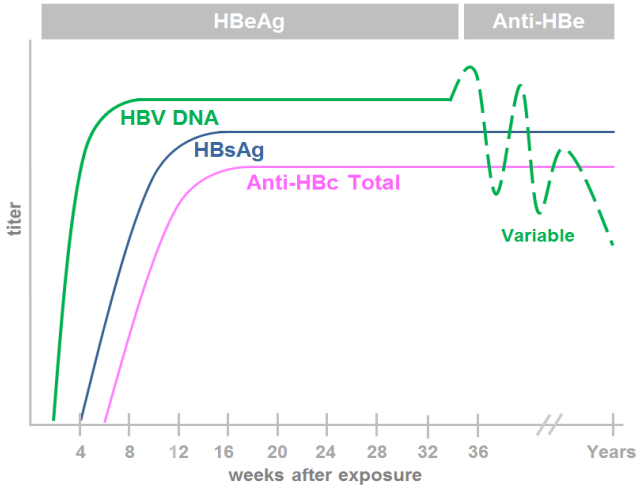


Figure 4-2: Chronic HBV infection (14, 24, 50-52)



4.2 Prenatal Sera

All pregnant women should be universally tested for HBsAg during first trimester, even if a complete hepatitis B vaccine series has previously been documented. It is not necessary to routinely include the other screening tests to detect infection, as anti-HBc Total will be positive in all HBsAg positive individuals (unless in window period) and anti-HBs is rarely positive when HBsAg positive. If testing has not been done during pregnancy, it must be done at the time of delivery.

In the absence of a documented hepatitis B vaccine series, if there are ongoing high-risk behaviours throughout pregnancy (e.g., multiple sex partners, IDU, recent history of STI), order anti-HBs, HBsAg and anti-HBc Total. If susceptible, recommend a complete hepatitis B vaccine series and follow-up post-vaccine serology (**1 month** after the last dose of vaccine) as soon as possible. If the mother refuses vaccination, consider repeating HBsAg later in pregnancy.

Identification of prenatal sera

Prenatal Sera may not be clearly identified as 'prenatal' on the results because the ordering health care provider may not clearly indicate 'prenatal' on the lab requisition form and private laboratories may not include this information when results are reported. This could impact Public Health's case management decisions in being able to follow-up and inform the expecting mother of transmission risk.

All HBsAg positive results originating from private or hospital laboratories that are identified as prenatal **should be** sent to the BCCDC PHL, as confirmatory testing and reflexive HBeAg testing will be done. The 'High Risk Neonatal Hepatitis B Immunization Programme' letter providing follow-up information is sent out by the BCCDC PHL to the ordering health care provider.

Practitioner Alert!

Prenatal and primary care providers are best placed to ensure all pregnant women with hepatitis B are identified for follow-up, working collaboratively with Public Health where appropriate.

The development of processes to follow-up on all HBsAg positive results for all women of child-bearing age can help identify chronically infected women who might otherwise be missed.

Refer to Section 5.3 and Section 8.2 for further recommendations, and to the BC Immunization Manual, Part 2-Immunization of Special Population, Infants at High Risk for Hepatitis B for more information.

4.3 Investigation of acute hepatitis

Order the following initial screening tests:

- Anti-HAV IgM
- HBsAg
- Anti-HBc Total (may be in window period)
- Anti-HCV
- ALT

If these initial tests are negative, test for HCV RNA. Although rare in Canada, consider testing for HEV.

Consider other infectious (e.g., cytomegalovirus, Epstein-Barr virus, enteroviruses) and non-infectious causes, including hepatotoxic drugs, herbal medicines, autoimmune hepatitis, Wilson's disease or other vascular causes (8, 15).

4.4 Pre-vaccination Testing

Screening for HBsAg, anti-HBs and anti-HBc Total is recommended for the following:

- Persons at high risk of having been infected (i.e., IDU, sex trade worker (STW), sexual partners of HBV infected individuals and persons born in a country of high hepatitis B prevalence). Testing will identify those already infected or immune, for whom vaccine will confer no benefit, and assist in the medical management and contact follow-up of those individuals found to be infected.
- Individuals with chronic HCV infection or other chronic liver diseases
- Students entering health care professions who have been previously vaccinated, but their response to initial vaccination is unknown

Refer to Section 5.2 for Post-Vaccination serology follow-up recommendations.

4.5 Post-vaccination Serology

Practitioner Alert!

For recommended post-vaccination serology indications, see Table 4-2.

Post-vaccination serology should be done **at least 1 month (up to 6 months)** after the last dose of hepatitis B vaccine or **at least 6 months** after HBIg is given, whichever is longer. Falsely elevated levels of vaccine related HBsAg can be detected for 3-4 weeks after vaccine administration, and falsely elevated levels of anti-HBs can be detected for 6 months after the administration of HBIg.

Post-vaccination serology done longer than 6 months after the last dose of hepatitis B vaccine differs in follow-up vaccination and testing recommendations, due to the challenge of differentiating between an anamnestic response and a non-responder.

Refer to Section 5.2 for recommended post-vaccination serology follow-up.

Refer to the BC Immunization Manual, Part 2-Immunization of Special Populations for information on:

- Infants at High Risk for Hepatitis B
- Perinatal Protocols for Hepatitis B
- Individuals with Chronic Kidney Disease, HIV infection or chronic liver disease, and those taking immunosuppressive or corticosteroid therapy

Table 4-2: Indications for post-vaccination testing

Scenario	HBsAg	Anti-HBs	Anti-HBc Total	Notes
Infants (less than 12 months): • Born to known HBsAg positive mother • With a mother who is at high risk for HBV infection (e.g., IDU, STW), but status is unknown at time of delivery • With a father, primary caregiver or household contact who has chronic HBV infection • With a father or primary caregiver who is at high risk for HBV infection	✓	✓		• Anti-HBc Total testing post-vaccination is not indicated, as high levels of false positives can occur for up to 12 months due to circulating maternal antibody • Accountability mechanisms should be in place to ensure that every infant born to a HBV infected mother receive HBIg and a full course of hepatitis B vaccine and testing for serologic response to vaccine • Infants who receive hepatitis B vaccine at birth should also be tested 1 month after the last dose of vaccine • Refer to Section 5.3, Prenatal HBsAg result follow-up)
Susceptible pregnant mothers at high risk for HBV infection	✓	✓	✓	• Multiple sex partners, PWID, recent history of STI
Immunocompromised individuals who may be expected to have a lower seroconversion rate	✓	✓	✓	• HIV, hematopoietic stem cell transplant recipients (HSCT), solid organ transplant candidates and recipients
Chronic liver disease	✓	✓	✓	• Including anti-HCV positive individuals • While hepatitis B vaccine is as effective in chronic HCV populations as in controls, the response is generally reduced in those clients with cirrhosis (58)
Post-exposure management: • Steady sexual partners and household contacts of persons with acute or chronic hepatitis B infection • Sexual assault victims • Individuals who have had a percutaneous or permucosal exposure to hepatitis B	✓	✓	✓	• Test prior to administration of HBIg, if indicated (see Section 6.0, Post-Exposure management)
Health care workers and students entering health care professions	✓	✓	✓	• Employers (Occupational Health program) are responsible for implementing testing and vaccination programs for health care workers • Employees should keep a personal record of immunization and testing results

4.6 Internationally Adopted Children

Many internationally adopted children come from hepatitis B endemic countries. Offer hepatitis B vaccine to adoptive family members prior to the arrival of the adopted child. Screen the child for HBsAg, Anti-HBs, and anti-HBc Total. Consider repeating these tests six months later, since the virus can have a long incubation period.

Refer to the BCCDC CD Manual, Chapter 1, Communicable Disease Screening for the Internationally Adopted Child.

Refer to the BC Immunization Manual.

5.0 INTERPRETATION AND RECOMMENDED FOLLOW-UP

Testing for hepatitis is complex and can be confusing. Ensure the correct interpretation is being applied and check for client understanding when reviewing results and follow-up care plans.

The following sections outline specific follow-up recommendations for post-vaccination serology, isolated anti-HBc Total results and prenatal HBsAg testing. Various combinations of equivocal/indeterminate HBV lab results can occur. Recommended follow-up will depend on the individual's clinical scenario. Consultation with a health care practitioner experienced with hepatitis B is recommended.

Refer to Table 5-1 for general guidance on interpretation of HBV testing results.

Table 5-1: Interpretation of HBV screening results

Interpretation	Results						
	Screening Tests						
+ Reactive (positive) – Non-reactive (negative)	HBsAg*	Anti-HBs**	Anti-HBc (total)	Anti-HBc IgM	HBeAg▲	Anti-HBe▲	HBV DNA
Susceptible, vaccinate	–	–	–	–			
Immune due to vaccination	–	+	–	–			
Immune due to past infection Ω	–	+	+	–			
"Isolated anti-core positive" four interpretations (refer to Section 5.4): 1. False positive anti-HBc Total 2. Resolved past infection 3. Resolving acute HBV infection 4. Occult blood infection	–	–	+	–			
Recent acute infection ("convalescent window" phase)	–	–	+	+			
Acute or chronic infection ϕ	+	–	+	+			variable
Chronic infection, highly infectious	+	–	+	+/–	+/–	+/–	variable
Chronic infection, lower infectivity	+	–	+	+/–	+/–	+/–	variable
Chronic infection, lower infectivity with possible resolution	+	–	+	–	–	+	variable

* HBsAg levels may be falsely elevated for 3-4 weeks after vaccine administration

** Anti-HBs may be reported as IU/L or mIU/mL. These are equivalent units. The international threshold for vaccine-induced immunity is 10 IU/L. Anti-HBs may also be passively elevated for 6 months following receipt of HBIg (2, 55).

▲ Not required for routine diagnosis. HBeAg is associated with higher HBV DNA and infectivity.

Ω Potential for reactivation in immune compromised individuals who have previously lost HBsAg

ϕ Clinical correlation required to differentiate between acute and chronic infection

5.1 Reactive HBsAg result follow-up

Individuals testing HBsAg reactive should undergo further evaluation and liver fibrosis assessment (e.g., HBV DNA, ALT and ultrasound). HBsAg levels may be falsely elevated for 3-4 weeks following hepatitis B vaccine administration.

In clinical practice, anti-HBc IgM is not routinely recommended to test for when evaluating an acute HBV infection. The anti-HBc IgM has traditionally been used to identify acute HBV infection and is used in current Public Health case definitions. While an anti-HBc IgM negative result is consistent with chronic HBV infection, an anti-HBc IgM positive result could indicate either an acute or chronic HBV infection. Clinical correlation is required to differentiate between acute and chronic HBV infection. Some individuals with chronic HBV infection can remain anti-HBc IgM positive for many years, while others can become anti-HBc IgM positive during exacerbations of chronic HBV infection (i.e., reactivation).

If desired, an anti-HBc IgM should be ordered if testing is done at a private or hospital laboratory. Anti-HBc IgM is reflexively done on all HBsAg reactive tests performed at the BCCDC PHL, however, not all private laboratories routinely forward HBsAg reactive specimens to the BCCDC PHL for follow-up testing.

Refer to Section 7.0 and Section 8.0 for further follow-up information. If pregnant, refer to Section 5.3.

5.2 Post-vaccination serology follow-up: boosters and re-immunization recommendations

Immune memory persists even when anti-HBs levels decline (< 10 IU/L) over time and become undetectable. Anti-HBs ≥ 10 IU/L is the established international threshold that is correlated with vaccine induced immune protection (when HBsAg and anti-HBc Total negative). If immune competent, the individual is considered to have protection against HBV and will be able to mount an anamnestic response in the development of anti-HBs if challenged with HBV. Routine boosters of hepatitis B vaccine are not required for immune competent individuals (2).

Approximately 5-10% of immune competent individuals are non-responders to a first series of hepatitis B vaccine. Of these, 50-70% will respond to a second series of hepatitis B vaccine. Less than 5% of individuals will not respond after receiving six doses of hepatitis B vaccine. There is no benefit to further vaccinating individuals who have not responded to 2 complete series of hepatitis B vaccine. A non-responder to 2 series of hepatitis B vaccine (whether 2 or 3-dose complete series) will require HBIg post-exposure prophylaxis if exposed to HBV (2, 10).

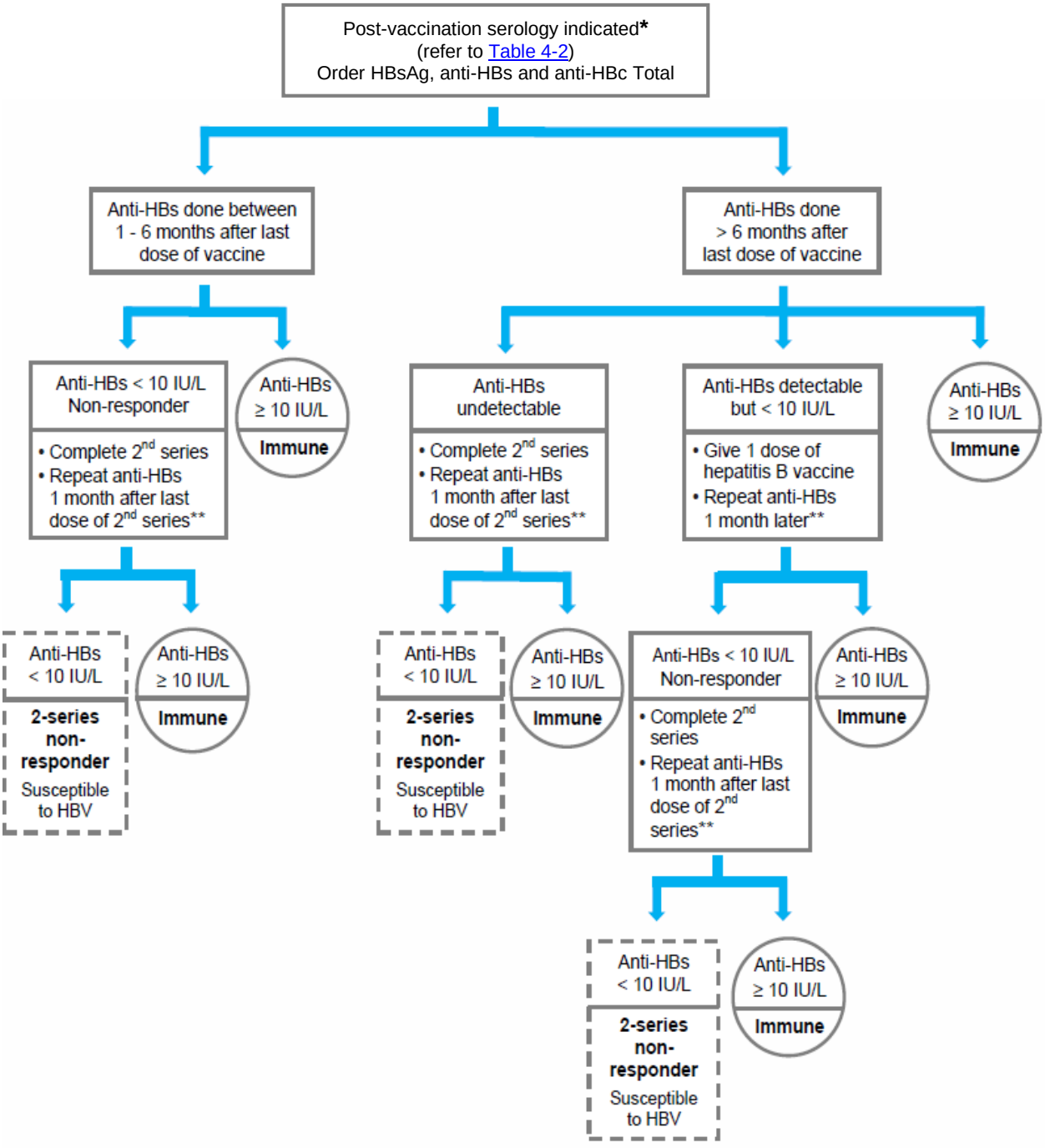
Certain manufacturers may report a range of results to be indeterminate or within a “grey zone” (e.g., BCCDC PHL reports equivocal results from 8.0 to less than 12.0 mIU/mL). For all practical purposes, such results should be considered to be just at the immune threshold. While anti-HBs levels below the grey zone may also be reported, this range can also vary depending on the manufacturer (e.g., the lower limit of detection of the current BCCDC PHL testing platform is 3.1 mIU/mL).

Timing of post-vaccination serology

Recommendations for anti-HBs post-vaccination serology follow-up, in the context of anti-HBc Total and HBsAg negative results, depends on the length of time between the last dose of hepatitis B vaccine and when post-vaccination serology was done. The timing of post-vaccination serology is important in avoiding unnecessary vaccination and case management follow-up (59).

Refer to Figure 5-1 for immunization and testing recommendations following post-vaccination serology. Refer to Section 6.0 for post-exposure prophylaxis recommendations.

Figure 5-1: Recommended follow-up of post-vaccination anti-HBs serology for immune competent individuals



* If HBsAg or anti-HBc Total positive, refer to Table 5-1, Section 5.1 and Section 5.4

** If there are on-going risk factors, new symptoms, or concerns that initial screening tests were done outside of the recommended window periods, repeat all 3 screening tests again (HBsAg, anti-HBs and anti-HBc Total)

Practitioner Alert!

A documented **anti-HBs level ≥ 10 IU/L** done **1 to 6 months** after the last dose of a complete vaccine series is considered to be protective for life. While anti-HBs levels wane over time, immune memory persists. The absence of detectable anti-HBs in a person who previously demonstrated an adequate level of anti-HBs does not mean lack of protection.

Post-vaccination serology done **more than 6 months** following the last dose of vaccine requires a different approach to follow-up, as it is difficult to distinguish between those who will be able to mount an anamnestic response, and those who have inadequate immunity.

Coverage for second hepatitis B vaccine series

A second series of hepatitis B vaccine is provided free ***only*** to the following groups:

- Infants born to HBsAg positive mothers
- Infants born to mothers at high risk of hepatitis B infection
- Susceptible pregnant mothers at high risk for HBV infection
- Clients with immunosuppressive disorders
- Chronic liver disease, including those with chronic HBV infection and those who are anti-HCV positive (i.e., may have cleared the HCV infection) *****
- Dialysis/pre-dialysis clients
- Health care students
- Health Care Workers (covered through employer's occupational health program)
- Individuals who have had an exposure to hepatitis B virus and require immunoprophylaxis

***** Standard dosing is recommended for those with chronic liver disease for the initial series; however, individuals with advanced liver disease (e.g., cirrhosis, physician-diagnosed advanced liver disease related to HCV infection) who are non-responsive to the initial hepatitis B vaccine series (standard dosing), should be immunized as per the 'Hepatitis B Vaccine Higher Dose Schedule' for the second series

Refer to the BC Immunization Manual, Part 2-Immunization of Special Populations and Part 4-Biological Products, for further information.

5.3 Prenatal HBsAg result follow-up recommendations

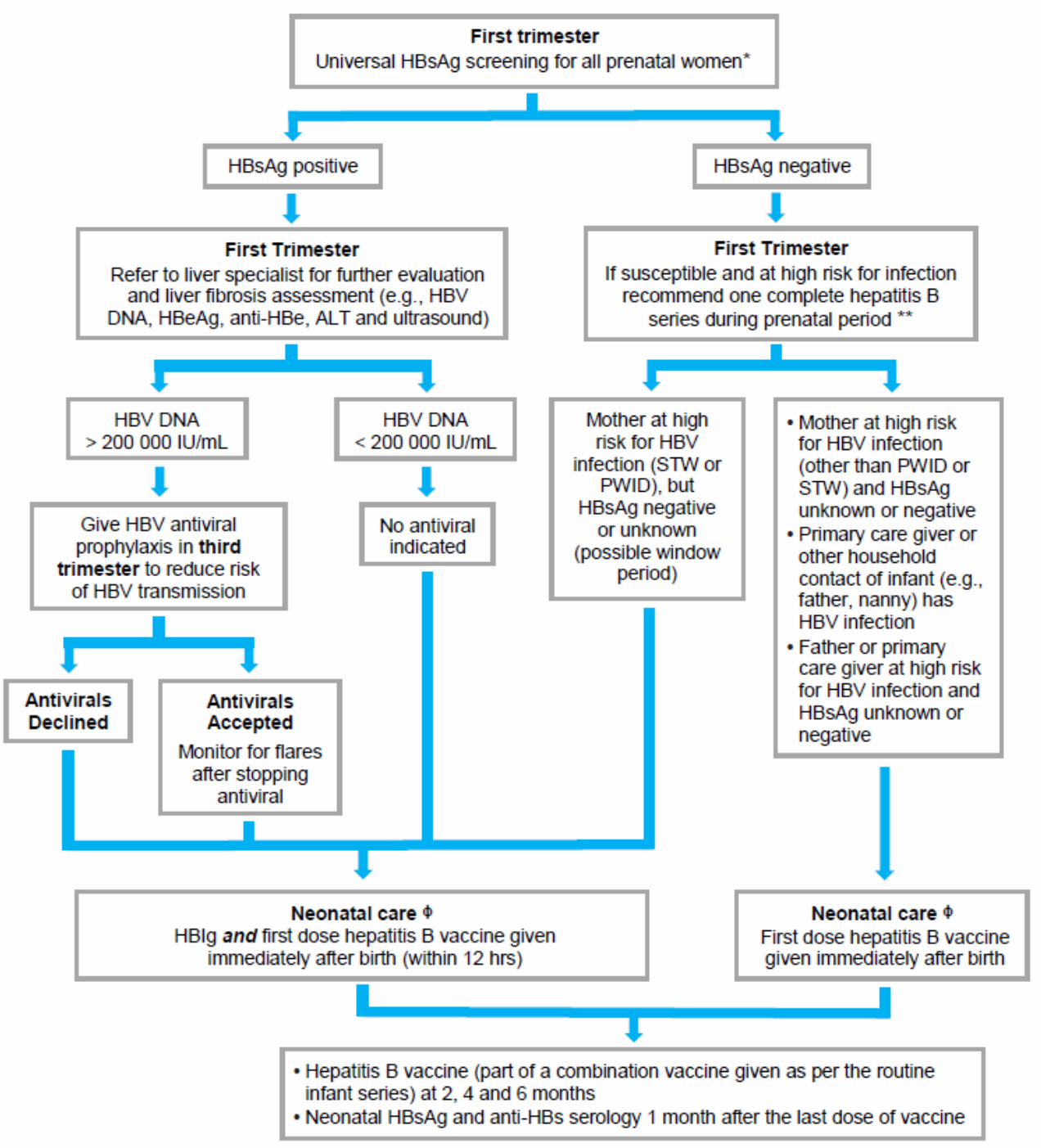
The strongest predictor of HBV vertical transmission is maternal serum HBV DNA (60). If HBV DNA > 200,000 IU/mL, antiviral therapy taken during third trimester can improve HBV suppression and decrease the risk of vertical transmission from mother to neonate, compared with HBIg and hepatitis B vaccine alone. The use of telbivudine, lamivudine, and tenofovir antivirals appears to be safe in pregnancy with no increased adverse maternal or fetal outcomes (7, 30, 45, 61, 62).

Refer to Figure 5-2 for recommendations following prenatal HBsAg positive results.

For further information, refer to:

- the Society of Obstetricians and Gynaecologists of Canada's Clinical Practice Guidelines, Hepatitis B and Pregnancy (https://sogc.org/clinical-practice-guidelines.html)
- Perinatal Services BC Guidelines and Standards (www.perinatalservicesbc.ca/)
- Section 8.2 for recommended follow-up care along the prenatal to postnatal continuum

Figure 5-2: Prenatal HBsAg result follow-up recommendations (7, 20, 63, 64)



* Order HBsAg, anti-HBs and anti-HBc Total if at high risk for infection (i.e., persons born in a country of high HBV prevalence, PWID, STW and sexual partners of HBV infected individuals)

** Hepatitis B vaccine is safe to use in pregnancy. Test for anti-HBs **1 month** after last dose of hepatitis B vaccine.

ϕ The sooner PEP is given following birth, the more effective it is in preventing HBV perinatal transmission. PEP should be given within 12 hours of birth. For infants weighing < 2000g, refer to the BC Immunization Manual, Part 2 –Immunization of Special Populations for the immunization of "Infants at High Risk for Hepatitis B".

5.4 Reactive anti-HBc Total results (Isolated Hepatitis B Core Antibody)

Based upon the clinical situation and estimated likelihood of infection, there are four possible scenarios to consider when reviewing anti-HBc Total reactive, HBsAg nonreactive results with anti-HBs undetectable ***or*** detectable, but < 10 IU/L, results. Although BC is considered to be a low HBV prevalence region, there is a high level of immigration from HBV endemic countries. For BC residents born in Canada, the most probable reason is a false positive test result. Among immigrants from endemic countries the most likely scenario is that of a remotely resolved infection. Most chronic HBV infection cases in BC are seen in individuals immigrating from HBV endemic countries and in individuals with HIV and HCV infection.

After an acute HBV infection, there may be a gap of several weeks to months, where anti-HBc Total is the only detectable marker of HBV infection, in the absence of detectable HBsAg. This is not likely in a low HBV prevalence area, where the vast majority of HBV cases reflect chronic infections acquired in their endemic country of origin.

Refer to the BC CDC Manual, for the 'Isolated Hepatitis B Core Antibody' sample letter that may be used by Public Health to communicate recommendations with the ordering provider.

Table 5-2: Recommended follow-up for Anti-HBc Total reactive, HBsAg nonreactive results, with anti-HBs undetectable *or* detectable, but < 10 IU/L result

Possible scenario*	Estimated likelihood	Anti-HBs is undetectable	Anti-HBs is detectable, but <10 IU/L
False positive anti-HBc Total	Most likely scenario in Canadian born BC residents.	• Offer one complete hepatitis B vaccine series • No routine follow-up, unless required for work/school • If there is ongoing risk of infection, test for anti-HBs 4 weeks after series completion	
Remote resolved infection with persistence of anti-HBc Total and waning anti-HBs level	Most likely scenario in BC residents born in endemic countries. More likely to be a true positive if individual has HIV or chronic HCV infection. If immunosuppressed, reactivation of latent HBV infection with detectable HBsAg can occur.	• Offer one complete hepatitis B vaccine series • No routine follow-up, unless required for work/school, or beginning immunosuppressive medication • If ongoing risk of infection, test for anti-HBs 4 weeks after series completion	• No follow-up required unless beginning immunosuppressive medication • Additional doses of vaccine have not been shown to improve anti-HBs levels • Assure anti-HBc Total is likely a true positive
Resolving acute HBV infection prior to the appearance of anti-HBs	Rare, given the high levels of immunizations in BC	• If acute HBV infection is suspected: ○ Test for anti-HBc IgM (note: anti-HBc IgM can also be positive with chronic HBV infection) ○ Repeat HBV screening tests (anti-HBc Total, HBsAg and anti-HBs) in 2 to 4 weeks	
Chronic infection with undetectable HBsAg level (Occult Blood Infection)	Rare. Patient may have a low level of viremia and could be infectious. More likely to be a true positive if individual has HIV or chronic HCV infection, or if from an endemic HBV area. If immunosuppressed, reactivation of latent HBV infection with detectable HBsAg can occur.	• If there is evidence of HIV infection, HIV/HCV co-infection, immunosuppression or liver disease, recommend HBV DNA, and ALT testing • If a chronic HBV infection is present: • Offer hepatitis A, pneumococcal and annual Influenza vaccines • Offer susceptible household and sexual contacts HBV testing and hepatitis B vaccine	

* HIV and HCV testing is recommended in all scenarios, as these results are seen more frequently in the presence of HIV infection or HIV/HCV co-infection

5.5 Insurance Companies

BCCDC receives notification of positive hepatitis B test results from insurance companies that use out-of-province physicians and/or laboratories for client assessment. BCCDC Communicable Disease Prevention and Control Services (CDPACS) triages these results prior to sending them out to the RHA's to ensure that the result has not been previously reported in BC. Further investigations can occur at the request of Public Health, should the individual report prior positive hepatitis B test results or diagnoses received in other provinces.

Practitioner Alert!

The client's primary care provider in BC may not always be copied on test results ordered by insurance companies, and the client may also be unaware of the results.

It is very common that these test results contain very little identifying information, making follow-up care very challenging at times. Follow-up counselling is not usually done by the Insurance Companies. Direct or indirect follow-up by Public Health of positive HBV test results is encouraged to ensure these patients are receive their results and are linked to care.

6.0 POST-EXPOSURE PROPHYLAXIS

The following information applies to immune competent individuals. If the individual is immunocompromised, consult with an infectious disease specialist.

HBIg is indicated in the case of higher risk sexual assault or if one of the individuals is known to be HBsAg positive or tests positive within 48 hours of exposure. In unvaccinated individuals, the risk of sexual or needlestick transmission is increased if the source has HBV DNA > 1000-2000 IU/mL (7, 48, 65).

For steady, long term sexual partners of individuals with chronic HBV infection, test for HBsAg, anti-HBs and anti-HBc Total to determine if susceptible or if previously infected prior to offering post-exposure prophylaxis. Because the risk of transmission is low and the number needed to treat to prevent infection is extremely high, consensual adult sex with a known sex trade worker or person who injects drugs (PWID), or community acquired needlestick injuries are **not** indications for HBIg.

Table 6-1: Hepatitis B post-exposure prophylaxis (2)

Vaccination history of exposed person	Test for HBsAg, anti-HBc Total and anti-HBs^	Source is HBsAg positive or tests positive within 48 hrs of exposure, and cases of higher risk sexual assault ▲	Source is unknown, not tested, or tests HBsAg negative within 48 hrs of exposure	Re-test HBsAg. anti-HBc Total and anti-HBs*. Offer 2nd hepatitis B vaccine series to non-responders.
Documented prior anti-HBs ≥ 10 IU/L	No follow-up			
No documentation/ unvaccinated Ω	Yes	Give HBIg and 1 complete hepatitis B vaccine series	Initiate hepatitis B vaccine series	Yes
Non-responder to 1 hepatitis B vaccine series			Complete 2nd hepatitis B vaccine series	Re-test only
1 dose of hepatitis B vaccine, anti-HBs status unknown	Yes	Give HBIg and complete hepatitis B vaccine series	Complete hepatitis B vaccine series	Yes
2 doses of a 3 dose hepatitis B vaccine series and anti-HBs status unknown	Yes. If anti-HBs < 10 IU/L,	Give HBIg and 3rd dose of hepatitis B vaccine. Repeat 3rd dose if given too early in the series.	Give 1 dose of hepatitis B vaccine. In 4 wks, retest anti-HBs; if < 10 IU/L, complete 2nd hepatitis B vaccine series.	Yes
	Yes. If anti-HBs ≥ 10 IU/L,	Complete hepatitis B vaccine series	Complete hepatitis B vaccine series	No
1 complete hepatitis B vaccine series (2 or 3 dose) and anti-HBs status unknown	Yes. If anti-HBs < 10 IU/L,	Give HBIg and 1 dose of hepatitis B vaccine	Give 1 dose of hepatitis B vaccine. Retest anti-HBs in 4 wks; if < 10 IU/L, complete 2nd hepatitis B vaccine series.	Yes
	Yes. If anti-HBs ≥ 10 IU/L,	No follow-up		
2-series non-responder to hepatitis B vaccine Φ	HBsAg and anti-HBc Total only	Give HBIg. In 4 weeks give a 2nd dose of HBIg.	No follow-up	Re-test HBsAg and anti-HBc Total only

^ One dose of hepatitis B vaccine may be given while waiting for serology results, regardless of prior immunization history.

Ω A verbal history of past immunizations is generally not considered acceptable. See BCCDC Immunization Manual.

▲ Examples of higher risk sexual assault: assailant is a PWID or is from a HBV endemic country. Evaluate on a case-by-case basis.

* Repeat serology at least **1 month** after last vaccine dose or **6 months** after HBIg, whichever is longer

6.1 Hepatitis B Immune Globulin (HBIg)

Distribution of HBIg is the responsibility of Canadian Blood Services and is available through Transfusion Medicine (Blood Bank) at the local hospital Blood Banks. A request for HBIg in a community setting should be discussed with local Public Health or a Hospital Emergency Department.

The following steps are recommended following a percutaneous, permucosal, sexual or non-intact skin exposure, when HBIg and/or hepatitis B vaccine is indicated:

1. Obtain details of the exposure
    - Use the BC Ministry of Health's forms for all types of HBV exposures (see http://www2.gov.bc.ca/):
        - Management of Percutaneous or Permucosal Exposure to Blood and Body Fluid Letter for Follow-Up Physician (HLTH 2340)
        - Management of Percutaneous of Permucosal Exposure to Blood and Body Fluid/Laboratory Requisition (HLTH 2339)

2. Determine testing requirements for HBV and other blood borne and sexually transmitted infections
    - Refer to Table 6-1 and the BC CDC Manual, Chapter 1: Blood and Body Fluid Exposure Management
    - If appropriate, refer to the BCCDC Non Certified Practice Decision Support Tool for Prophylaxis Post Sexual Assault and the BC Women's Hospital Sexual Assault Service Protocols and Tools
    - Ask the exposed person's physician to arrange for testing of the blood of both the exposed person and source person, as indicated in the guidelines
    - Determine eligibility for HBIg and hepatitis B vaccine(s)

3. If HBIg is indicated, contact the supervisor of the Blood Bank at the nearest hospital as soon as possible
    - Arrange for the administration of HBIg and/or hepatitis B vaccine

4. Timing of post-exposure prophylaxis
    - **Percutaneous exposure**:
        - Give HBIg as soon as possible, preferably **within 48 hours** of exposure. May be given up to **7 days** following the exposure date.
        - If the client presents more than **7 days** following the exposure, give the hepatitis B vaccine only
    - **Permucosal exposure:**
        - Give HBIg as soon as possible, preferably **within 48 hours** of exposure. May be given up to **14 days** following the exposure date.
        - If the client presents more than **14 days** following the exposure, give the hepatitis B vaccine only

5. If indicated, arrange for post-exposure serology. Review follow-up plan with client and provide local Public Health contact information.

For complete HBIg product information, see the BC Immunization Manual, Part 4-Biological Products, Hepatitis B Immune Globulin.

6.2 Management of Accidental Exposures

Needle stick accidents should be reported and documented as per agency guidelines.

Refer to BC CDC Manual, Chapter 1: Blood and Body Fluid Exposure Management for:

- Blood and Body Fluid Exposure Procedures
- Blood and Body Fluid Laboratory Requisition Form (HLTH 2339)
- Management of Percutaneous or Permucosal Exposure to Blood and Body Fluid Physician Letter

Refer to the BC Immunization Manual, Part 4-Biological Products, for information on:

- HBIg
- Hepatitis B vaccine

7.0 CASE IDENTIFICATION AND PUBLIC HEALTH REPORTING

The information presented here may be used to guide the documentation of cases for the purposes of public health reporting to allow surveillance data to be gathered in a consistent manner. Clinical care and public health reporting for a patient can differ, and not all cases requiring clinical follow-up require public health reporting.

Definitions used in daily clinical practice may employ the same terminology, but can differ significantly in their use and meaning. One key distinction is that anti-HBc IgM may be present in both acute and chronic scenarios. The presence or absence of anti-HBc IgM as defined in Table 7-1 is used to classify cases of HBV infection for the purposes of Public Health reporting.

Individuals with acute HBV infection are an important population whose risks represent current transmission and acquisition risk factors. The documentation and attribution of 'acute' HBV cases can support case management by gathering acquisition risk factors. From this information, the linkage to care can be facilitated by the provision of timely education and service referrals.

Reportable cases of hepatitis B infection are documented as 'acute', 'chronic' or 'undetermined'. Asymptomatic HBsAg positive cases who have immigrated from a HBV endemic country most likely have chronic HBV infection. For immigrant clients who are HBsAg positive and asymptomatic, classify as a chronic case. Efforts should be made to complete immigration status when documented.

Table 7-1: Classification of confirmed cases of hepatitis B for the purposes of Public Health reporting

	Clinical Criteria	Laboratory Criteria
Acute Hepatitis B	Discrete onset of symptoms and jaundice **OR** elevated serum aminotransferase levels	Hepatitis B surface antigen (HBsAg) and immunoglobulin M antibody to hepatitis B core antigen (anti-HBc IgM) positive **AND** compatible clinical history or probable exposure **OR** Clearance of HBsAg, where there is a documented HBsAg positive within the last six months in the context of a compatible clinical history or probable exposure
Chronic Hepatitis B	No symptoms	HBsAg positive for more than 6 months **OR** Detection of HBsAg in the documented absence of anti-HBc IgM **OR** Detection of HBV DNA for more than 6 months
Undetermined	No symptoms	HBsAg positive **AND** does not fit the criteria for either an acute case or a chronic infection

Reporting

Enter 'confirmed' cases of hepatitis B into the electronic public health information system used for reportable disease notification.

The BCCDC 'Acute HBV Case Report Form' can be found on the Surveillance page, under 'Sexually Transmitted and Blood Borne Infections' or 'Vaccine Preventable and Respiratory':
http://www.bccdc.ca/health-professionals/professional-resources/surveillance-forms

8.0 CASE MANAGEMENT

The following information outlines case identification and reporting as performed by public health and suggested follow-up for individuals diagnosed with HBV infection, which may be performed by public health, primary care, or other health care providers. Follow RHA guidelines and refer to Section 7.0 for information on the entry of acute infections in a local public health electronic charting system. The public health follow up of chronic and prenatal HBV will vary between health authorities.

All persons who are HBsAg positive are potentially infectious. The level of infectivity depends on the HBV DNA levels, with greater risk when levels are above 2000 IU/mL. A medical evaluation is required for referral to a specialist and determination of appropriateness for antiviral therapy.

8.1 New Case Follow-up Overview

This section describes a suggested practice for follow-up of individuals who are newly diagnosed with HBV infection, to be carried out by public health personnel or other testing health care provider. Refer to local agency guidelines for further guidance.

Public health reporting

- Lab notification received confirming HBV infection
- Review clinical and laboratory criteria and consult with other care providers if appropriate to review exposure risks and medical history, to determine case classification
- Use the electronic public health information system to report 'confirmed' cases of hepatitis B
- If reporting a new acute HBV, complete the BCCDC 'Acute HBV Case Report Form' which can be found on the Surveillance page, under 'Sexually Transmitted and Blood Borne Infections' or 'Vaccine Preventable and Respiratory' (http://www.bccdc.ca/health-professionals/professional-resources/surveillance-forms)
- If reporting perinatal transmission, follow local agency guidelines

Case Management

- If the initial testing provider is unable to provide ongoing care (e.g., a public health nurse or emergency physician) then the ordering provider is responsible for connecting the patient with a health care provider who can provide further clinical evaluation and longitudinal care. Testing should be repeated after 6 months to determine if there is chronic infection.
- Comprehensive care should include the following if appropriate:
  - Immunization update
  - Alcohol and harm reduction strategies
  - Drug and harm reduction strategies (e.g., opioid agonist therapy, naloxone training)
  - Mental health and addictions counselling
  - STI and hepatitis A and C screening
  - General health and education resources (e.g., diet, housing resources)
  - Community support groups and services
- All new case of HBV should receive counseling from a health care provider on the following topics:
  - How hepatitis B is transmitted and how to prevent transmission
  - Discuss when disclosure is needed and the potential for stigma
  - Discuss notification and follow-up of household and sexual contacts, including local testing and immunization resources

Refer to Section 5.3 and Section 8.2 if the client is pregnant.

8.2 Management of Non-pregnant Adults

8.2.1 First Contact by Public Health

Direct client contact by public health staff varies between regional health authorities. When direct contact is necessary, it can be useful to gather information about the context for testing and other relevant medical history from the testing provider before contacting the client. In situations where confirmation with the testing provider cannot be established, direct contact with a client may be appropriate.

There can be a lot of stigma around HBV, including amongst some of BC's Asian communities. Due to societal and economic conditions, and restrictions surrounding HBV infections in some countries, individuals may be anxious to discuss a new diagnosis. Refer to Section 8.4 for further information on stigma and HBV infection.

Determine if an interpreter is required and if there is a preference for which language educational materials are provided. There may be situations where the individual is unaware of prior testing and vaccination history and may not have a good understanding of what the test results mean. HBV testing is complex, and requires supportive counseling and education to avoid any miscommunication, and to address any myths (66).

8.2.2 Contact Tracing and Disclosure

Give a rationale for the purpose of the interview and provide reassurance regarding privacy and confidentiality. It is recommended that the first health care professional (e.g., public health personnel, primary care provider) who interviews the client discusses contacts, as there may not be another opportunity to do so.

For an acute HBV infection:

- Obtain a history of risk factors and potential exposure(s) for the **6 month** period preceding serological diagnosis.
- If reporting a new acute HBV, complete the BCCDC 'Acute HBV Case Report Form' which can be found on the Surveillance page, under 'Sexually Transmitted and Blood Borne Infections' or 'Vaccine Preventable and Respiratory' (http://www.bccdc.ca/health-professionals/professional-resources/surveillance-forms)
- Identify case contacts in the **6 months** prior to the onset of symptoms, or if asymptomatic, 6 months prior to the date of diagnosis.
- Initiate appropriate immunoprophylaxis of contacts.

If the client has a newly identified chronic HBV infection and there is no determination of when acute HBV infection occurred, it is recommended that the testing provider offer screening and vaccination to current household and sexual partners. By convention, some jurisdictions offer this same intervention to contacts in the **6 months** prior to chronic status being known.

Information sharing among providers can improve the quality and appropriateness of care, reduce duplication of vaccine administration and ensure completion of immunization series (67).

For further information on post-exposure prophylaxis, refer to:

- Section 6.0 Post-exposure Management
- BC Immunization Manual, Part 4-Biological Products, for HBIg and hepatitis B vaccine post-exposure indications product pages
- BCCDC Manual, Chapter 1: Blood and Body Fluid Exposure Management

8.2.3 Health Teaching to Prevent HBV Transmission

Counsel about minimizing further transmission of hepatitis B virus. This can include**:**

- Inform sexual partner(s) and household members to follow-up with their health care provider for HBV testing and hepatitis B vaccine as needed. Protection from infection cannot be ensured until receipt of a complete vaccine series and/or when a protective anti-HBs level has been demonstrated through post-vaccination testing.
- If HBsAg positive and pregnant or considering pregnancy, consultation with a specialist is advised to discuss reduction of risk for perinatal transmission
- Harm reduction education: do not share any drug use equipment (e.g., needles, syringes, cookers, filters, straws or pipes)
- Use latex condoms to reduce the risk of HBV and other STI transmission
- Keep all open cuts and sores covered with a bandage until healed
- Put articles with blood on them (e.g., tampons, pads, Kleenex, dental floss and bandages) in a separate plastic bag before disposing into household garbage
- Disposing of bloody sharp items (e.g., razor blades, needles) into a hard container and tape shut
- Using bleach to clean up blood spills. Wet surfaces with 1 part bleach to 9 parts water and leave sitting for 10 minutes before wiping off. Anything that is tuberculocidal will kill HBV. Although not obligated, advise health care providers and anyone who might come into contact with their blood (e.g., during electrolysis, acupuncture, body piercing, and tattooing) of the HBV infection
- Inquire about infection control policies and procedures if engaging in any activities that involve tattooing, body piercing or other percutaneous exposures
- Do not share needles or ink used for tattooing
- Do not share needles used for body piercing
- Do not donate blood, semen, breast milk, body organs or tissues
- Do not share toothbrushes, dental floss, razors, earrings, glucometers, manicure equipment or any other articles that might have traces of blood
- Do not pre-chew food for babies

Practitioner Alert!

Key teaching points (1)

- HBV infection is **NOT** transmitted by sharing eating utensils, hugging, kissing, hand holding, coughing or sneezing
- HBV does not spread via water or food
- Individuals who are HBsAg positive can safely:
  - share meals and cutlery with others
  - participate in all activities, including contact sports
  - attend and interact with other children in daycare or school, because of BC's universal vaccination program

8.2.4 General Health and referrals

All individuals testing positive for hepatitis B will require longitudinal care. Individuals with chronic HBV infection require regular follow-up indefinitely, including bloodwork and ultrasound monitoring generally every six to twelve months, to assess for liver damage and treatment consideration. If the initial testing provider is unable to provide this care then they should assist in linkage to care.

Liver fibrosis can progress in the presence of coinfection with HBV or HIV, alcohol consumption (> 2-3 drinks/day), non-alcoholic fatty liver disease, obesity and insulin resistance. Discuss limiting or avoiding alcohol, avoiding hepatotoxic drugs (e.g., acetaminophen) and eating a well-balanced diet, as part of a healthy lifestyle and to minimize liver damage. Clients should consult with their primary care provider before using over-the-counter medications and herbal remedies, as some can be potentially hepatotoxic.

If appropriate, assess for other STI's and offer supportive harm reduction education and counselling. Engage individuals to assess for readiness to reduce of stop use of illicit drugs. Provide information on local harm reduction services, including drug use supply, distribution and recovery sites, supervised injection facilities, opioid agonist therapy (e.g., methadone, Suboxone), and other harm reduction strategies aimed at reducing the risk of acquiring HIV infection and reducing harms associated with illicit drug use.

Resources

- For general healthy living guidelines for those with liver disease: http://www.liver.ca
- For Harm Reduction resources (e.g., Take Home Naloxone Program): http://www.bccdc.ca/health-professionals/clinical-resources/harm-reduction and http://towardtheheart.com/
- For information on the College of Physicians and Surgeons of BC Methadone Maintenance Program (includes Suboxone): https://www.cpsbc.ca/programs/drug-programs/mmp
- For the Primary Care Management of Hepatitis B – Quick Reference: http://www.phac-aspc.gc.ca/publicat/hep/hbv-vhb/index-eng.php
- For requisitions and information about testing performed at the BCCDC PHL: http://www.bccdc.ca/health-professionals/professional-resources/laboratory-services
- For client education materials, see the Healthlink BC files: https://www.healthlinkbc.ca/services-and-resources/healthlinkbc-files

8.2.5 Breastfeeding

Breastfeeding is considered to be safe with proper immunization of neonates. If nipples are cracked or bleeding, transmission is plausible; however, given that neonates born to HBsAg positive mothers should be receiving HBIg, a complete hepatitis B vaccine series, and follow-up post-vaccination serology, this is unlikely (3, 51).

If electing not to breastfeed while nipples are cracked or bleeding, to prevent cessation of milk supply, mothers may consider expressing and discarding breast milk until their nipples are healed. Breastfeeding is **not** recommended for mothers co-infected with HIV.

8.2.6 Immunizations

In addition to routine vaccinations, the following are recommended for individuals with chronic HBV infection:

- hepatitis A vaccine series, if susceptible
- pneumococcal vaccine
- annual influenza vaccine

Refer to the BC Immunization Manual.

8.2.7 Insurance Company Testing

Clients identified through insurance applications may go through a different process when reporting to Public Health and their care provider may first receive notification of the test from public health. The elements of follow up are the same as for other all other newly identified cases. In some instances, these clients may be contacted directly by public health personnel to begin follow-up.

8.2.8 Transfusion Transmission

If risk factors indicate the possibility of a transfusion transmissible infection, where the client has been a donor or recipient, follow the reporting process for 'Transfusion Transmissible Infection' in the BC CDC Manual, Chapter 1: Communicable Disease Control.

8.3 Pregnancy – Perinatal Case Management

BC's universal perinatal screening program remains of vital importance in protection against HBV infection during infancy, where the risk of chronic HBV infection is highest. Around 95-99% of pregnant women in BC routinely have HBsAg perinatal screening done prior to delivery (68, 69). Of all deliveries in BC, 0.7 to 1.2% are to HBsAg positive women.

Unimmunized Infants born to mothers who are HBsAg positive during pregnancy, have a 10-90% risk of developing HBV infection (10, 13, 14). Around 25% of these infants will go on to develop cirrhosis and HCC (14). BCCDC continues to recommend HBIg and hepatitis B vaccine at birth, in addition to post-vaccination serology for all neonates born to HBsAg positive women (63).

The benefits of prenatal screening depend on the timely administration of post-exposure prophylaxis. This is dependent upon the timely and accurate transfer of information between the healthcare provider (family physician/NP/midwife), the delivering hospital (or midwife), the post-natal care provider and public health (70). Because multiple care providers are involved case management strategies can improve completion of the care pathway. Accountability mechanisms must be in place to ensure appropriate HBV follow-up for all infants at higher risk for acquiring HBV infection at birth. Accountability mechanisms should be designed to rest with those best placed to ensure timely delivery of care, and ensure the shortest structural delays when errors occur.

Where possible, a program monitoring and evaluation plan should be put in place to monitor processes, and outcomes for all pregnancies affected by hepatitis B, and to identify areas for program improvement.

Overview of recommended perinatal HBsAg processes

1. Prenatal Care

The BC maternity care pathway recommends the following as part of routine prenatal care:

- Test for HBsAg in first trimester for each pregnancy regardless of prior immunization or testing results
- If there is risk for the acquisition of HBV infection during pregnancy, it is recommended that prenatal providers screen for hepatitis B (HBsAg, anti-HBs and anti-HBc Total) unless there is proof of immunity (i.e., natural HBV infection or immunization)
- It is recommended that prenatal providers offer at risk, susceptible pregnant women a full hepatitis B vaccine series
- Inquiry into HBV infected household or sexual contacts is recommended to determine if a birth dose of hepatitis B vaccine is indicated
- Results of prenatal testing should be routinely forwarded to the hospital as part of the Perinatal Services BC Antenatal Record Part 1 and 2

2. Prenatal Lab Results

- Private and hospital laboratories should send notification of prenatal HBsAg positive lab results to the BCCDC PHL
- BCCDC PHL forwards a copy of the lab result to the ordering HCP and Public Health. A letter is sent to the ordering HCP (BC Immunization Manual, Part 2-Immunization of Special Population, Infants at High Risk for Hepatitis B).

3. Client Education

- All pregnant women with HBV infection should receive counseling from a health care provider about their diagnosis, the implications for the health of their infant, and the required follow-up. Consider giving a copy of the lab result to the mother to facilitate understanding around the care needed, and to help communicate with other members of the health care team. Topics for counseling should include:
  - The need for HBV DNA testing in pregnancy and possible referral to a specialist
  - Post-natal prophylaxis (i.e., HBIg and first dose of HBV vaccine) at birth
  - Immunization of all susceptible household and sexual contacts
  - Transmission prevention

  General prenatal and liver health education (e.g., avoid alcohol)

4. Intrapartum care

- Although hepatitis B serology results are included in the BC Perinatal Record, it is best practice for admitting staff to independently verify hepatitis B lab reports prior to delivery
- If no prenatal HBsAg result is available, arrange for immediate HBsAg testing
- If prenatal HBV antiviral therapy has been initiated, it may be stopped after delivery or may continue past delivery, as per the specialist's prior recommendations
- Give HBIg and hepatitis B vaccine **immediately after birth** (**within 12 hours**)
- Document the date of prophylaxis administration on the Perinatal Services BC:
  - BC Newborn Record Part 1 and 2 form

    and
  - BC Community Liaison Record – Newborn and Postpartum form
- Transfer documentation to the primary health care provider, Public Health and the mother

5. Post-partum/post-natal care

- Both the post-natal care providers and public health should receive documentation of receipt of post-exposure prophylaxis from the delivering care provider
- Post-discharge, care providers should ensure that HBIg and vaccine were given at birth
- Post-partum, the care plan should be reviewed. This includes:
  - Routine vaccination with hepatitis B vaccine at 2, 4 and 6 months of age
  - Post-vaccination serology **1 month** after the last dose of hepatitis B vaccine
- Provide mother with a copy of the neonate's vaccination records and a lab requisition for HBsAg and anti-HBs post-vaccine serology. Anti-HBc Total is **not** indicated as maternal core antibodies can also be detected, which can cause confusion.
- If the infant is HBsAg positive, refer the infant to a liver specialist. The neonate will be highly infectious. Immunize susceptible household or close contacts.
- If the infant is HBsAg negative and anti-HBs < 10 IU/L, liaise with Public Health

8.3 Stigma and HBV Infection

In North American Asian communities, the prevalence of HBV infection is higher, while self-reported rates of screening is lower (71). Varied knowledge gaps have been identified regarding transmission, health consequences, vaccination status, and confusion around types of hepatitis, that may stem from southeast Asian folk models or misunderstanding of biomedical knowledge and contribute to misconceptions about HBV infection (66, 72, 73).

In particular, China has had a long history of stigma against people with HBV infection, including discriminatory education admission and employment practices against individuals with chronic HBV that have only been addressed in law over the past decade (74, 75). This has manifest in many North American Chinese avoiding HBV screening for fear of diagnosis and resultant social isolation from spouses, families and friends, reflecting the significant societal and internalized stigma associated with HBV infection (72, 74).

A BC study noted that compared to Chinese populations, other Asian communities have even lower awareness and knowledge of HBV (76). Multi-pronged approaches to HBV health campaigns have been recommended as a best approach to target Asian communities, with emphasis on physician-based screening interventions (75, 77). Shifting educational program tasks to culturally appropriate lay workers has been found to effectively increase the uptake of HBV screening, however further research is needed to examine key steps along the HBV continuum of care (78).

Refer to table 8-1 for strategies on how to address stigma in communities.

Table 8-1. Strategies to address HBV stigma

Point of entry	Target HBV client's point-of-entry into the health care system. Not all HBV clients have access to a family physician (71)
Task Shifting	Provision of educational programs by culturally appropriate, same-language trained lay health workers (78)
Location	Consider alternate community locations to increase engagement (e.g., churches, language study programs) (78)
Multi-pronged approach	Consider community-level public health campaigns via newspapers, ethnic TV programs and the internet (77)
Knowledge	Assess for adequate knowledge of aetiology, symptoms, transmission, prevention strategies and treatment (66, 72, 73) Address any assumptions or myths that may be influencing decisions to participate in screening and follow-up treatment and monitoring programs (66, 72, 73) Culturally tailor HBV education information (78)
Engagement	Partner with existing community organizations Have a consistent presence in communities to help foster trusting relationships Employ an interdisciplinary approach to address social determinants of health and any psycho-social issues that may be barriers to accessing care
Empower	Support and advocate for communities and individuals to take active roles in their HBV screening and care

8.4 HBV Treatment

A virological cure (complete elimination of HBV) remains elusive, as even when serological levels of HBV fall below detection, HBV can persist in the liver. The loss of HBsAg is an ideal target, but this is rarely achieved through treatment. Recommendations for duration of treatment are highly variable, and are influenced by HBsAg and HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis/decompensation.

Hepatic decompensation in the presence of HBV infection should be addressed urgently with treatment to help prevent flares and decrease viral replication while waiting to be considered for liver transplant. HBV infected individuals with compensated cirrhosis are candidates for treatment if HBV DNA ≥ 2000 IU/mL, while those with lower HBV DNA levels may be considered for therapy, or can undergo close observation.

Interferon remains one of the first-line treatment options. It causes more side effects and is less effective than nucleos(t)ide analogues; however, there is no concern about the development of resistance and duration of therapy is shorter. Oral antivirals have fewer side effects, but the length of treatment can be lifelong and mutations can occur when used, resulting in HBV antiviral resistance. Tenofovir or Entecavir is recommended as first-line therapy, because of their potency and low risk of resistance. While resistance and cross-resistance to other antivirals can occur over time when Lamivudine is used, it continues to be met with some degree of success.

After a chronic HBV infection has been confirmed the primary care provider can undertake further clinical evaluation prior to a referral to a specialist to help expedite evaluation for treatment readiness. This may include:

- bloodwork for further HBV testing and liver enzymes
- clinical exam
- fibrosis staging (e.g. Fibroscan®, liver biopsy, APRI, FIB-4)
- imaging to assess for cirrhosis

If an individual shows evidence of past or present HBV infection, and are undergoing intensive immunosuppressive therapy (e.g., rituximab regimen, treatment for lymphoma), a referral to a specialist must be made for HBV DNA testing and further monitoring. If the HBV DNA is positive, these patients may also be considered for antiviral therapy (7, 24, 30, 79, 80).

Resources

For CASL recommended treatment options, see the 2012 Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines: http://www.hepatology.ca/

For AASLD recommended treatment options, see the 2015 AASLD Guidelines for Treatment of Chronic Hepatitis B: http://www.aasld.org/publications/practice-guidelines-0

For EASL recommended treatment options, see the 2012 Management of Chronic Hepatitis B virus infection guidelines: http://www.easl.eu/research/our-contributions/clinical-practice-guidelines

Information on available treatments and requirements for coverage in BC can be found: http://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents

For further guidelines on managing HBV reactivation during immunosuppressive therapy, see the AGA's Hepatitis B Reactivation During Immunosuppressive Drug Therapy Guidelines (81, 82)

APPENDIX A: Laboratory testing of Hepatitis D

When markers for HBV infection are present, HDV laboratory testing may be ordered. HDV testing should be considered in the following clinical scenarios (7, 83):

- **Acute HBV infections**: if individual engages in IDU or is from an endemic country, or is presenting with especially severe or prolonged acute HBV hepatitis
- **Acute hepatitis in those with chronic HBV**: rule out HDV superinfection. Consider when ALT levels are elevated, but HBV DNA levels are low to undetectable.
- **HBsAg-positive chronic liver disease:** rule out concurrent chronic HDV infection

Table A-1: Laboratory testing of HDV (34, 84, 85)

HDV serologic marker	Term	Clinical correlation
Anti-delta	Hepatitis D antibody	• Indicates if an individual has ever been infected with HDV • Appears after ~ 4 weeks after exposure • Anti-HDV antibodies can persist for years, and may not disappear even after an infection has resolved
HDV PCR	Hepatitis D Polymerase Chain Reaction	• Detects HDV RNA • Serology results must show markers to HDV prior to ordering this test

All HDV testing ordered in BC is referred to the National Microbiology Laboratory.

For further information, refer to the:

BCCDC PHL, PHSA Laboratories Guide to Programs and Services
http://www.bccdc.ca/health-professionals/professional-resources/laboratory-services

Public Health Agency's National Microbiology Laboratory Guide to Services
https://www.nml-lnm.gc.ca/index-eng.htm

APPENDIX B: Case Studies

During the 2017 review process, a provincial working group comprised of Public and Community Health nurses and physicians gathered to discuss the BCCDC Hepatitis B Guidelines revisions. Related to this work, a series of case studies were put together with the goal of addressing commonly occurring scenarios and other frequently asked questions.

The follow-up detailed in each scenario below are recommendations that were made through discussions amongst the provincial working group members and BCCDC's Hepatitis Program clinical leadership team, for the purposes of training and education. These case studies are not meant to be prescriptive, as there may be other considerations and alternate recommendations applicable to individual clinical scenarios that are not addressed here.

Note that throughout the case studies:

- Non-reactive = Negative
- Reactive = Positive
- IU/L = mIU/mL

Case study #1
Isolated core (HBsAg nonreactive, anti-HBc Total reactive, anti-HBs undetectable)

Clinical History/Lab results

Immune competent individual with no prior documented hepatitis B vaccinations or HBV testing, born in Canada.

HBsAg	Nonreactive
Anti-HBs	Undetectable
Anti-HBc Total	Reactive

Explanation

If the individual was born in Canada, this is more likely to be a false positive. If the individual immigrated from an HBV endemic country, this is more likely to be the result of a remote resolved infection with persistence of anti-HBc Total and undetectable anti-HBs level. Such individuals may be at risk of reactivation if immunocompromised

Recommended follow-up

- ☐ Offer one complete hepatitis B vaccine series. No routine follow-up indicated unless there is ongoing risk of infection, or documentation is required for work or school purposes.
- ☐ Testing for HIV and HCV is recommended, as isolated anti-HBc Total is more common with HIV, and potentially with HCV infection as well.

References

- Section 5.4 Reactive anti-HBc Total results
- BCCDC Isolated Hepatitis B Core Antibody positive test results physician letter
- Section 5.2 Post-vaccination serology follow-up for immune competent individuals
- HIV Testing Guidelines for the Province of BC (http://hivguide.ca/)

Case study #2
HBsAg nonreactive, anti-HBc Total reactive, anti-HBs detectable but less than 10 IU/L

Clinical History/Lab results:

Immune competent individual with no prior documented hepatitis B vaccinations or HBV testing, born in China.

HBsAg	Nonreactive
Anti-HBs	Detectable, but less than 10 IU/L
Anti-HBc Total	Reactive

Explanation:

If the individual was born in Canada, this is more likely to be a false positive. If the individual immigrated from an HBV endemic country, this is more likely to be the result of a remote resolved infection with persistence of anti-HBc Total and a detectable, but less than 10 IU/L, anti-HBs level. Such individuals may be at risk of reactivation if immunocompromised. Consider HIV or HCV coinfection as a cause of anti-HBs loss.

Clinical history is required to rule out a recently resolved acute infection. Additional doses of vaccine have not been shown to improve anti-HBs levels.

Recommended follow-up:

- ☐ If symptomatic, or an acute infection is suspected, refer as appropriate and assess for any household contacts that require HBV testing and hepatitis B vaccination
- ☐ Test for HIV and HCV
- ☐ No further follow-up required unless beginning immunosuppressive medication

References:

- Section 5.4 Reactive anti-HBc Total results (Isolated Hepatitis B Core Antibody)
- HIV Testing Guidelines for the Province of BC (http://hivguide.ca/)

Case study #3
Anti-HBs detectable, but less than 10 IU/L, after prior vaccination

Clinical History/Lab results

Immune competent individual presents without documentation of any prior hepatitis B vaccinations or HBV testing. Born in 1980, raised in BC, and completed elementary and high school in BC. This individual is a Health Care Worker, requiring hepatitis B immunization for work purposes.

HBsAg	Nonreactive
Anti-HBs	9.2 IU/L
Anti-HBc Total	Nonreactive

Explanation

We know that after vaccination, anti-HBs levels will wane and people will be protected from chronic HBV, because they will develop a protective anamnestic immune response. Most people will be protected for multiple decades post-vaccination. If there are on-going risks, a booster of HBV vaccine is recommended.

This detectable, but not protective anti-HBs level is considered to be just at the immune threshold of the internationally accepted anti-HBs protective level of 10.0 IU/L. This can depend on the testing platform used. If tested at BCCDC PHL, 8.0 to < 12.0 mIU/mL is considered to be an equivocal result, or in the “grey zone”.

When an individual presents without documentation of prior vaccine history, a verbal history of immunization is generally not considered proof of immunity. Here, HBV testing proceeded without prior documentation of a complete hepatitis B series. Given BC’s high hepatitis B immunization rates and low number of acute HBV cases, clinical judgement was used in presuming that this individual had received prior hepatitis B vaccine through BC’s universal hepatitis B immunization program.

Recommended follow-up

- ☐ Offer one dose of hepatitis B vaccine and repeat anti-HBs in 1 month
- ☐ If anti-HBs ≥ 10 IU/L, consider immune. No further hepatitis B vaccination is required.
- ☐ If anti-HBs < 10 IU/L, consider a non-responder. Complete a second hepatitis B vaccine series and repeat anti-HBs 1 month after the last dose of hepatitis B vaccine.
  - If anti-HBs ≥ 10 IU/L, consider immune. No further hepatitis B vaccination is required.
  - If anti-HBs < 10 IU/L, consider a 2-series non-responder and susceptible to HBV infection. If exposed, individual will require appropriate post-exposure prophylaxis.
- ☐ Offer an HIV test every time you test for or diagnose hepatitis B (http://hivguide.ca/)

References:

- Section 4.5 Post-vaccination serology
- Section 5.2 for Post-vaccination serology follow-up for immune competent individuals
- HIV Testing Guidelines for the Province of BC (http://hivguide.ca/).
- BC Immunization Manual, Part 4-Biological Products
- Canadian Immunization Guide: Part 3 – Vaccination of Specific Populations, Immunization of Persons with inadequate Immunization Records
- CDC General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Unknown or Uncertain Vaccination Status.

Case study #4
Undetectable surface antibody levels after prior vaccination

Clinical History/Lab results:

Immune competent individual presents without documentation of any prior hepatitis B vaccinations or HBV testing. Born in 1980, raised in BC, and completed elementary and high school. This individual is a Health Care Worker, requiring hepatitis B immunization for work purposes.

HBsAg	Nonreactive
Anti-HBs	0.9 IU/L (Undetectable)
Anti-HBc Total	Nonreactive

Explanation

This can depend on the manufacturer. If tested at BCCDC PHL, anti-HBs < 3.1 is undetectable. This is below the internationally accepted anti-HBs protective level of 10.0 mIU/mL (or 10.0 IU/L). Some testing platforms used in private laboratories in BC define undetectable as < 2.0 mIU/mL or <1.0 mIU/mL.

In this scenario, this could reflect waning immunity or failure of a first complete hepatitis B vaccine series.

When an individual presents without documentation of prior vaccine history, it is considered best practice to consider them susceptible and to immunize as appropriate. However as in this scenario, HBV testing proceeded without prior documentation of a complete hepatitis B series. Given BC's high hepatitis B immunization rates and low number of acute HBV cases, it was presumed that this individual had received prior hepatitis B vaccine through BC's universal hepatitis B immunization program.

Recommended follow-up

- ☐ Provide a complete hepatitis B vaccine series
- ☐ If anti-HBs ≥ 10 IU/L, consider immune. No further hepatitis B vaccination is required.
- ☐ If anti-HBs < 10 IU/L, consider a 2-series non-responder and susceptible to HBV infection. If exposed, individual will require appropriate prophylaxis.
- ☐ Offer an HIV test every time you test for or diagnose hepatitis B (http://hivguide.ca/)

References:

- Section 4.5 Post-vaccination serology
- Section 5.2 Post-vaccination serology follow-up for immune competent individuals
- HIV Testing Guidelines for the Province of BC (http://hivguide.ca/). Refer to reference for recommended testing frequency.

Case study #5
Post-sexual assault follow-up

Clinical History/Lab results

A 24 year old female born in Canada, presented in the ER following a reported sexual assault the night prior. HBIg was not administered at the ER and the client was advised to follow-up with Public Health for hepatitis B vaccinations. The client presented at the local Public Health unit one day later. The Public Health Nurse was unable to locate any documentation of prior hepatitis B vaccine. As far as the PHN could tell, this individual appeared to be immune competent. HBV screening tests were ordered.

HBsAg	Nonreactive
Anti-HBs	4.2 IU/L
Anti-HBc Total	Nonreactive

Explanation

Post-exposure prophylaxis is indicated in this scenario. In the case of a sexual assault, or if the source individual is known to have acute or chronic hepatitis B infection, HBIg is indicated to provide passive immunity. In addition, an assessment of the individual's capacity to mount an active immune response to a potential HBV infection is required, in ensuring anti-HBs levels are ≥ 10 IU/L.

As in case study #4, these HBV results could reflect waning immunity or failure of a first complete hepatitis B vaccine series. When an individual presents without documentation of prior vaccine history, it is best practice to consider them susceptible and to immunize as appropriate.

Recommended follow-up

- ☐ HBIg should be given as soon as possible, preferably within 48 hours of exposure. Contact the supervisor of the Blood Bank at the nearest hospital as soon as possible. HBIg may be given up to 14 days after exposure.
- ☐ Complete one hepatitis B vaccine series and repeat HBV screening tests (HBsAg, anti-HBs and anti-HBc Total) 1 month after the last dose of hepatitis B vaccine, or 6 months after HBIg was given, whichever is longer.
- ☐ Assess for the need to test/treat for other sexually transmitted infections and address potential for unwanted pregnancy and forensic involvement (e.g., HIV PEP, CT/GC treatment, managing forensic samples, emergency contraception), and refer as appropriate.
- ☐ Review follow-up plan with the individual:
  - Dates for remainder of hepatitis B vaccines and post-vaccination serology
  - Provide a copy of the prophylaxis and immunization records, and the local Public Health unit contact information
  - Connect individual with other appropriate supports (e.g., crisis counselling, advocacy and support)

References

- Section 6.0 Post-exposure Prophylaxis
- Section 5.2 Post-vaccination serology follow-up for immune competent individuals
- BC Women's Hospital and Health Centre Sexual Assault Services Resources (http://www.bcwomens.ca/health-professionals/professional-resources/sexual-assault-service-resources)
- BC Centre for Excellence in HIV/AIDS Non-Occupational Post-Exposure Prophylaxis Guidelines (http://www.cfenet.ubc.ca/npep)

Case study #6
Reactivation

Clinical History/Lab results

82 year old male of Korean ancestry received routine HBV testing related to lymphoma in 2017. History of colon cancer and lymphoma.

2013		
HBsAg	Nonreactive	Client asymptomatic. No risk factors. Testing related to colon cancer.
Anti-HBs	15 IU/L	
Anti-HBc Total	Reactive	

In 2013, the client was diagnosed and treated for colon cancer. No HBV antiviral prophylaxis was administered.

In 2017, the client was diagnosed and treated for lymphoma. No HBV anti-viral prophylaxis was administered prior to starting treatment.

2017		
HBsAg	Reactive	Client asymptomatic. No risk factors except for recent scaling at dentist. No sexual partners in the past 5 years.
Anti-HBs	Undetectable	
Anti-HBc Total	Reactive	
AST	101 (normal < 36)*	
ALT	193 (normal < 50)*	

* Normal ranges noted on lab results can vary, depending on the reporting laboratory

Explanation

In 2013, this individual had evidence of a past HBV infection which had resolved. In 2017, HBsAg converted to reactive, suggesting reactivation of HBV infection. HBV reactivation is more common in the scenario of immunosuppressive therapy (e.g., chemotherapy, biologic therapy) and has been reported when direct-acting antivirals are used for HCV treatment. Further lab testing should be done to confirm this individual's status.

2017	
Hep B DNA	DNA detected
HBsAg	Reactive
Anti-HBs	Undetectable
Anti-HBc Total	Reactive
AST	94 (normal < 36)*
ALT	199 (normal < 50)*

The detection of HBV DNA and persistently elevated liver enzymes in the context of previously cleared HBV infection (i.e., HBsAg nonreactive) is further supportive of HBV reactivation. HBV prophylaxis prior to chemotherapy would have ideally been recommended to help decrease risk for reactivation of HBV infection.

Recommended follow-up

- ☐ Refer to a liver specialist for further follow-up care. This individual will require ongoing clinical assessments (e.g., bloodwork, ultrasounds, Fibroscan®).
- ☐ Assess for any household contacts that require HBV testing and hepatitis B vaccination

References

- Section 3.2.2 HBV Reactivation
- Section 3.3.1 Coinfection with Hepatitis C Virus (HCV)
- Section 5.1 Reactive HBsAg result follow-up and Section 5.4 Isolated anti-HBc Total results
- HIV Testing Guidelines for the Province of BC (http://hivguide.ca/).

Case Study #7
HBsAg reactive, anti-HBc Total reactive and anti-HBs greater than 10 IU/L

Clinical History/Lab results

A 65 year old female China had HBV testing done related to an Immigration Medical Examination (IME). This individual appears to be immune competent and does not have any other medical conditions. Prior history of hepatitis B vaccine or disease is unknown.

HBsAg	Reactive
Anti-HBs	44 IU/L
Anti-HBc Total	Reactive

Explanation

There are a few possible scenarios:

- Most common: this individual is in the process of resolving a HBV infection and mounting an immune response. This is more commonly seen in people from countries where HBV is endemic. Further clinical assessment is required to determine whether this is an acute HBV infection.
- False positive results
- Hepatitis B vaccine was given within the past 3-4 weeks and/or HBIg was given within the prior 6 months

This individual should be considered infectious.

Recommended follow-up

- ☐ Refer to a liver specialist for further assessment. This individual will require additional clinical assessments (e.g., bloodwork, ultrasounds, Fibroscan®)
- ☐ If this individual is symptomatic and an acute infection is suspected, recommend re-testing (HBsAg, anti-HBc Total and anti-HBs) in 1 month
- ☐ Assess for any household contacts that require HBV testing and hepatitis B vaccination
- ☐ HIV Testing Guidelines for the Province of BC (http://hivguide.ca/)

References

- BCCDC Hepatitis Team Clinical Leadership team
- Section 4.0 Laboratory and Testing Information
- Section 4.5 Post-vaccination serology
- HIV Testing Guidelines for the Province of BC (http://hivguide.ca/)

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