

# Hepatitis B immunization



Technical Report  
July 2017

## Public Health Ontario

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## Purpose

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This report aims to summarize the best available evidence and existing expert recommendations relevant to the timing of universal pre-exposure hepatitis B (HB) immunization in Ontario and was developed after a recognition of variation in provincial/territorial publicly-funded hepatitis B immunization programs in Canada. It provides relevant background information and summarizes the objectives, methods and results of an analysis conducted by Public Health Ontario staff to assist the Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I) in its deliberations regarding HB immunization. The analysis compares adolescent versus infant HB immunization in the Ontario context through a:

- jurisdictional scan
- descriptive epidemiological analysis of reported HB cases in Ontario
- synthesis of relevant economic evaluation literature
- narrative analysis of equity considerations

## Background

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### Transmission

HB is a communicable disease that is reportable in the province of Ontario.<sup>1</sup> HB can be transmitted by contact with infected blood or blood products, or mucosal contact with infected bodily fluids including semen, vaginal and anal secretions, and saliva.<sup>2-4</sup> In areas of high HB endemicity, HB is most commonly spread vertically (i.e., perinatally, from mother to child), or horizontally during the first five years of life. In low endemicity areas like Canada, HB is most commonly transmitted horizontally (e.g., via sexual, percutaneous, or close household contact), although vertical transmission remains a risk.<sup>2-4</sup> In line with these transmission patterns, most acute cases of HB are reported in unimmunized adults aged 25 years and older in Canada.<sup>4</sup>

### Clinical presentation and disease progression

Acute HB infection is asymptomatic in up to 50% of adults and 90% of children. When the infection is symptomatic, it may include sudden onset of abdominal pain, nausea, vomiting, jaundice, and/or fever.<sup>5,6</sup> The risk of fulminant hepatitis associated with acute infection is approximately 1%, and fulminant hepatitis has a case fatality of 63% to 93%.<sup>7</sup> Chronic HB infection is frequently asymptomatic for decades; however, one-third of chronic HB carriers develop cirrhosis and/or chronic liver failure, and approximately 5% develop hepatocellular carcinoma (HCC).<sup>5,8</sup>

The risk of chronic HB varies inversely with age at time of infection. The younger an individual is when infected with HB, the more likely he or she is to become a chronic HB carrier. Approximately 90% of

infants, 25-50% of children one to five years of age, and 5% of adults over 18 years of age infected with HB will become chronically infected.<sup>7</sup>

## HB diagnosis and under-diagnosis

The diagnosis of HB relies on laboratory test results and/or clinically compatible symptoms. Under-diagnosis may occur due to asymptomatic infection, mild or non-specific symptoms, failure to seek health care, and/or lack of HB testing by health care providers.<sup>4,9</sup> There is no universal HB screening program in Ontario. Canadian guidelines recommend screening for pregnant women, immigrants from intermediate/high prevalence areas and for other high risk groups.<sup>4,10-11</sup> To our knowledge, the uptake of the screening recommendations for any of these groups has not been formally evaluated in Ontario. The availability and use of a common prenatal screening laboratory requisition form, is likely to facilitate the screening of pregnant women. In contrast, no such practice prompts exist for other risk groups. The absence of HB screening as part of the Canadian Immigration Medical Examination<sup>11</sup> places the responsibility for screening on primary care clinicians in the context of routine health care services, where screening must compete with other health concerns.

## Estimated burden of HB in Ontario and Canada

Due to under-diagnosis and a lack of representative HB seroprevalence estimates for the Ontario population, estimating the true burden of HB in Ontario is challenging. However, the Ontario Burden of Infectious Diseases Study estimated HB as the fourth most burdensome infectious disease in Ontario as assessed through years of life lost and health adjusted life years.<sup>9</sup> The Canadian Health Measures Survey (CHMS) estimated that in 14 to 79 year olds HBsAg (the surface antigen of HB virus used to determine infection status) seroprevalence is 0.4% (95% CI: 0.2%-0.8%), however excluded risk groups may result in underestimation of the burden of HB.<sup>12</sup> There is a range of published estimates of HBsAg positive seroprevalence among immigrants in Canada that exceeds estimates for the general population (e.g. 1.6%<sup>12</sup> in the CHMS, 4%<sup>13</sup> and 6.7%<sup>14</sup> in two recent systematic reviews). It is estimated in the 2007 to 2011 CHMS results that 23% of the population was foreign born,<sup>12</sup> which is comparable to the estimate of 20% that the 2006 Canadian Census reported.<sup>15</sup> A detailed analysis of HB epidemiology in Ontario, derived from reportable disease information, is included within this document.

## Prevention and control of HB in Ontario

In addition to prenatal screening, the cornerstones of HB prevention and control in Ontario are: HB immunization (see below); infection prevention and control in health care settings; public health case and contact management (e.g., education, counselling, post-exposure prophylaxis);<sup>1</sup> and, other preventive measures (e.g., early diagnosis through targeted physician testing of immigrants, harm reduction services, blood donor screening, sexual health promotion).

In the specific context of day nurseries/child care centres (where most staff and attendees would currently not be eligible for publicly-funded HB immunization in Ontario), local public health HB prevention and control activities may also include follow up of reported human biting incidents involving



a skin puncture, and follow up as needed related to reported HB immunization status of staff and/or attendees.<sup>16</sup>

## Publicly-funded HB immunization in Ontario

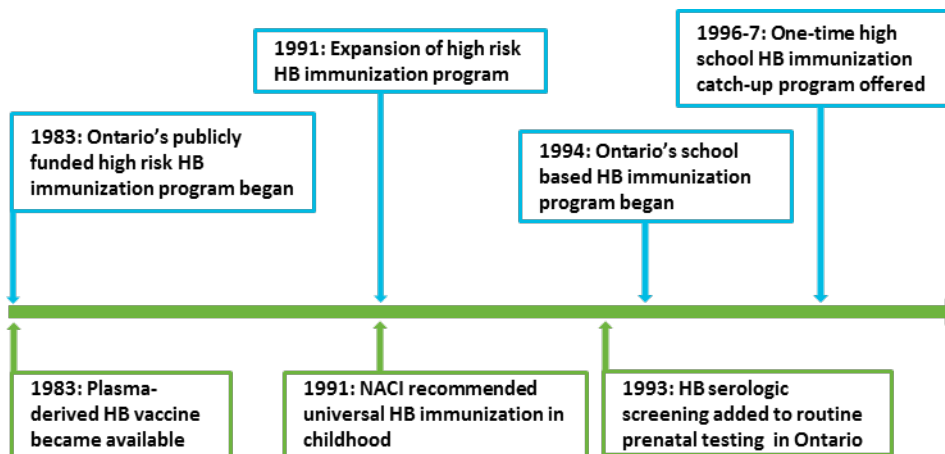
In Canada, policy makers in each province and territory determine their respective publicly-funded immunization schedules, with consideration given to the recommendations of Canada's National Advisory Committee on Immunization (NACI). NACI currently recommends either an infant or an adolescent strategy for universal pre-exposure HB immunization (i.e., routine HB immunization).<sup>4</sup>

Publicly-funded HB immunization in Ontario began with a high-risk program in 1983 (Figure 1). The current high-risk eligibility criteria in Ontario are summarized in Table 1. The full series is publicly-funded by the Ministry of Health and Long-Term Care (MOHLTC) for all risk groups with the exception of persons on renal dialysis, those with diseases requiring frequent receipt of blood products, and persons awaiting liver transplants for whom only the second and third doses are publicly-funded.<sup>17</sup>

Ontario introduced a publicly-funded, three-dose routine HB immunization program for grade seven students (approximately 12 years of age) in September 1994,<sup>18</sup> with the intent of protecting against HB before exposure via sexual transmission and other high risk behaviours. In 2000, Ontario's grade seven HB immunization program switched from three to two doses, given four to six months apart depending on the vaccine product, in keeping with updated recommendations from NACI.<sup>4,19</sup>

This school-based HB immunization program is delivered by Ontario's 36 public health units. There was a one-time catch-up campaign for high school students in 1996-1997.<sup>18</sup> Program eligibility continues to the end of grade eight for students who missed one or both doses during their grade seven year. However, there is no ongoing publicly-funded catch-up program beyond this single year of extended eligibility.<sup>17</sup>

**Figure 1.** Timeline of publicly-funded Hepatitis B immunization in Ontario<sup>20</sup>



**Table 1. High-risk eligibility criteria for publicly-funded Hepatitis B immunization in Ontario**

Ontario’s high risk eligibility criteria <sup>17</sup>	NACI recommended recipients of HB vaccine for pre-exposure prevention <sup>4</sup>
<ul style="list-style-type: none"> <li>• Children &lt;7 years old whose families have immigrated from countries of high prevalence for HB</li> <li>• Household and sexual contacts of chronic carriers and acute cases</li> <li>• History of a sexually transmitted disease</li> <li>• Infants born to HBV-positive carrier mothers</li> <li>• Intravenous drug use</li> <li>• Liver disease (chronic), including hepatitis C</li> <li>• Awaiting liver transplants</li> <li>• Men who have sex with men</li> <li>• Multiple sex partners</li> <li>• Needle stick injuries in a non-health care setting</li> <li>• On renal dialysis or those with diseases requiring frequent receipt of blood products (e.g., haemophilia)</li> </ul>	<ul style="list-style-type: none"> <li>• All adults and children who have immigrated from areas of high HB prevalence</li> <li>• Children born in Canada whose families have immigrated from areas of high HB prevalence</li> <li>• Children and workers in child care settings in which there is a child or worker who has acute HB or is an HB carrier.</li> <li>• Household and sexual contacts of acute HB cases and HB carriers</li> <li>• Household or close contacts of children adopted from HB-endemic countries if the adopted child is HBsAg positive</li> <li>• Populations or communities in which HB is highly endemic</li> <li>• Residents and staff of institutions for the developmentally challenged</li> <li>• Staff and inmates of correctional facilities</li> <li>• Persons with lifestyle risks for infection, including:               <ul style="list-style-type: none"> <li>○ persons who have unprotected sex with new partners</li> <li>○ persons who have had more than one sexual partner in the previous 6 months</li> <li>○ persons with a history of sexually transmitted infections</li> <li>○ persons seeking evaluation or treatment for a sexually transmitted infection</li> <li>○ persons who engage in high risk sexual practices</li> <li>○ persons who use injection drugs</li> <li>○ men who have sex with men (MSM)</li> </ul> </li> <li>• Persons with chronic liver disease from any cause, including hepatitis C. Hemophiliacs and other people receiving repeated infusions of blood or blood products</li> <li>• Persons with chronic renal disease or who are undergoing chronic dialysis (hemodialysis or peritoneal dialysis)</li> <li>• Persons with congenital immunodeficiencies</li> <li>• Persons who have undergone hematopoietic stem cell transplantation (HSCT) or are awaiting solid organ transplant</li> <li>• HIV-infected persons</li> <li>• Travellers to HB endemic areas</li> <li>• Health care workers, emergency service workers, and others with potential occupational exposure to blood, blood products and bodily fluids that may contain HB virus</li> <li>• Any person who wishes to decrease his or her risk of HB</li> </ul>

## HB vaccines authorized for use in Canada

Six HB-containing vaccines are authorized for use in Canada: three monovalent HB vaccines, two combined hepatitis A and HB vaccine products, and one hexavalent vaccine product (Table 2).<sup>4</sup> In Ontario, the adolescent program uses a monovalent HB vaccine. As per NACI recommendations for use, a routine infant HB immunization program could use either a monovalent HB vaccine or a hexavalent product that combines HB with other routine childhood immunization antigens.

**Table 2. Approved Hepatitis B-containing vaccine products in Canada<sup>4</sup>**

HB-containing vaccine product	Antigens	NACI-recommended use
<b>Monovalent HB</b> ENGERIX®-B, RECOMBIVAX HB®*, and RECOMBIVAX HB Adult Dialysis Formulation	HB	<b>3-dose</b> schedule for infants (e.g., month 0, 1 and 6); <b>2- or 3-dose</b> schedules are approved for adolescents (11-15 years of age) <b>3-dose</b> schedule approved for the Adult Dialysis Formulation (month 0, 1 and 6)
<b>Hepatitis A and B combined</b> TWINRIX® and TWINRIX® Junior	Hepatitis A and HB	<b>3-dose</b> standard schedule for 1-18yrs (TWINRIX® Jr.) and 19yrs+ (TWINRIX®) (month 0, 1, and 6) <b>2-dose</b> alternative schedule for 1-15yrs (TWINRIX®) (month 0 and 6)
<b>Hexavalent product containing HB</b> INFANRIX hexa™	Diphtheria and tetanus toxoids, acellular pertussis, HB [recombinant], inactivated poliomyelitis and conjugated <i>Haemophilus influenzae</i> type b	<b>3-or 4-dose</b> schedule may be given at 2, 4, 6 and 12 to 23 months 4 <sup>th</sup> dose unlikely to provide significant additional HB protection

\*A schedule of 0, 1 and at least 2 months is approved for the Recombivax HB® product; however, the NACI preferred schedule is months 0, 1 and 6

# Jurisdictional scan

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## Objective and methods

To inform a comparison of HB immunization schedules and recommendations in Canada and internationally, we conducted a focused jurisdictional scan of selected publicly accessible web sites of national and international public health organizations and immunization advisory bodies (i.e., in Canada, the United States (U.S.), Australia, Europe, and the World Health Organization (WHO)).

## Results

NACI currently recommends either universal infant or adolescent HB immunization in Canada, and recognizes that the timing of universal HB immunization programs for children varies across Canadian provinces and territories.<sup>19</sup> Current NACI recommendations do not state a preference for one of these strategies over the other, and has not made a recommendation for routine HB immunization at the time of birth (i.e. as soon as possible after birth, preferably within 24 hours), henceforth referred to as a birth dose.

NACI also recommends that “in jurisdictions where children do not receive HB vaccine in infancy, children at increased risk should be given HB-containing vaccine as soon as the risk is identified.”<sup>4</sup> This includes: children who have emigrated from high HB prevalence areas; children born in Canada whose families have emigrated from high HB prevalence areas (e.g., potential for exposure via extended family members, travel); and, household and sexual contacts of acute HB cases and HB carriers (see Table 1 for all risk groups).

Currently, three provinces and one territory have infant HB programs using the approved hexavalent vaccine product; one province and two territories have birth HB programs; and, the remaining six provinces have school-based adolescent or pre-adolescent HB immunization programs (Table 3).<sup>21</sup> In British Columbia (BC), Quebec (QC), and Northwest Territories (NT), school-based programs are used to ‘catch up’ children who were not immunized against HB at the scheduled time (i.e., at birth or infancy).

**Table 3. Publicly-funded Hepatitis B immunization programs in Canada<sup>21</sup>**

Province/Territory	Program
BC	Infant (2, 4, 6 months) <sup>a</sup>
AB	Grade 5
SK	Grade 6
MB	Grade 4; moving to Grade 6 in Sept 2017
<b>ON</b>	<b>Grade 7</b>
QC	Infant (2, 4, 18 months) <sup>a</sup>
NB	Birth (0, 2, 6 months)
NS	Grade 7
PE	Infant (2, 4, 18 months) <sup>a</sup>
NL	Grade 6
NT	Birth (0, 1, 6 months)
YT	Infant (2, 4, 6 months) <sup>a</sup>
NU	Birth (0, 1, 9 months)

Notes:

<sup>a</sup>Hepatitis B vaccine given in a 3-dose combination vaccine (DTaP-HB-IPV-Hib) in infancy

NACI's HB immunization recommendations differ from the schedules endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE),<sup>22</sup> the Advisory Committee on Immunization Practices (ACIP) in the U.S.,<sup>23</sup> and the Australian Technical Advisory Group on Immunisation (ATAGI).<sup>24</sup> In 2009, SAGE recommended that all infants should receive their first dose of HB vaccine as soon as possible after birth, preferably within 24 hours.<sup>22</sup> SAGE emphasized that their recommendation applies "even in countries where there is intermediate endemicity or low endemicity an important proportion of chronic infections are acquired through early transmission."<sup>22(p.418)</sup> ACIP endorses universal HB immunization starting at birth, but also recommends an infant program.<sup>23</sup> In addition to routine universal immunization, ACIP also recommends routinely vaccinating children and adolescents who are not yet immunized, as well as vaccinating high-risk adults.<sup>23</sup> ATAGI recommends that all newborns be immunized within 24 hours of birth.<sup>24</sup>

Countries in Europe have varying universal HB immunization schedules. Birth and infant HB immunization programs are the most common. Of the 53 countries in the WHO European Region, 26 countries have universal birth programs; 18 have infant programs; two have adolescent programs; one has a child program (age five to six); and six countries do not offer a universal program.

## Discussion

The most frequent recommendation internationally for HB immunization schedules in the jurisdictions included in this scan is universal HB immunization starting with a birth dose. However, the U.S. and many European countries, with low HB endemicity comparable to Canada, also recommend a universal infant HB immunization program. The WHO and ATAGI statements on HB immunization highlight the importance of preventing HB infection in infants both due to the increased risk of chronic HB infection and the increased risk of exposure to HB virus if infants are born into families with household members with HB infection, including in countries with low HB prevalence .

A limitation of this jurisdictional scan is that it was not exhaustive, and includes jurisdictions and organizations advising on HB immunization in epidemiological contexts that may be different from Ontario.

# Epidemiology of Hepatitis B in Ontario

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## Objectives and methods

The objective of this analysis was to describe trends in reported cases of HB in Ontario from 1991 to 2014. A subgroup analysis was conducted to describe the epidemiology of cases of acute HB in children under the age of 12 years occurring from 2006 to 2014, and to identify HB cases that may have been potentially preventable via routine infant HB immunization and not preventable by the grade seven program. This time period was selected because all public health units were using Ontario's integrated Public Health Information System (iPHIS) to report HB cases for a full year as of 2006, with comparable reporting of risk factor data.

Data for confirmed acute and chronic cases of HB from 1991 to 2014 were extracted from iPHIS. A manual iPHIS case record review was conducted for all acute HB cases reported from 2006 to 2014 in infants and children under the age of 12 years. A data abstraction tool was developed, and two PHO staff independently abstracted and reviewed iPHIS data for each case, applying pre-established criteria for potential preventability. Potentially preventable acute HB cases were defined as:

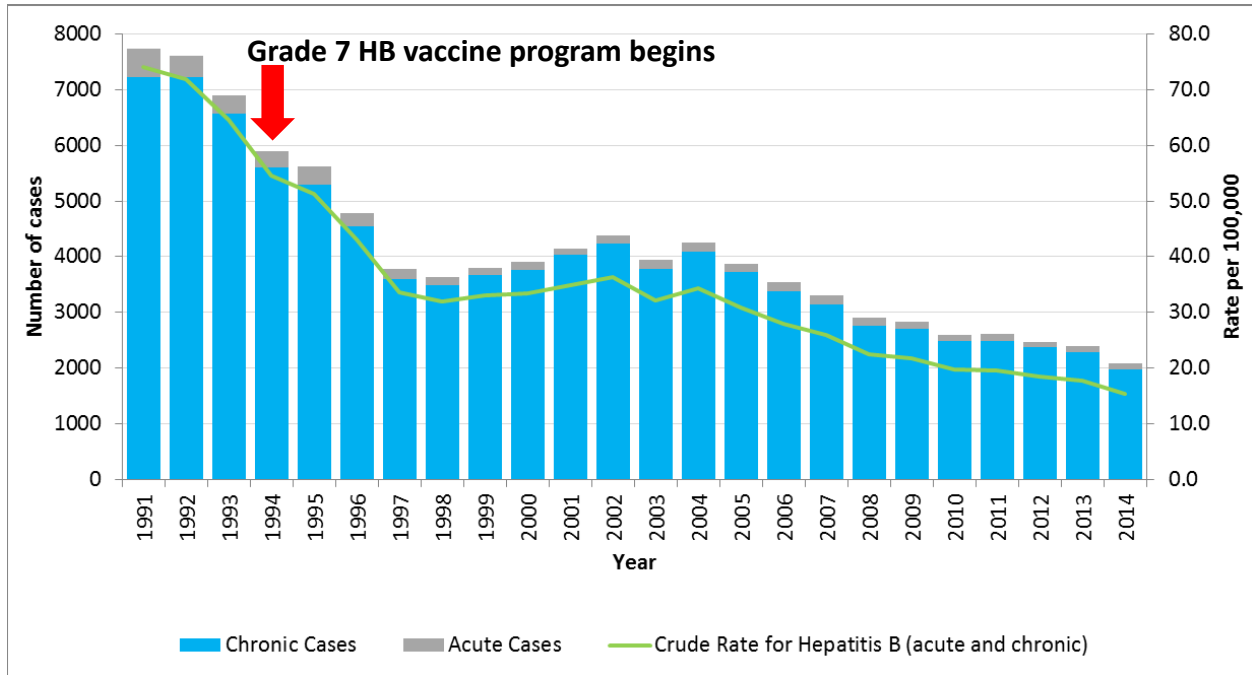
- Mother HBsAg negative OR mother's HBsAg status unknown, AND
- The case was born in Canada OR if born outside of Canada, the case was in Canada for more than six months prior to acute HB illness OR the timing of arrival was unknown, AND
- Case's HB immunization status unknown OR not immunized.

Please see [Appendix B](#) for details regarding the iPHIS data caveats and the data fields used in these analyses. Rates were calculated using annual population estimates from Statistics Canada (1991-2013) obtained through IntelliHEALTH Ontario and the Ontario MOHLTC. The 1991 Canadian population was used when calculating age standardized rates. Statistical analyses were performed using SAS 9.3.

## Results

The overall number of acute and chronic HB cases reported in Ontario has been declining since 1991. There has also been a decline in crude annual and age standardized rates per 100,000 population per year. The age standardized rates are not displayed in the figures below because they only show minor differences when compared to the crude rates. The decline started prior to and continued after the grade seven HB immunization program was introduced in 1994 (Figure 2). Approximately 100 acute HB cases per year have been reported in Ontario in recent years (Figure 3).

**Figure 2. Reported cases of acute and chronic Hepatitis B and rate per 100,000 per year: Ontario, 1991-2014**

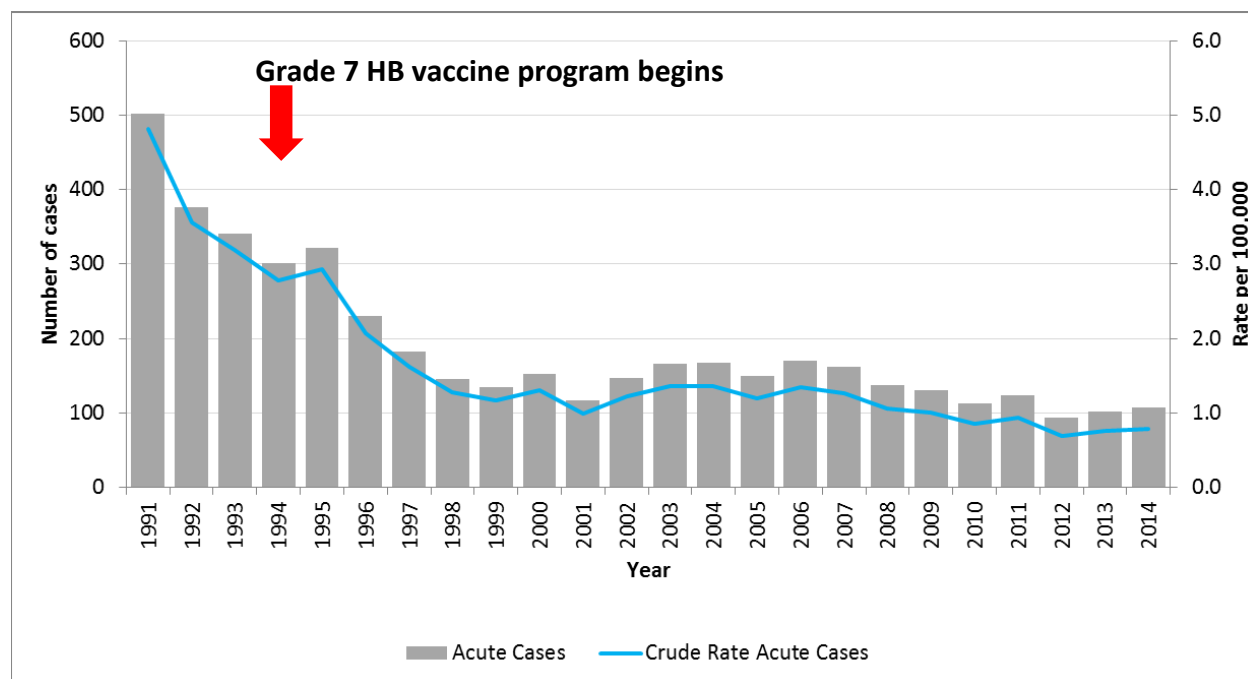


**Source:** Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2015/09/04]

**Population data:** Ontario - Population Estimates 1991-2013, Ontario Ministry of Health and Long-Term Care, IntelliHEALTH ONTARIO, Date Extracted: [2014/07/02].



**Figure 3. Reported cases of acute Hepatitis B and rate per 100,000 per year: Ontario, 1991-2014**



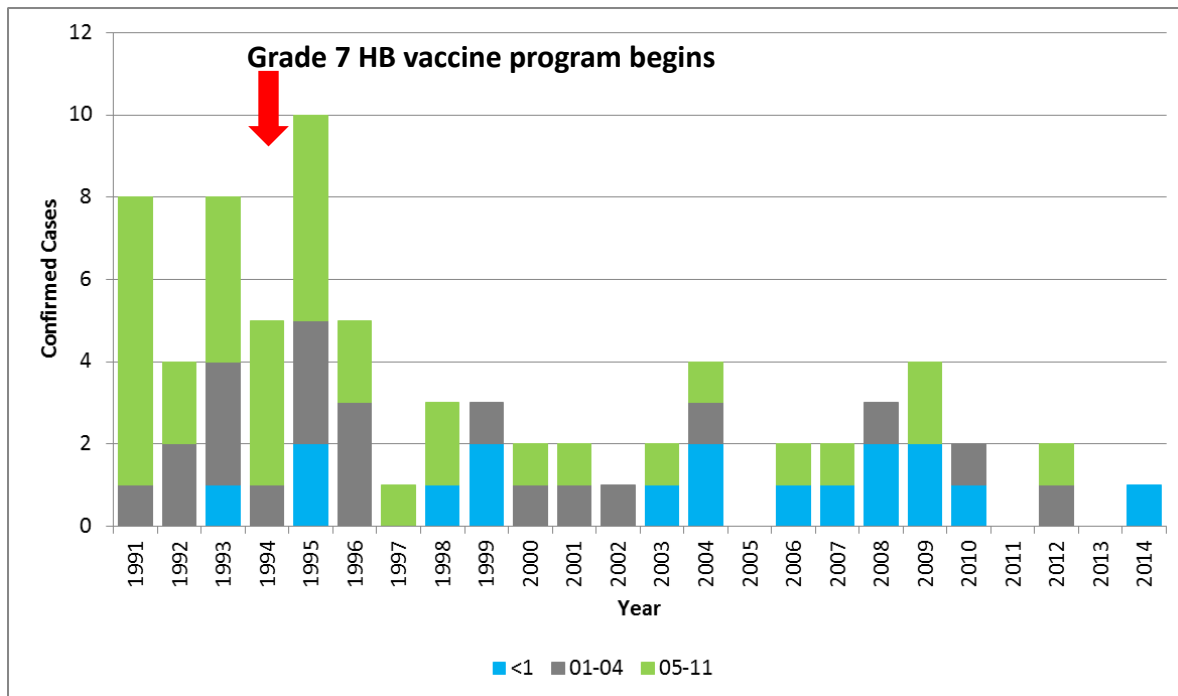
**Source:** Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2015/09/04]

**Population data:** Ontario - Population Estimates 1991-2013, Ontario Ministry of Health and Long-Term Care, IntelliHEALTH ONTARIO, Date Extracted: [2014/07/02].

The number of acute and chronic HB cases among children under the age of 12 years has also declined since 1991 (Figure 4). Between 2006 and 2014, there were 16 acute HB cases reported in this age group, with only three acute cases reported during the later years of 2011 to 2014. The 16 acute HB cases were reported from nine public health units, mainly in southern Ontario. Of these, half occurred in infants under the age of one year. Using data entered into iPHIS, three of the 16 acute HB cases were classified as foreign born. These three cases were between the ages of one and 11 years. The remaining 13 cases were either born in Canada (n=11) or their place of birth could not be confirmed (n=2). Applying the pre-established criteria to the 16 acute HB cases, five were assessed as potentially preventable through routine infant HB immunization (Figure 5). These five cases were between the ages of one and 11 years. Three of the five cases were identified as foreign born, two of whom had an HB onset date that occurred at least six months after their arrival in Canada. It was unclear when the arrival date of the third was in relation to the onset of their acute HB infection. The HBsAg status of all three foreign born cases prior to their arrival was unknown, but all were entered into iPHIS as acute cases. With regards to maternal HBsAg status among the three foreign born cases, in two cases it was unknown and in one case was negative. Of the two remaining cases, one was born in Canada and lived overseas for some time before developing symptoms related to HB more than six months after their return to Canada, while the place of birth for the remaining case could not be determined. This case had only a travel-related risk factor reported. Maternal HBsAg status was unknown for both of these cases.

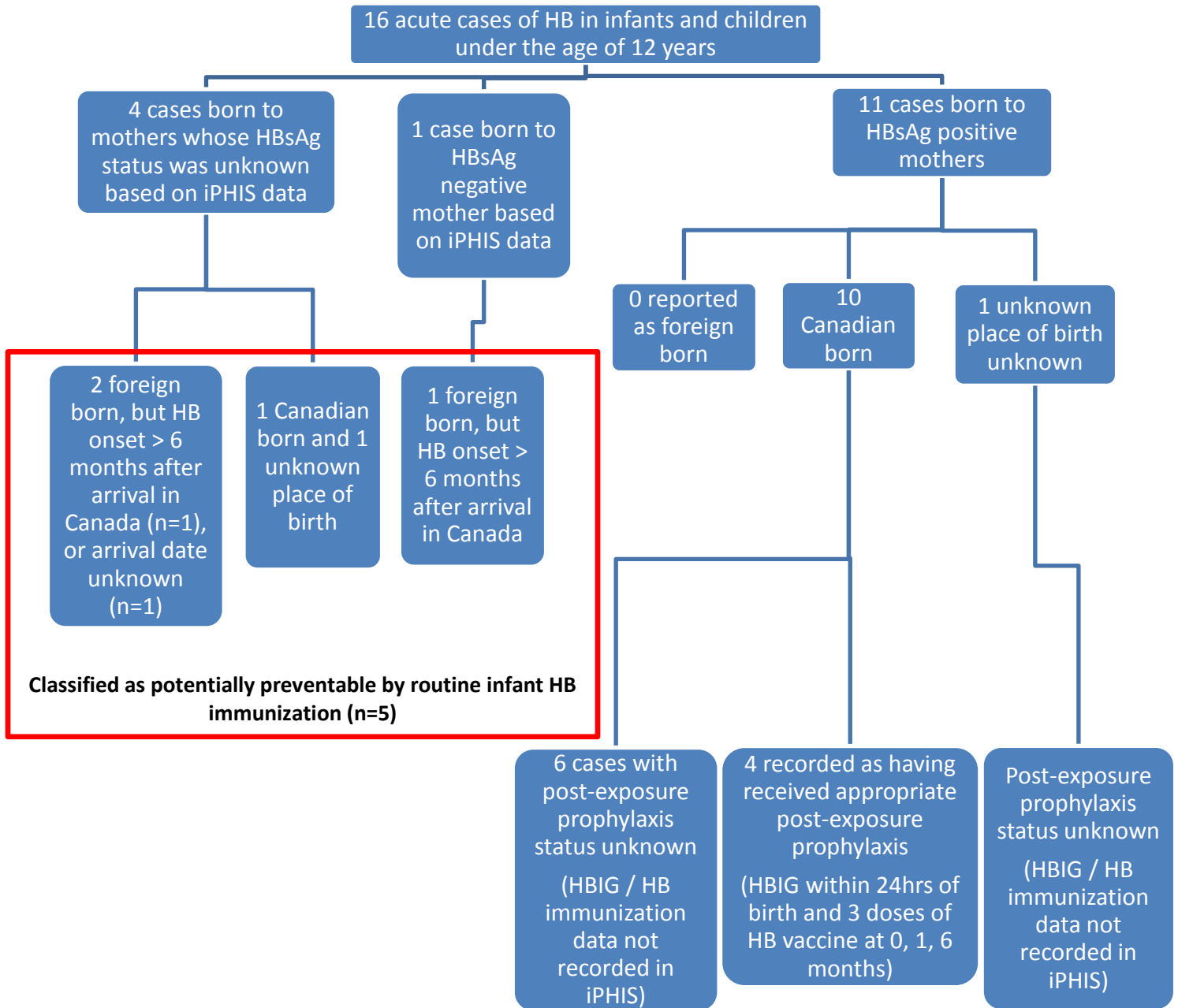
Children born to HBsAg positive mothers should be offered active and passive immunization at the time of birth and therefore the 11 cases born to HBsAg positive mothers were not judged as potentially preventable from a routine infant HB immunization program. Ten of these 11 cases were born in Canada. Of these 10 cases, four had information in iPHIS with regards to appropriate post-exposure prophylaxis (HBIG and a full course of HB vaccine). The remaining six Canadian born cases and the one case where place of birth was unknown had no documentation in iPHIS with regards to post-exposure prophylaxis.

**Figure 4. Reported cases of acute Hepatitis B among children under 12 years of age: Ontario, 1991-2014**



**Source:** Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2015/09/04]

**Figure 5. Potential preventability assessment of 16 acute Hepatitis B cases reported in infants and children under the age of 12 years in Ontario, 2006-2014**



**Source:** Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2016/01/13]

## Discussion

The number and rates of acute and chronic cases of hepatitis B reported in Ontario declined from 1991-2014. While this decline began before the introduction of the grade seven HB immunization program, Ontario's routine HB immunization program likely contributed to the continuation in the decline in rates. Other HB prevention and control measures may also have contributed to this decline, including infection prevention and control measures, sexual health promotion and safer sex practices, and/or HB immunization of persons meeting the high-risk eligibility criteria or due to occupational health considerations. Recognizing the limitations of routine public health surveillance for HB, additional data sources (i.e., health administrative and/or laboratory data) would help to inform a comprehensive evaluation of the impact of Ontario's grade seven HB immunization program.

Despite the steady decline in reported HB cases in Ontario over the last decade, both acute and chronic HB cases continued to be reported in infants and children under the age of 12 years. These cases were not prevented by Ontario's existing strategies targeting infants and young children at highest risk of chronic HB and its sequelae (e.g., routine prenatal HB screening, timely public health management of HBsAg positive mothers and their infants, and high-risk eligibility criteria for publicly-funded HB immunization). Our record review of the 16 acute HB cases reported in children under 12 years from 2006 to 2014 suggest that five of these cases were potentially preventable by routine infant, rather than adolescent, HB immunization. An additional seven cases of acute HB, including six cases born in Canada, were born to HBsAg positive mothers with no information in iPHIS regarding post-exposure prophylaxis (i.e., HBIG and vaccine) which raises important questions around iPHIS data quality and additional questions regarding implementation of current recommendations for screening and post-exposure prophylaxis in this particularly vulnerable group of infants.

The strengths and limitations of this analysis merit consideration. A key strength was the use of Ontario's provincial reportable disease database, the most complete dataset available with respect to counts of HB in Ontario and risk factor information. In addition, data were abstracted from iPHIS using a systematic process with two abstractors to enhance data quality. In terms of limitations, the data only represent cases that were diagnosed and subsequently reported to public health, and likely underestimate the true population burden of HB in the Ontario population. This may, in turn, underestimate the number of cases potentially preventable by routine infant HB immunization. The inclusion of cases of acute HB where the mother's HBsAg status was unknown may overestimate our assessment of cases potentially preventable by a routine infant program if we included children who acquired HB through unrecognized vertical transmission. The analysis of pediatric HB also revealed important data quality limitations including missing and/or inconsistently entered data in multiple iPHIS fields (e.g., immunization data, data entry into free text fields where fields with specific values for data entry exist such as birth country or maternal HBsAg status). Furthermore, laboratory test results, HB immunization records, and relevant immigration / travel histories were not consistently available in iPHIS. It was beyond the scope of this analysis to validate or supplement the information available in iPHIS using alternate data sources but an improvement in HB data quality within iPHIS will be essential to support future program evaluations. Finally, we were not able to assess whether reported cases of chronic HB in children under 12 years of age were potentially preventable by routine HB immunization.

This would also underestimate the true burden of HB that may be preventable by a routine infant HB immunization program as many children will not develop acute symptoms of HB and only be diagnosed in the chronic stage of infection. The fact that over the period of our analysis (2006 to 2014) chronic infections greatly outnumbered acute cases of HB in Ontario (256 versus 16) among children under 12 years of age further underscores this point. Additional iPHIS data considerations and limitations are outlined in [Appendix B](#).

## Synthesis of economic evaluations

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### Background on economic evaluation

Cost-effectiveness is a recognized consideration for immunization program decision-making in Canada.<sup>25</sup> A full economic evaluation compares both the health outcomes and costs of at least two interventions (e.g., a cost-effectiveness analysis comparing costs and health outcomes associated with HB immunization strategies).<sup>26-28</sup>

The perspective of economic evaluations may differ and should be considered (e.g., societal versus healthcare payer perspective). The model's time horizon should capture relevant resource consumption and events related to the intervention. Different decision models may inform the value for money of immunization programs (e.g., decision tree and Markov models), and each of these has its strengths and limitations.<sup>29</sup> The recommended discounting rate for health economic evaluations in Canada is 5% per year.<sup>26</sup> Discounting in economic evaluation is important because it incorporates the idea that costs and benefits that occur at different times are valued differently.<sup>30</sup> Thus, discounting has important implications for assessments of HB immunization strategies which aim to prevent not only acute infection but the longer term health events of cirrhosis and HCC. While there is no established cost-effectiveness threshold in Canada, \$50,000 per quality-adjusted life year (QALY) gained is commonly used. Both life years gained (LYG) and QALY are used as outcome measures in cost-effectiveness studies. A QALY takes into account both quantity and health-related quality of life.<sup>31</sup>

Some of the recognized challenges in economic evaluation of public health interventions include: the complexity of interventions, measurement of effectiveness, measurement of costs and benefits, using an appropriate time horizon, and lack of special consideration of equity concerns.<sup>32</sup>

### Objective and methods

#### Objective

This evidence synthesis aimed to answer the following research question: In countries with low HB endemicity, is a publicly-funded universal pre-exposure infant HB immunization program cost-effective compared to an adolescent program?

## Search strategy

With the assistance from PHO Library Services, we conducted a systematic search of the following electronic databases: MEDLINE, Embase, EconLit, Health Technology Assessments, NHS Economic Evaluation Database, Health Policy Reference Center, Health Business Elite, and Proquest Dissertations. Key search terms included: hepatitis B; immunization schedule or vaccination; and, economics, cost analysis, quality-adjusted life year, QALY, cost-benefit analysis, or economic evaluation. The search was limited to English and French language articles published between January 1, 1995 and November 10, 2015. See [Appendix C](#) for detailed electronic database search strategies.

We also conducted a grey literature search using a customized Google search of the following organizations' web pages: British Columbia Centre for Disease Control, Institut national de santé publique du Quebec, Public Health Agency of Canada, Canadian Agency for Drugs and Technologies in Health, Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, National Institute for Health Care Excellence, World Health Organization, and Public Health England. These organizations were selected due to their jurisdictions' similarity in HB endemicity and health system characteristics with Ontario. See [Appendix D](#) for the detailed grey literature search strategy.

## Selection criteria and screening process

The search strategy was left intentionally broad in order to maximize sensitivity. Articles then had to meet the following inclusion criteria: report an original economic evaluation study (i.e., not a review or meta-analysis; any model type); compare cost-effectiveness of universal infant and adolescent/preadolescent HB immunization strategies; and, have a study population with similar HB epidemiology and overall health status as the Ontario population (e.g., United Kingdom (U.K.), Australia, U.S. and countries in Western Europe). The same criteria were applied at both the title and abstract relevancy screen and the full text review.

A single reviewer (LR) performed a title and abstract screen, excluding articles that did not meet the inclusion criteria at this stage. Two reviewers (LR and GC) conducted a full text review of articles that passed the title and abstract screen. Through discussion, the reviewers and other review team members (SD, LM, BS, MWY) reached consensus on articles that met inclusion criteria.

## Quality appraisal and synthesis

Two reviewers extracted study data and applied the PHO Meta-tool for Quality Appraisal for Public Health Evidence (MetaQAT) and Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist to critically appraise the included articles. Iterative review and consensus discussion were undertaken with other team members as needed to consolidate and summarize quality appraisal findings.

A narrative synthesis of key results and quality appraisal findings of the included studies was prepared. Where possible, incremental cost-effectiveness ratios (ICERs) were calculated using data abstracted from the study to compare a universal infant immunization program with a universal adolescent

immunization program, if this comparison was not otherwise presented. The ICERs were converted into 2016 Canadian dollars using the Organisation for Economic Co-operation and Development (OECD) historical purchasing power parity (PPP) conversion rates and the Bank of Canada inflation calculator.<sup>33,34</sup>

## Results

The electronic database search yielded 736 unique articles; the grey literature search did not identify any additional unique results. After title and abstract screening and full text review, four studies met the inclusion criteria.<sup>35-38</sup> See [Appendix E](#) for a flow diagram of the results of the search strategy. Studies were from the U.K. (n=2), Switzerland (n=1), and the U.S. (n=1). Two studies used a decision tree model, one used a Markov model, and one used cause-specific mortality data to retrospectively measure the effect that an intervention may have had. Studies used the healthcare payer (n=3) and societal (n=1) perspectives (Table 4).

### Study characteristics and key results

All four studies used a targeted high-risk program as the reference to evaluate the cost-effectiveness of a universal program using either an infant or adolescent strategy. In no study was an infant program directly compared with an adolescent program. Siddiqui et al. found that in the U.K., where the reference scenario was a targeted immunization program for infants born to high-risk mothers, a universal infant HB immunization program would be more cost-effective than an adolescent program (GBP 263,000 per QALY gained compared to GBP 493,000 per QALY gained, respectively).<sup>35</sup> However, neither strategy was considered cost-effective using conventional thresholds.<sup>35</sup> A 3.5% discount rate was applied to both costs and health gains, and undiscounted results were not reported in this study.

In Switzerland, Zurn and colleagues found that a universal infant HB immunization program would have a lower undiscounted incremental cost per year of life saved than a universal adolescent program. A targeted high-risk immunization program for infants born to high-risk mothers was the reference scenario.<sup>36</sup> However, this model was sensitive to discounting (both costs and health gains were discounted); with 5% discounting, the adolescent strategy became more cost-effective than the infant strategy.

In England and Wales, Mangtani and colleagues also reported cost-effectiveness results that were sensitive to discounting health gains (life years gained), but did not discount costs.<sup>37</sup> Without discounting life years gained, they found universal infant HB immunization to be more cost-effective than an adolescent program (GBP 1,537/LYG vs GBP 1,658/LYG) when compared to a targeted high-risk immunization program for adults.<sup>37</sup> However, when a discount rate of 6% was applied to health gains, the adolescent strategy became more cost-effective.

Finally, in the U.S., the analysis by Margolis et al. found a universal infant HB immunization strategy to be more cost-effective than an adolescent strategy, when compared to a targeted high-risk immunization program for infants born to high-risk mothers.<sup>38</sup> Costs were discounted at 5% and the model was not sensitive to discounting years of life gained.

In summary, undiscounted results favoured universal infant HB immunization strategies compared to adolescent strategies in the three studies that reported undiscounted results.<sup>36-38</sup> When discounting was applied, two studies favoured a universal infant HB immunization strategy over an adolescent strategy,<sup>35,38</sup> and two studies favoured an adolescent strategy.<sup>36,37</sup>

Two studies reported primary data for life years saved and total program costs necessary to calculate an ICER for the comparison of a universal infant versus a universal adolescent program (base program). The results were converted to 2016 Canadian dollars from the original currencies reported in the studies. Zurn et al. provided a discounted (3%) analysis for a universal adolescent program, a universal infant program, as well as a universal infant program with a 12-year catch up program. The infant program with no catch-up period was the dominant strategy, as it improved health outcomes at lower costs. The incremental cost per life year gained of the infant program plus a 12 year catch-up program was \$5,646/LYG despite a twelve year period where two distinct cohorts would require immunization until the first infant cohort reaches 12 years of age. Undiscounted and discounted life years (6%; costs were not discounted) ICER results from Mangtani and colleagues showed varying results. Undiscounted results found an ICER of \$2,418/LYG; the data show that the infant program would save more life years but also cost more money. Discounted results showed that the infant program saves fewer life years than the adolescent program but also costs more money.



**Table 4. Summary of cost-effectiveness results\***

Citation, year of publication, jurisdiction	Model type	Perspective	Incremental cost-effectiveness ratio Universal infant HB immunization vs. targeted high-risk program**	Incremental cost-effectiveness ratio Universal infant HB immunization vs. targeted high-risk program**	Incremental cost-effectiveness ratio Universal adolescent HB immunization vs. targeted high-risk program**	Incremental cost-effectiveness ratio Universal adolescent HB immunization vs. targeted high-risk program**
			Undiscounted	Discounted	Undiscounted	Discounted
Siddiqui et al., 2010, U.K. <sup>35</sup> (reported first in 2007 British Pounds)	Markov	Healthcare payer	Not reported	Discounted costs and health gains 3.5% \$569,085/QALY gained	Not reported	Discounted costs and health gains 3.5% \$1,066,764/QALY gained
Zurn et al., 2000, Switzerland <sup>36</sup> (reported first in 1996 Swiss Francs)	Decision-Tree	Healthcare payer	No catch-up \$1,162/LYG  With 12 year catch-up \$6,045/LYG	No catch-up, discounted costs and health gains 5% \$141,810/LYG  With 12 year catch-up, discounted 5% \$124,827/LYG	\$5,829/LYG	Discounted costs and health gains 5% \$120,503/LYG
Mangtani et al., 1995, England and Wales <sup>37</sup> (reported first in 1993 British Pounds)	Other	Healthcare payer	\$4,377/LYG	Discounted health gains 6% \$219,533/LYG	\$4,722/LYG	Discounted health gains 6% \$91,485/LYG
Margolis et al., 1995, U.S.A. <sup>38</sup> (reported first in 1993 US Dollars)	Decision-Tree	Societal	Not reported	Discounted costs 5% \$2,787/LYG  Discounted costs 5% and health gains (unknown rate) \$37,755/LYG	Not reported	Discounted costs 5% \$6,830/LYG  Discounted costs 5% and health gains (unknown rate) \$51,123/LYG

\*Additional details on study design and parameters used can be found in [Appendix F](#)

\*\*Converted to 2016 Canadian Dollars

## Quality appraisal findings

[Appendix F](#) presents the quality appraisal, and includes a summary of key study characteristics and their implications for relevancy and applicability to the Ontario context.

### Relevancy

The included articles were all from high income countries with low HB endemicity (all are from jurisdictions with estimated HBsAg prevalence <1%).<sup>35-38</sup> Nevertheless, some important differences between the study populations, pre-existing HB immunization strategies, and health systems were identified ([Appendix F](#)). The implications for applicability to the Ontario context for routine HB immunization are discussed below.

### Reliability

No significant reliability concerns were identified in the quality appraisal. The models, their assumptions, time horizons, discounting rates and sensitivity analyses were clearly reported in all four papers.<sup>35-38</sup> Two studies<sup>36,37</sup> reported both discounted and undiscounted results, while one study<sup>35</sup> only reported discounted results (3.5% discount rate), and one<sup>38</sup> reported results for both discounted costs and discounted costs and health gains. None of the four studies included a conflict of interest statement or an ethics statement.

### Validity

Three studies used modeling techniques: a decision-tree model was used in two studies<sup>36,38</sup> and one study<sup>35</sup> used a Markov model. These modelling techniques are commonly used in cost-effectiveness analyses for health interventions, and are appropriate for modelling HB interventions due to the long natural history of disease (i.e., chronic HB).

The remaining study employed a retrospective approach using mortality data to estimate the impacts of the different immunization strategies.<sup>37</sup> In general, this is viewed as a weaker methodological approach than decision-tree or Markov modelling.

The epidemiological and cost data sources (e.g., intervention costs and health care costs associated with the disease) appear to be appropriate for the included studies.<sup>26-29</sup> All four studies used published data and national statistics when available, relying on an expert panel either in addition to or in the absence of published data. Specific data sources included national laboratory reports and national statistics (e.g., epidemiological, wages, vaccine prices),<sup>26-28</sup> serologic surveys,<sup>37</sup> and other published data.<sup>35-38</sup> One study based health care costs on hepatitis C health care literature.<sup>35</sup> While the parameters used were likely appropriate for the settings in which the studies were conducted, they may not reflect the current epidemiological or health care context for HB prevention and treatment in Ontario.

All four studies applied discounting rates ranging from 3% to 6% and conducted an appropriate sensitivity analysis to test the impact that changes in key parameters have on the cost-effectiveness results. Key parameters that were manipulated in one-way sensitivity analyses included vaccine price,

vaccine coverage, discount rate, and lifetime risk of HB infection. One of the studies conducted both one-way and multivariate sensitivity analyses.<sup>35</sup> Three of the studies<sup>35-37</sup> were sensitive to changes in the discounting rate.

An important validity limitation of the models used in three studies<sup>26,27,29</sup> is that they are static (i.e., assume a closed cohort, and do not account for complex infectious disease transmission dynamics). These models consider only the costs and effects for the included cohort, but not anyone else who may be in contact with this cohort. They do not account for changing patterns of disease transmission after a strategy has been in place for some time; for example, they do not incorporate herd effects achieved through high vaccine coverage.

## Applicability

One strength in terms of potential generalizability of the results to the Ontario population were the HB immunization coverage assumptions of three of the studies<sup>35-37</sup> for both infant and adolescent strategies (e.g., 90% coverage assumed for both infant and adolescent strategies in one study<sup>26</sup>). These coverage estimates were similar to what may be expected in Ontario.<sup>18,39,40</sup> For example, it was estimated that Ontario's grade seven HB immunization program achieved 86.9% coverage in 2012.<sup>18</sup> In British Columbia, where universal infant HB immunization was introduced in 2001, 88.9% of kindergarten students had up-to-date HB immunization status in 2012.<sup>39</sup>

Another strength in regards to generalizability was the assumption in all four studies that delivery of infant HB immunization would be integrated into routine infant medical visits, reducing immunization program costs.<sup>35-38</sup> This would be similar to the implementation context in Ontario, should a universal infant HB immunization strategy be adopted and delivered by primary care providers at routine well child visits (e.g., at two, four and six months).

However, each of the four studies also had significant limitations in terms of applicability to the current Ontario context for universal HB immunization. Key limitations are summarized below.

*Reference case:* None of the articles assessed a situation in which the starting point was a universal strategy. They each started with a high-risk strategy that targeted babies born to mothers who are HBsAg positive, and in some cases high-risk adults. This is an important consideration to be aware of because transmission rates and observed changes between strategies may affect the cost-effectiveness outcomes in comparison to switching between universal programs, which would be the case in Ontario. This could result in overestimating the cost-effectiveness of switching between programs in Ontario.

*Closed cohort:* As noted above, the studies included in the review all relied on a closed cohort. Thus, the costs and benefits that were included in the model were for the same individuals over time and did not account for people entering or leaving the model (e.g., via immigration) or transmission to people outside of the cohort. The studies included in the review do not provide insight into Ontario's unique demographic patterns, where immigration is an important factor. This is particularly relevant because HB prevalence is estimated to be higher in immigrants and refugees than in the general population in Canada.<sup>12-14</sup>

## Discussion

Despite concerns about the applicability of the results of the studies to the current Ontario epidemiological and health care context for universal HB immunization, the studies included in this synthesis highlighted some key considerations for evaluating the cost-effectiveness of infant versus adolescent HB immunization strategies. For example, each study assumed a reduction in costs associated with integrating HB vaccine delivery into routine well child visits that could also be reasonably be anticipated in Ontario.

Only four studies were included in the synthesis and no study directly compared routine immunization strategies by examining the cost-effectiveness of an infant program to a reference scenario of a pre-existing adolescent universal program. This is the comparison that is of greatest relevance to Ontario which has an existing routine HB immunization program in place.

It was only possible to calculate ICERs directly comparing universal infant versus adolescent strategies for two studies,<sup>27-28</sup> which produced conflicting results. The results were also divergent in the comparison of universal infant and adolescent strategies when compared to targeted high-risk immunization programs. Notably, infant HB immunization strategies were found to be more cost-effective than adolescent strategies when no discounting was applied in the three studies that reported these results,<sup>36-38</sup> and when discounting was applied, two studies favoured universal infant programs and two studies favoured universal adolescent programs. It is expected that discounting would favour an adolescent HB immunization strategy, given the long latency of chronic HB's sequelae and the older age of acute infection typical of high income, low HB prevalence settings. Finally, the population-level estimates of acute and chronic HB risk and HB immunization coverage for different strategies did not include sensitivity analyses to account for potential differential impacts of different immunization strategies for some key priority / high-risk subgroups in the Ontario context (e.g., infants and young children belonging to newcomer groups from high HB endemicity areas; marginalized adolescents and young adults at highest risk for acquiring HB via sexual transmission or other high-risk behaviours).

## Equity considerations

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### Objective and methods

Equity is an important consideration for immunization decision-making in Canada, as evidenced by established frameworks<sup>25</sup> and the inclusion of health equity as a cross-cutting action in Ontario's Immunization 2020 Strategic Framework.<sup>41</sup> For this reason, we set out to identify key equity considerations of policies in relation to publicly-funded HB immunization in infancy compared to grade seven. To do so, we adopted the definition of equity articulated in the Ministry of Health and Long-Term Care's (MOHLTC) Health Equity Impact Assessment (HEIA) tool:<sup>42(p.11)</sup>

*“Within the health system, equity means reducing systematic barriers in access to high quality health care for all by addressing the specific health needs of people along the social gradient, including the most health-disadvantaged populations. Equity planning acknowledges that health*

*services must be provided and organized in ways that contribute to reducing overall health disparities.”*

Different tools and frameworks are available to guide health equity assessments;<sup>43</sup> we chose to draw on elements of the MOHLTC’s HEIA tool to identify equity considerations of the two HB immunization strategies. This report focuses on the equity considerations for which we were able to identify evidence in the published or grey literature to inform our discussion. Specifically, this report focuses on: (1) the period of susceptibility to HB, (2) populations at increased risk of exposure to HB, (3) populations with a higher ability to benefit from HB immunization, and (4) populations less likely to accept and access publicly-funded HB immunization.

## Period of susceptibility to Hepatitis B

The period of susceptibility to HB extends from the perinatal period until either successful immunization or natural infection with HB (or death if neither immunization nor infection events occur). Therefore, the timing of HB immunization would be expected to impact the duration of susceptibility to HB. Specifically, infant immunization (at two, four, and six months of age) reduces the period of susceptibility to the first six months of life, whereas school-based immunization in grade seven results in children remaining susceptible to HB during the first 12 years of life, unless the child is eligible and receives immunization under an existing high risk HB program.

Waning immunity over time following HB immunization is generally not felt to be a major consideration. Instead, HB immune memory is best predicted by the strength of the antibody response following primary immunization.<sup>44</sup> It is thought that immune memory persists despite the disappearance of anti-HB antibodies,<sup>4</sup> and may last a lifetime.<sup>45</sup> Among healthy individuals who initiated hepatitis B immunization at six months of age and older, studies indicate that immunity remains intact for at least 20 years.<sup>46</sup>

## Increased risk of exposure to Hepatitis B

In Ontario, infants and children at higher risk of exposure to HB include those: (1) born to mothers who are chronic HB carriers, (2) living in a household with chronic HB carrier(s), (3) whose families have emigrated from high HB endemic countries and who may be exposed to HB carrier(s) through their extended families either in Ontario or when they visit their families’ country of origin, and (4) attending day nurseries/child care centres,<sup>47</sup> depending on the epidemiology of HB within the community.

*Newborns of mothers who are chronic HB carriers:* Vertical transmission of HB from mother to baby may be prevented by routinely screening all pregnant women for HB, and providing post-exposure prophylaxis to newborns of chronic HB carrier mothers, an intervention that successfully prevents HB in 85-95% of identified infants.<sup>4</sup> Infants born to mothers who did not access prenatal screening for HB prior to delivery, as well as infants born to mothers who are chronic HB carriers and who were not provided with post-exposure prophylaxis following birth are also at higher risk of HB infection. Neither an infant nor a school-based immunization strategy adequately prevents vertical HB transmission.

*Infants and children living in a household with a chronic HB carrier(s):* These infants and children are at increased risk of exposure (including increased risk of horizontal transmission) to HB for as long as they remain susceptible (unimmunized) to or uninfected with HB. The MOHLTC offers publicly-funded HB vaccine for household contacts of chronic HB carriers,<sup>17</sup> but this strategy relies on healthcare providers to identify eligible infants and children. For those who don't access publicly-funded immunization for high-risk infants and children, a universal infant immunization strategy would reduce the period of susceptibility from the first 12 years to the first six months of life.

*Infants and children whose families have emigrated from high HB endemic countries:* These infants and children are at higher risk of exposure to HB through contact with their extended families either in Ontario or when they visit their families' country of origin. In the U.S., multiple studies have reported likely horizontal HB transmission via household contacts of American-born children of foreign-born parents from highly endemic regions.<sup>48-50</sup> A small study examining HB transmission in six U.K.-born children living in inner-city multi-ethnic areas found that five of the six children were infected through horizontal transmission by a sibling and the remaining child by vertical transmission.<sup>51</sup> In addition, there is some evidence that travelers visiting family and relatives infrequently seek pre-travel care,<sup>54</sup> inaccurately perceive their personal risk as low,<sup>52,55</sup> and face cost-related barriers to pre-travel consultation and/or immunization when it is an uninsured service,<sup>53</sup> as is the case in Ontario.

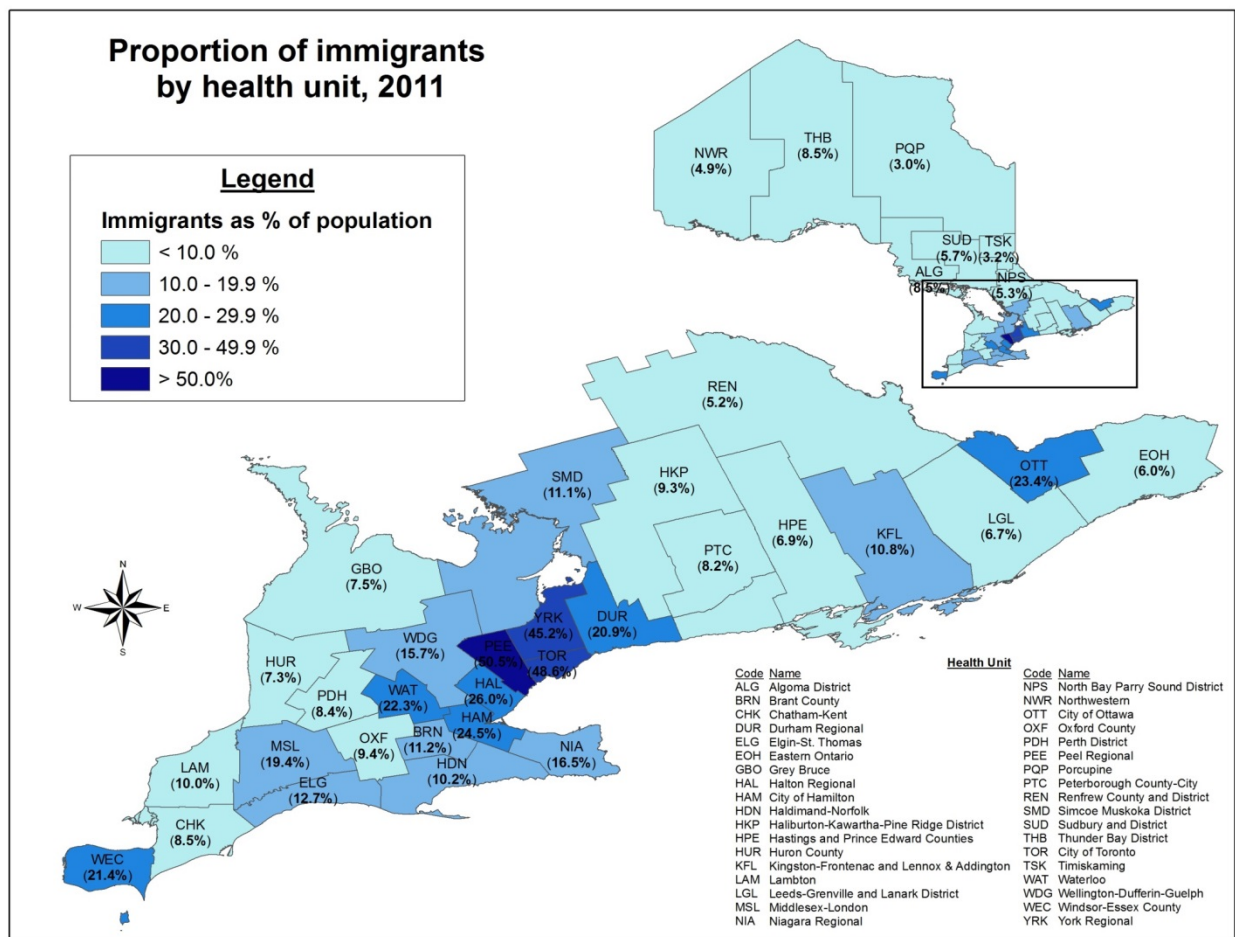
The MOHLTC offers publicly-funded HB vaccine for "children <7 years old whose families have emigrated from countries of high prevalence for HBV and who may be exposed to HBV carriers through their extended families",<sup>17</sup> but this strategy also relies on healthcare providers to identify those eligible infants and children. Given high levels of immigration to Ontario (Figure 6), the size of the population born in an intermediate/high HB endemic country currently living in Ontario is important. For example, of the 95,814 permanent residents that landed in Ontario in 2014,<sup>54</sup> the majority emigrated from areas of intermediate/high HB endemicity, including Asia and Pacific region, Africa and the Middle East (Table 5).<sup>5</sup> For Canadian-born infants of parents who have emigrated from a high HB endemic country who don't access the high-risk HB immunization program, a universal infant immunization strategy would potentially reduce the period of susceptibility from the first 12 years to the first six months of life.

An estimated 19.2% of permanent residents who arrived in Canada from 2006-2011 were children aged 0-14 years, and it was estimated that 43.1% arrived in Ontario.<sup>55</sup> A universal infant immunization strategy would only be expected to cover those infants who immigrated to Canada during their first six months of life, unless a catch-up program was in place. Given that these children's age at immigration was fairly evenly distributed between 0 and 14 years,<sup>56</sup> approximately half (9.6%) would arrive before eight years of age and would be eligible for the MOHLTC's high-risk HB immunization program. The other half (9.6%) were not eligible for publicly-funded HB immunization, and would have remained susceptible to HB for up to five years, until the school-based immunization in grade seven.

Currently, children who emigrate from high HB endemic countries after grade eight are not eligible for publicly-funded HB immunization, because the school-based immunization program is in grade seven, with a catch-up period limited to grade eight.

Infants and children who attend day nurseries / child care centres: Attendees of day nurseries / child care centres may be at increased risk of HB exposure, due to the low but non-negligible risk from human biting incidents involving skin punctures, depending on the local epidemiology of HB. The risk of HB infection through contact with other infants or children attending the day nursery / child care centre is dependent on the presence of a chronic HB carrier(s) in that setting. A higher risk of chronic HB carriage is expected among children whose families emigrated from high HB endemic countries. A routine infant HB immunization strategy has the potential to promote health equity by protecting this disproportionately exposed group of children from HB before entering child care and before reaching the peak developmental age for human biting.<sup>57</sup>

Figure 6. Proportion of immigrants in the Ontario population by health unit, 2011



**Table 5. Permanent residents landed in Ontario by source area, 2014**

Source area	Number of permanent residents landed in Ontario, 2014	Prevalence of HB infection (2005) <sup>58</sup>
Asia and Pacific	52,445	2% - 7% (intermediate)
Africa and the Middle East	20,073	2% - >8% (intermediate to high)
Europe and the UK	9,626	<2% - 4% (low to intermediate)
South and Central America	9,514	<2% - 4% (low to intermediate)
United States	3,769	<2% (low)
Not stated	387	N/A
<b>Total</b>	<b>95,814</b>	

## Ability to benefit from HB immunization

In principle, infants have a greater ability to benefit from HB immunization than grade seven students, because infants have the highest risk of developing chronic HB.<sup>7,38</sup> As previously outlined, the risk of becoming a chronic HB carrier varies inversely with age, with infants having the highest risk. In contrast, the likelihood of symptomatic infection increases with age;<sup>38,59</sup> symptomatic infection is more likely to be clinically recognized. The potential complications from chronic HB infection, including cirrhosis and hepatocellular carcinoma, can be severe, long-lasting, and lead to high healthcare costs and resource use.

## Acceptability of and access to HB immunization

The current Ontario grade seven HB immunization program is delivered in schools by public health units (PHUs). School-based immunization programs are thought to promote equity of access to immunization by removing pragmatic and economic barriers to services. However, some groups are potentially missed through this delivery method, including children with frequent school absences and home-schooled children. For example, an Australian study found that children attending schools in the lowest socio-economic and remote areas were less likely to be immunized against HB through school-based immunization programs.<sup>56</sup> A study of school-based HPV immunization in Ontario found that, whereas girls of low-income were equally likely as their higher-income counterparts to initiate the immunization series, they were less likely to complete the series.<sup>60</sup>

It is anticipated that if a universal infant HB immunization program were implemented in Ontario it would be delivered by the infant's usual primary care provider during routine well-baby visits. This strategy would be expected to reach infants who regularly visit their primary care provider for well-baby check-ups. Because infant immunization programs require attending a clinic or program, some infants may be missed by this strategy. For example, in Germany, a study on infant immunization against



measles by primary care providers found that foreign-born children had lower vaccine coverage than German-born children; however, this finding was not observed in the U.S., where immunizations are also delivered by primary care providers.<sup>61</sup> An Ontario study examining influenza immunization among young school-aged children found uptake was higher among foreign-born children, after controlling for health status and socio-demographic characteristics.<sup>62</sup>

There may also be differences in parental acceptability of infant versus adolescent HB immunization. Parents may be more likely to experience vaccine hesitancy towards an infant HB immunization strategy, for example, because of the perception that infants are already receiving several other immunizations.<sup>63</sup> However, this may potentially be avoided through the use of a hexavalent vaccine containing HB. Current coverage estimates for infant versus adolescent immunization do not suggest a difference in parental acceptability between the two. The adolescent immunization program reached 86.9% coverage in Ontario in 2012;<sup>18</sup> that same year in BC, where there is an infant HB immunization program, HB vaccine coverage in kindergarten students who received the vaccine in infancy was 88.9%.<sup>39</sup> Unfortunately, the characteristics of those who may be disproportionately represented among the students not covered by the grade seven program in Ontario are not known, nor do we know the characteristics of the infants missed by the BC infant immunization program.

A final consideration that may impact access and uptake of HB immunization is the duration of the eligibility period. In Ontario, students are currently eligible to receive HB vaccine until grade eight if they missed one or both doses of the HB vaccine in grade seven.<sup>17</sup> A program with longer eligibility or a “once eligible, always eligible” program could allow greater access to immunization to those students who don’t initiate or complete the HB series before high school, including newcomers to Canada.

## Discussion

This section highlighted several equity considerations of routine infant versus adolescent HB immunization strategies for Ontario, drawing on key concepts and elements of the MOHLTC’s HEIA tool. A key challenge for considering equity implications, as well as effectiveness and cost-effectiveness, of these two strategies is the gap in available data needed to examine HB immunization coverage by socioeconomic, immigration and behavioural risk factors. Improving data collection related to health equity is critical, and will be important for monitoring the overall and equity-related impacts of universal HB immunization in Ontario in the future.

## Conclusion

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In order to assist PIDAC-I in its deliberations on HB immunization, we have summarized the evidence and existing expert recommendations relevant to the timing of universal pre-exposure HB immunization, conducted a jurisdictional scan of HB immunization program practices, provided an epidemiological analysis of reported HB cases in Ontario, conducted a synthesis of relevant HB economic evaluation literature and, finally, identified equity considerations pertinent to HB immunization strategies.

## References

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## Appendix A: PIDAC-I Members

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## Appendix B: Data caveats

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The following summarizes data sources and caveats specific to the iPHIS hepatitis B analyses.

### Data source – cases:

- Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario on [2015/09/04] for general analyses and extracted on [2016/09/04] for detailed analyses of acute hepatitis B cases on children under the age of 12.
- iPHIS is a dynamic disease reporting system which allows ongoing updates to data previously entered. As a result, data extracted from iPHIS represent **a snapshot at the time of extraction** and may differ from previous or subsequent reports.
- The data only represent acute and chronic hepatitis B reported to public health **and** recorded in iPHIS. As a result, all counts will be subject to varying degrees of underreporting depending on factors such as disease awareness, medical seeking behaviours, changes in laboratory testing, reporting behaviours, and severity of illness.
- Records are classified in iPHIS according to the Ontario Ministry of Health and Long-Term Care (MOHLTC) surveillance case definitions used at the time the case was identified. Please note that the case definitions available online as part of the [Infectious Diseases Protocol](#) represent the most recent definitions, and cases reported in prior years may have been classified according to different case definitions or disease classifications, which may impact analysis of trends.
- A provincial chronic case definition not added until 2012; however, detailed instructions on how to report and enter chronic cases of HB within iPHIS and its precursor system were provided to PHUs prior to this time.
- Cases of hepatitis B are reported based on 'episode date'. In order to determine this date, the following hierarchy is in place in iPHIS: Onset Date > Specimen Collection Date > Lab Test Date > Reported Date.
- Acute hepatitis B case counts include only the following classification in iPHIS: Confirmed.
- For acute cases under the age of 12 the following iPHIS fields were reviewed in detail:
  - Immigration-related fields such as 'Origin' and 'Birth Country'
  - Case Comments
  - Case and Client Notes
  - Exposures
  - Risk Factors
  - Immunization

- Maternal HBsAg status was assigned based on information in any of these fields indicating that the mother was HBsAg positive.
- Country of Birth was assessed in this manner as well. For cases without definitive country of birth information entered an assessment as to whether the case was born in Canada was made based on the following criteria:
  - Pre-existing Hepatitis B record for the mother in iPHIS
  - OR
  - Information indicating that the case received HBIG and immunization series following birth
  - OR
  - Case < 2 months of age
- Chronic hepatitis B case counts include only the following classification in iPHIS: Carrier.
- Chronic cases of hepatitis B reported through iPHIS represent the identification of hepatitis B infections that occurred months, years, or decades prior to their diagnosis.
- Records for which the diagnosing health unit was reported as MOHLTC (to signify a case that is not a resident of Ontario) have been excluded. Cases previously assigned to Muskoka Parry Sound (a health unit that no longer exists) have been reassigned to North Bay Parry Sound or Simcoe Muskoka health units, based on the address of the case.
- Records for which the Episode Status was reported as ENTERED IN ERROR, DOES NOT MEET DEFINITION, DUPLICATE-DO NOT USE, or any variation on these values have been excluded.
- The possibility of duplicates exists because duplicate sets were not identified and excluded unless they were resolved prior to data extraction either at the local or provincial level.

#### **Data source – population:**

- Ontario - Population Estimates 1986-2013, Ontario Ministry of Health and Long-Term Care, IntelliHEALTH ONTARIO, Date Extracted: [2014/07/02].
  - The 2013 population estimates were used when calculating rates for 2014.
- 1991 Canadian population - Source: Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted), CANSIM (database). Accessed: [2015/09/08]

## Appendix C: Detailed electronic database search strategies

### Research question:

In countries with low hepatitis B (HB) endemicity, is a publicly-funded universal preexposure infant HB immunization schedule cost effective compared to an adolescent/preadolescent schedule?

### Databases:

- MEDLINE
- Embase
- EconLit
- Health Technology Assessments
- NHS Economic Evaluation Database
- Health Policy Reference Center
- Health Business Elite
- Proquest Dissertations

### Search limits:

- Date of publication: 1995 – current
- Language of publication: English or French

### Search strategy:

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	exp Hepatitis B/ or Hepatitis B Vaccines/ or Hepatitis B virus/ or ("hepatitis B" or "hep B").ti,kw,kf.	66172
2	Immunization Schedule/ or Hepatitis B Vaccines/ or Vaccines/ or Immunization/ or Vaccination/ or Mass Vaccination/ or Immunization Programs/ or (vaccin* or immuniz* or immunis* or inoculat*).ti,kw,kf.	227377
3	Economics/ or "Costs and Cost Analysis"/ or Cost Allocation/ or Cost-Benefit Analysis/ or Cost Control/ or Cost Savings/ or Cost of Illness/ or Cost Sharing/ or exp Health Care Costs/ or Health Expenditures/ or Economics, Behavioral/ or exp Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or Healthcare Financing/ or Financing, Government/ or Financing, Organized/ or Resource Allocation/ or Investments/ or economics.fs. or (cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value adj2 (money or dollar?)) or "quality adjusted life year?" or QALY? or "disability adjusted life year?" or DALY?).ti,kw,kf.	520691
4	1 and 2 and 3	626
5	limit 4 to yr="1995 -Current"	381

#	Searches	Results
6	limit 5 to (English or French)	356
7	remove duplicates from 6	340

Embase 1974 to 2015 Week 45

#	Searches	Results
1	hepatitis B/ or hepatitis B virus/ or hepatitis B vaccine/ or ("hepatitis B" or "hep B").ti,kw,hw.	118681
2	vaccination/ or hepatitis B vaccine/ or vaccine/ or immunization/ or mass immunization/ or (vaccin or immuniz or immunis or inoculat).ti,kw,hw.	215737
3	*economic aspect/ or *cost/ or *economics/ or *funding/ or *profit/ or *resource allocation/ or exp *health care cost/ or *health economics/ or *cost benefit analysis/ or exp *economic evaluation/ or *cost control/ or *cost of illness/ or *"cost control"/ or *cost effectiveness analysis/ or *behavioral economics/ or *pharmacoeconomics/ or *health care financing/ or *investment/ or *hospital cost/ or *hospitalization cost/ or *nursing cost/ or *drug cost/ or (cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value adj2 (money or dollar?)) or "quality adjusted life year?" or QALY? or "disability adjusted life year?" or DALY?).ti,kw.	294993
4	1 and 2 and 3	553
5	limit 4 to yr="1995 -Current"	426
6	limit 5 to (English or French)	398

EconLit

#	Query	Results
S1	( "hepatitis B" OR "hep B" ) AND ( vaccin* OR immuniz* OR immunis* OR inoculat* )	17
S2	DT 19950101-20151231	1,099,002
S3	S1 AND S2	14
S4	LA English OR French	1,512,857
S5	S3 AND S4	14

### Health Technology Assessments

#	Query	Results
S1	( "hepatitis B" OR "hep B" ) AND ( vaccin* OR immuniz* OR immunis* OR inoculat* )	13
S2	DT 19950101-20151231	15,233
S3	S1 AND S2	13

### NHS Economic Evaluation Database

#	Query	Results
S1	( "hepatitis B" OR "hep B" ) AND ( vaccin* OR immuniz* OR immunis* OR inoculat* )	77
S2	DT 19950101-20151231	17,132
S3	S1 AND S2	76

### Health Policy Reference Center

#	Query	Results
S 1	TI ("hepatitis B" or "hep B") OR SU ("hepatitis B" or "hep B") OR KW ("hepatitis B" or "hep B")	1,203
S 2	TI (vaccin* or immuniz* or immunis* or inoculat*) OR SU (vaccin* or immuniz* or immunis* or inoculat*) OR KW (vaccin* or immuniz* or immunis* or inoculat*)	11,141
S 3	TI (cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value adj2 (money or dollar*)) or "quality adjusted life year?" or QALY or QALYs or "disability adjusted life year*" or DALY or DALYs) OR SU (cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value adj2 (money or dollar*)) or "quality adjusted life year?" or QALY or QALYs or "disability adjusted life year*" or DALY or DALYs) OR KW (cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value adj2 (money or dollar*)) or "quality adjusted life year?" or QALY or QALYs or "disability adjusted life year*" or DALY or DALYs)	81,990
S 4	S1 AND S2 AND S3	61
S 5	LA ( French OR English )	676,358
S 6	S4 AND S5	61

#	Query	Results
S7	DT 19950101-20151231	605,755
S8	S6 AND S7	61

#### Health Business Elite

#	Query	Results
S1	"hepatitis B" or "hep B"	1,018
S2	vaccin* or immuniz* or immunis* or inoculat*	15,546
S3	cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value adj2 (money or dollar*)) or "quality adjusted life year?" or QALY or QALYs or "disability adjusted life year*" or DALY or DALYs	837,861
S4	S1 AND S2 AND S3	81
S5	DT 19950101-20151231	2,650,414
S6	S4 AND S5	77

#### NHS Economic Evaluation Database

#	Query	Results
S1	all("hepatitis b" OR "hep B") AND all(vaccin* or immuniz* or immunis* or inoculat*) AND all(cost* or economic* or expenditure* or financ* or afford* or "return on investment" or ROI or (value NEAR/2 (money or dollar*)) or "quality adjusted life year*" or QALY* or "disability adjusted life year*" or DALY*) AND LA(French OR English)	27
<b>Limits applied</b> Publication date: 1995-2015		

## Appendix D: Grey literature search strategy

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### Research question:

In countries with low hepatitis B (HB) endemicity, is a publicly-funded universal pre-exposure infant HB immunization schedule cost effective compared to an adolescent/preadolescent schedule?

### Grey literature sources:

1. BCCDC | [bccdc.ca](http://bccdc.ca)
2. INSPQ | [inspq.qc.ca](http://inspq.qc.ca)
3. PHAC | [phac-aspc.gc.ca](http://phac-aspc.gc.ca)
4. CADTH | [cadth.ca](http://cadth.ca)
5. CDC | [cdc.gov](http://cdc.gov)
6. ECDC | [ecdc.europa.eu](http://ecdc.europa.eu)
7. NICE | [nice.org.uk](http://nice.org.uk)
8. WHO | [who.int](http://who.int)
9. Public Health England | [gov.uk/government/organisations/public-health-england](http://gov.uk/government/organisations/public-health-england)

### Custom search engine:

<https://cse.google.ca/cse/publicurl?cx=011835638776738460640:i3n0jlacnvi>

### Search queries:

Review the first 100 results retrieved by the custom search engine for each of the following queries:

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:bccdc.ca

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:inspq.qc.ca

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:phac-aspc.gc.ca

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:cadth.ca

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:cdc.gov

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:ecdc.europa.eu

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:nice.org.uk

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:who.int

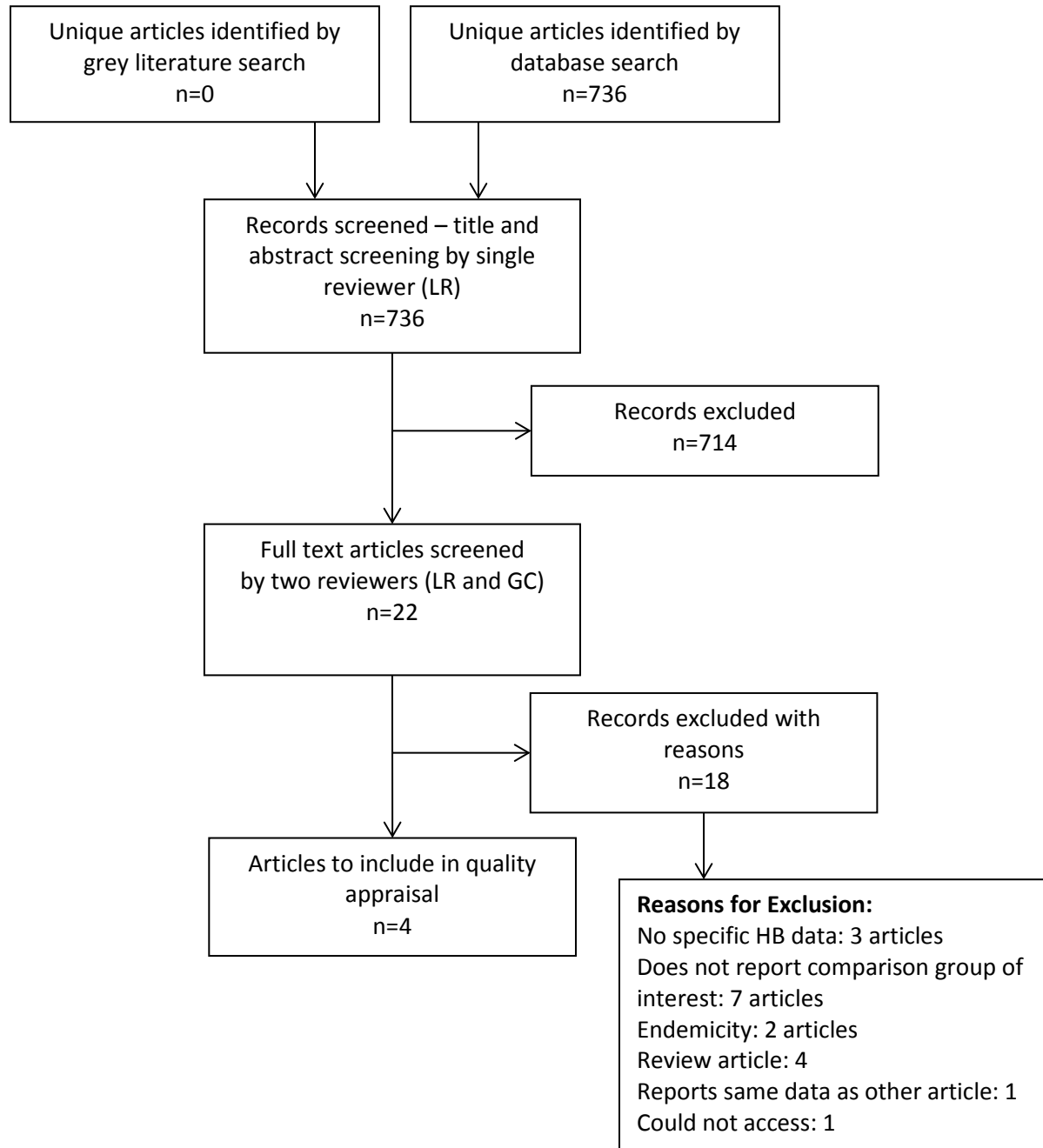


"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" site:gov.uk

"hepatitis B" vaccination OR immunization cost OR economic OR expenditure OR financial OR affordable OR "return on investment" OR ROI OR "value for money" OR "value for dollar" infant OR child OR adolescent OR preadolescent

## Appendix E: Flow diagram of search strategy and screening results

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## Appendix F: Summary of quality appraisal findings for four included articles

Citation, year of publication, jurisdiction, similarity to Ontario population	Reliability: Methodology	Reliability: Key Assumptions	Internal Validity	External Validity/Applicability (i.e., to cost-effectiveness of universal infant vs. adolescent HB immunization in Ontario)
<p><b>Siddiqui et al., 2010, UK<sup>35</sup></b></p> <p>Similar HBV endemicity to Ontario - prevalence of HBsAg &lt; 1%</p> <p>High immigrant-receiving country</p> <p>Universal immunization strategies also included prenatal screening, HB vaccine and HBIG at birth for infants born to HBsAg positive mothers, as in Ontario</p>	<p><b>Model:</b> Used a clearly described Markov model to compare three immunization strategies:</p> <ol style="list-style-type: none"> <li>1) Universal Infant (3 dose monovalent HB vaccine given with other routine immunizations, starting at age 2 months)</li> <li>2) Universal Adolescent (2 doses of monovalent HB vaccine at 12 years)</li> <li>3) Selective program based on ethnicity</li> </ol> <p><b>Perspective:</b> Healthcare payer</p> <p><b>Time horizon:</b> Lifetime (to death)</p> <p><b>Discounting rate:</b> 3.5% applied to both costs and health gains</p> <p><b>Sensitivity analysis:</b> Univariate and multivariate analysis; however, reported results with parameters adjusted at the 30,000 British pounds per QALY gained threshold; key parameters: duration of protection of HB immunization, HB-associated health care costs, discounting (0-4%), female HCC incidence; multivariate analysis of HB incidence, progression to chronic disease, QALY losses, treatment costs</p>	<p>Estimated HB incidence rates from routine laboratory reports to the UK Health Protection Agency and adjusted for underreporting and undiagnosed HB</p> <p>Age-specific risks of chronic HB: Used age-specific proportions of infections that led to acute and chronic infections based on published data</p> <p>Excluded infections in children &lt;1yr from model, based on an assumption that prenatal screening would prevent 100% of HB infections in infants &lt;1 y</p> <p>Lifetime HB risk estimate: Unclear</p> <p>Coverage: 90% for both infant and adolescent</p> <p>Used hepatitis C costing literature to estimate HB costs</p> <p>Sensitivity analysis results reported in the paper's narrative not easily</p>	<p><b>Strengths:</b></p> <p>Model accounted for age-dependent chronic HB risk</p> <p>Robust univariate and multivariate sensitivity analysis; model insensitive to variations of vaccine coverage</p> <p>Acceptable use of published hepatitis C health care cost literature</p> <p><b>Limitations:</b></p> <p>Reported that the model was very sensitive to discounting (i.e., the most cost-effective strategy changed due to discounting), but undiscounted results not reported</p> <p>Model does not account for transmission changing over time due to immunization (i.e., not dynamic)</p> <p>Unable to assess validity of HBV risk estimate used as not reported</p> <p>Assumption that prenatal screening program would</p>	<p><b>Strengths:</b></p> <p>Assumptions related to integration of infant HB immunization into routine visits likely applicable to Ontario</p> <p>Coverage estimates for infant and adolescent HB programs similar to recent Ontario coverage estimates</p> <p><b>Limitations:</b></p> <p>Data reported did not enable calculation of the ICER comparing universal adolescent to infant HB immunization strategies, so applicability to infant vs. adolescent in Ontario is limited in general.</p> <p>Exclusion of HB infections in infants &lt;1 y limits both internal and external validity</p> <p>Unclear whether UK epidemiological data applies to Ontario / some epidemiological parameters unclear (e.g., lifetime HB risk)</p> <p>Only considered monovalent HB costs for infant program</p>

Citation, year of publication, jurisdiction, similarity to Ontario population	Reliability: Methodology	Reliability: Key Assumptions	Internal Validity	External Validity/Applicability (i.e., to cost-effectiveness of universal infant vs. adolescent HB immunization in Ontario)
		reproducible Vaccine cost: GBP 9 per dose	prevent 100% of HB infections in children <1 y could have introduced bias; unclear whether this would differentially impact cost-effectiveness results for infant vs. adolescent strategy	
<p><b>Zurn et al., 2000, Switzerland</b><sup>36</sup></p> <p>Similar HB endemicity to Ontario - prevalence of HBsAg &lt; 1%</p> <p>High immigrant-receiving country</p> <p>Universal immunization strategies also included prenatal screening, HB vaccine and HBIG at birth for infants born to HBsAg positive mothers, as in Ontario</p>	<p><b>Model:</b> Used a clearly described decision-tree model to compare five immunization strategies:</p> <ol style="list-style-type: none"> <li>1) prenatal screening and immunization of high-risk newborns</li> <li>2) universal infant beginning at 2months</li> <li>3) universal school-children (age 12 years)</li> <li>4) universal infant with 12 year catch up program</li> <li>5) universal infant with 15 year catch up program</li> </ol> <p><b>Perspective:</b> Healthcare payer</p> <p><b>Time horizon:</b> Lifetime</p> <p><b>Sensitivity analysis:</b> Lifetime risk of HB infection, prevalence of chronic HB, treatment cost, vaccine price, discounting</p> <p><b>Discounting rate:</b> 3% (0-5% sensitivity analysis) applied to both costs and health gains</p>	<p>Estimated HB variables for infant and adolescents from published data and/or expert panel</p> <p>Estimated costs from hospital data, review of patient records, and/or Swiss Federal Office Statistics; 1996 vaccine costs used to estimate costs of immunization strategies</p> <p>Age-specific risks of chronic HB: Probabilities associated with disease progression in decision-tree adapted from US Centers for Diseases Control and Prevention model</p> <p>Coverage: 90% for infant strategy; 85% for 12 year olds</p> <p>Lifetime risk of HB infection: 5%, based on global prevalence estimates / expert opinion</p> <p>Vaccine price: “wholesale price”</p>	<p><b>Strengths:</b></p> <p>One way sensitivity analysis performed</p> <p>Most costing and epidemiology estimates from published work and national data</p> <p>Accounted for age-dependent chronic HB risk in model</p> <p><b>Limitations:</b></p> <p>The model is sensitive to discounting rate, lifetime risk of HB infection (“prevalence”), and vaccine price</p> <p>Model does not account for transmission changing over time due to immunization (i.e., not dynamic)</p>	<p><b>Strengths:</b></p> <p>Data reported enabled calculation of the ICER comparing universal adolescent to infant HB immunization strategies, improving applicability to current Ontario timing considerations.</p> <p>Assumptions related to integration of infant HB immunization into routine visits likely applicable to Ontario</p> <p>Coverage assumptions likely similar to Ontario, based on recent infant and grade 7 HB coverage estimates</p> <p>Considered infant program with a 12-year catch-up program (strategy 4), which would likely be needed in Ontario</p> <p><b>Limitations:</b></p> <p>See internal validity</p> <p>Unclear if 5% lifetime risk of HB infection applies in Ontario population</p> <p>Unclear if there are differences in HB high-risk immigrant groups/communities that could limit application to Ontario epidemiology / immigration trends</p>

Citation, year of publication, jurisdiction, similarity to Ontario population	Reliability: Methodology	Reliability: Key Assumptions	Internal Validity	External Validity/Applicability (i.e., to cost-effectiveness of universal infant vs. adolescent HB immunization in Ontario)
<p><b>Mangtani et al., 1995, England and Wales<sup>37</sup></b></p> <p>Similar HBV endemicity to Ontario - prevalence of HBsAg &lt; 1%</p> <p>High immigrant receiving country</p> <p>Universal immunization strategies also included prenatal screening, HB vaccine and HBIG at birth for infants born to HBsAg positive mothers, as in Ontario</p>	<p><b>Model:</b> Authors described a method of “working backwards from mortality data” to compare the cost-effectiveness of two universal HB immunization strategies to the UK <i>status quo</i> at the time (i.e., a high risk HB immunization program targeting adults):</p> <ol style="list-style-type: none"> <li>1) Infant program, given at the same time as other childhood vaccines (i.e., by NHS nurses, general practitioners or pediatricians)</li> <li>2) Pre-adolescent program (age not specified, but methods suggest likely age 12; school-based)</li> </ol> <p><b>Perspective:</b> Healthcare payer</p> <p><b>Time horizon:</b> Lifetime</p> <p><b>Sensitivity analysis:</b> Nursing time, vaccine cost, HB prevalence, relative risk HB-attributable mortality, % of high risk adults in population</p> <p><b>Discounting:</b> 6% applied to health gains (costs not discounted)</p>	<p>Health benefits estimated from the incidence of deaths related to liver disease in England and Wales</p> <p>Serological surveys used to estimate HBV prevalence of 0.2%-0.7%; used 0.5% HBsAg prevalence in model</p> <p>Coverage: 92% infant and 80% adolescent</p> <p>Excluded deaths in &lt;12y in adolescent program</p> <p>Costs were estimated based on 1993 salaries, vaccine prices</p> <p>Vaccine price: GBP 7.36 per dose</p>	<p><b>Strengths:</b></p> <p>One-way sensitivity analysis showed that the model was insensitive to changes in nursing time, and vaccine uptake</p> <p>HBV parameters and cost was appeared to be appropriately estimated from national data and published work</p> <p><b>Limitations:</b></p> <p>The retrospective model used (working backwards from mortality data) is viewed as a less robust design than prospective models (e.g., versus decision tree analysis)</p> <p>Model did not appear to account for age-dependent risk of chronic HB (i.e., based on age at infection)</p> <p>Health service cost savings from reducing incidence of acute and chronic liver disease were not included</p> <p>The model was sensitive to discounting future health gains</p>	<p><b>Strengths:</b></p> <p>Data reported enabled calculation of the ICER comparing universal adolescent to infant HB immunization strategies, improving applicability to current Ontario timing considerations.</p> <p>Coverage estimates, HBsAg prevalence, and infant and adolescent program delivery comparable to Ontario context</p> <p><b>Limitations:</b></p> <p>See internal validity; key limitation is retrospective design’s limitations, lack of age-based risk of chronic HB reflected in model</p> <p>Unclear if 1990’s UK epidemiological and/or costing data applies to Ontario context</p>

Citation, year of publication, jurisdiction, similarity to Ontario population	Reliability: Methodology	Reliability: Key Assumptions	Internal Validity	External Validity/Applicability (i.e., to cost-effectiveness of universal infant vs. adolescent HB immunization in Ontario)
<p><b>Margolis et al., 1995, USA<sup>38</sup></b></p> <p>Similar HBV endemicity to Ontario - prevalence of HBsAg &lt; 1%</p> <p>High immigrant-receiving country</p> <p>Universal immunization strategies also included prenatal screening, HB vaccine and HBIG at birth for infants born to HBsAg positive mothers, as in Ontario</p>	<p><b>Model:</b> Used a clearly described decision tree model using a 1991 US birth cohort to compare three HB immunization strategies:</p> <ol style="list-style-type: none"> <li>1) Prenatal screening and immunization of infants born to high risk mothers</li> <li>2) Universal infant</li> <li>3) Universal adolescent (11-13 years)</li> </ol> <p><b>Perspective:</b> Societal; Included direct medical costs, costs of prevention programs and indirect costs (e.g., work-loss costs due to hospitalization, premature death)</p> <p><b>Sensitivity analysis:</b> One-way sensitivity analysis was performed;</p> <p><b>Time horizon:</b> Lifetime (to death)</p> <p><b>Discounting:</b> 5% applied to all future costs; show discounted health gains at unknown rate</p>	<p>Age-specific risk estimates of chronic HB: Included in model (e.g., 90% for infants born to HBsAg and HBeAg + mothers; 30% if infected between 1-5 years; 6% if infected at 6y +), which translated into 3% of HB infections estimated to occur in early childhood, accounting for 17% of chronic HB infections.</p> <p>Lifetime HB risk estimate: 4.8%; race-adjusted, based on published data on selected subgroups with higher risk of perinatal / early childhood transmission (Alaskan Native, Pacific Islanders, children of South Asian-born mothers)</p> <p>Medical costs for HBV infection were obtained from published data</p> <p>HBV epidemiological data were obtained from published data and some expert judgement</p> <p>Coverage: Infant: 60%; Adolescent: 40%</p> <p>Vaccine price: infant – USD 6.67 per dose, adolescent – USD 13.34 per dose</p>	<p><b>Strengths:</b></p> <p>One-way sensitivity analysis was performed</p> <p>Model accounted for age-dependent risk of chronic HB (i.e., based on age at infection)</p> <p>Medical costs and HBV epidemiological data were obtained from published data</p> <p>The cost-effectiveness interpretation was insensitive to 5% discounting</p> <p><b>Limitations:</b></p> <p>Model does not account for transmission changing over time due to immunization (i.e., not dynamic)</p> <p>Vaccine coverage was estimated based on authors assumptions</p> <p>Undiscounted ICER results not reported</p>	<p><b>Strengths:</b></p> <p>Assumed infant program would be given at same visits as other routine immunizations</p> <p><b>Limitations:</b></p> <p>Data reported did not enable calculation of an ICER comparing universal adolescent to infant HB immunization strategies, so applicability in general is limited.</p> <p>Some model parameters may not reflect Ontario HB epidemiology or HB immunization program experience:</p> <ul style="list-style-type: none"> <li>• 4.8% race-adjusted lifetime risk of HB (unclear if applies, particularly given US-specific subgroups based on estimates from the 1990s or earlier)</li> <li>• Age-specific risk of chronic HB and estimated burden of early childhood HB infection and attributable chronic HB burden (unclear how dis/similar this is to current Ontario epidemiology, given ongoing iPHIS analyses, underreporting of asymptomatic infection, and lack of seroprevalence estimates in Ontario children)</li> <li>• Both infant and adolescent coverage estimates lower than recent coverage data for infant immunizations and grade 7 HB coverage in Ontario</li> </ul>

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