

## Appendix 5: Hepatitis B: evidence review for newly arriving immigrants and refugees

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### ABSTRACT

**Background:** Immigrant populations have higher mortality from chronic viral hepatitis and from hepatocellular carcinoma than the Canadian-born population. The greatest part of this burden is likely attributable to undetected chronic infection with hepatitis B, most often acquired in the perinatal period or early childhood. Despite this, there are no organized screening programs in Canada for chronic infection with hepatitis B, and immigrants are not routinely offered hepatitis B vaccination outside of the universal childhood vaccination program. We conducted an evidence review to determine the burden of hepatitis B infection among immigrants and to assess the effectiveness of screening and treatment programs for chronic hepatitis B infection and hepatitis B vaccination programs.

**Methods:** We conducted a systematic search for evidence on hepatitis B infection among immigrants and the benefits and harms, applicability, clinical considerations and implementation of screening programs for chronic hepatitis B infection and hepatitis B vaccination programs in the general and the immigrant populations. The quality of this evidence was assessed and ranked using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

**Results:** Approximately 4% of immigrants are chronically infected with hepatitis B resulting in associated increased morbidity and mortality. Treatment of chronic infection with hepatitis B decreases morbidity from chronic liver disease. Targeted screening programs for hepatocellular carcinoma decrease associated mortality. Universal hepatitis B vaccination programs in infancy and early childhood in areas where hepatitis B is endemic decrease mortality from hepatocellular carcinoma, and hepatitis B vaccination of adults reduces development of acute hepatitis B infection.

**Interpretation:** Immigrants bear a disproportionate burden from chronic hepatitis B infection; screening and treatment programs and targeted vaccination programs for hepatitis B infection would be beneficial.

**Competing interests:** Lavanya Narasiah received speaker fees from GlaxoSmithKline for travel health presentations, advice and vaccination in general (2009 only). Pierre Plourde received speaker fees from GlaxoSmithKline for presentations on travel health and tropical medicine. Marc Deschenes has attended Gilead Sciences Advisory Board, but his attendance does not affect statements in this article. David Wong receives educational grants for hosting an annual meeting The University of Toronto Sheila Sherlock Liver Research Day. He also has received honoraria for educational sessions from Roche, Schering, Gilead, Bristol-Myers Squibb and Novartis. In all instances slides were his own. None declared for Christina Greenaway, Erin Ueffing and Susan Kuhn.

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### Box 1: Recommendations on Hepatitis B from the Canadian Collaboration for Immigrant and Refugee Health

#### Screening:

Screen adults and children from countries where chronic hepatitis B virus infection is moderate or high, i.e.  $\geq 2\%$  (HBsAg positive), to decrease disease severity, to possibly reduce incidence of hepatocellular carcinoma, and to decrease transmission of hepatitis B infection. In those found to have chronic infection with hepatitis B, refer for evaluation and assessment of the need for treatment and screen risk groups for hepatocellular carcinoma. Lifelong monitoring is required.

#### Basis of recommendation

- **Balance of benefits and harms:** Screening for and then treating advanced chronic infection with hepatitis B reduces the development of progressive liver failure (number needed to treat [NNT] 19, 95% confidence interval [95% CI] 15–44). Screening for hepatocellular carcinoma (ultrasonography and  $\alpha$ -fetoprotein [ $\alpha$ FP] serologic testing every six months) in certain risk groups with chronic hepatitis B infection decreases the risk of mortality from hepatocellular carcinoma (number needed to screen 2058, 95% CI 1462–4412). Prevalence of chronic hepatitis B infection is higher in immigrants and refugees, mean of 4% compared with  $< 0.5\%$  for North Americans. Toxicity varies by treatment regimen, but most therapies are well tolerated.
- **Quality of evidence:** Moderate
- **Values and preferences:** The Guideline Committee attributed more value to preventing death from hepatocellular carcinoma and less value on the burden of screening for and treatment of adverse effects.

#### Vaccination:

Screen adults and children from countries where chronic hepatitis B virus infection is moderate or high, i.e.  $\geq 2\%$  (HBsAg positive) for prior immunity to hepatitis B (hepatitis B core antibody [anti-HBc], hepatitis B surface antibody [anti-HBs]) and vaccinate those found to be susceptible (negative for all three markers; hepatitis B surface antigen, anti-HBc and anti-HBs) to decrease transmission of and morbidity and mortality from acute and chronic hepatitis B.

## The cases

Ousman is a 48-year-old man from Mali who has been living in Canada for five years. He is admitted to hospital with a one-month history of jaundice, ascites and weight loss and is diagnosed with cirrhosis and hepatocellular carcinoma secondary to chronic infection with hepatitis

### Box 1: Continued

#### Basis of recommendation

- **Balance of benefits and harms:** Universal perinatal and childhood vaccination in countries where chronic hepatitis B infection is endemic, have dramatically reduced chronic infection with hepatitis B (number needed to vaccinate 12, 95% CI 11–12) and decreased mortality from hepatocellular carcinoma (relative risk 0.725, 95% CI 0.518–1.015) 15 years following immunization program initiation. In countries with lower prevalence of chronic hepatitis B virus infection ( $< 2\%$  HBsAg positive), vaccination of adults decreases development of acute hepatitis B infection. Adverse reactions to vaccination are minor and self-limited.
- **Quality of evidence:** Moderate
- **Values and preferences:** The Guideline Committee attributed more value to reducing disparity of chronic hepatitis B infection, a preventable disease with longer term consequences, and more value on protecting family and friends than on the burden of screening and vaccination.

B. What type of screening could he have benefited from when he arrived in Canada?

Xiu is a 30-year-old Chinese woman who has been living in Canada for three years. She is 16 weeks pregnant and, during routine prenatal screening, tests positive for hepatitis B surface antigen (HBsAg). She is married and has two children at home who are four and eight years old. What screening or preventive actions could her family have benefited from at the time of arrival in Canada?

## Introduction

Hepatitis B infection is an important global health problem that infects 350 million people worldwide and leads to one million premature deaths from chronic liver disease and hepatocellular carcinoma annually.<sup>1</sup> Approximately 4% of immigrants versus 0.5% of Canadian-born people have chronic infection with hepatitis B.<sup>2,3</sup> Most people with chronic infection are asymptomatic and go undetected and untreated. This is likely why mortality from viral hepatitis and hepatocellular carcinoma in immigrants is two to four times higher than in the Canadian-born population.<sup>4</sup> Over the past 10 years, several medications have become available that decrease viral replication and morbidity from chronic liver disease. Screening for chronic infection with hepatitis B in high-risk populations and targeted treatment have, therefore, become important strategies to decrease the burden of chronic infection with hepatitis B. An effective hepatitis B vaccine

(available in Canada since 1982) is an important tool to control transmission of hepatitis B. Despite this disparity in populations and availability of a safe and effective vaccine, no programs in Canada systematically screen immigrants for chronic hepatitis B, nor are there systematic targeted or catch-up hepatitis B vaccination programs outside of the childhood vaccination program.<sup>5</sup> We conducted a review to quantify the burden of chronic hepatitis B in immigrants, to search for evidence of the effectiveness of screening and vaccination programs, and to identify barriers or challenges to implementing such programs. The Recommendations on screening for and vaccinating against hepatitis B from the Canadian Collaboration for Immigrant and Refugee Health are found in Box 1.

## Methods

We used the 14-step approach developed by the Canadian Collaboration for Immigrant and Refugee Health.<sup>6</sup> The clinician summary table highlights the epidemiology of disease within immigrant populations, considerations and potential key clinical actions (Appendix 2). We then constructed a logic model to define the clinical preventive actions (intervention), outcomes and key clinical questions.

### *Search strategy for systematic reviews and guidelines*

We designed a search strategy in consultation with a medical librarian to identify relevant systematic reviews and guidelines to address the burden of hepatitis B and to ascertain the effectiveness of screening for infection and of hepatitis B vaccination among immigrants. For this search we reviewed five electronic databases MEDLINE (Ovid), MEDLINE InProcess, EMBASE, CINAHL, and Cochrane Database of Systematic Reviews from 1950 to Dec. 17, 2008. We conducted a similar search for systematic reviews and guidelines for hepatitis B with the same objectives in the general population for the same five databases but restricted the search dates from Jan 1, 1996 to Dec. 17, 2008. We hand-searched for guidelines on hepatitis B screening and vaccination from the following databases until Sept 6, 2010 : the CMA Infobase, the National Guideline Clearinghouse, the Canadian Task Force on Preventive Health Care, the Public Health Agency of Canada, the National Advisory Committee on Immunization, the Canadian Association for the Study of the Liver, the US Preventive Services Task Force, Centers for Disease Control and Prevention, the Advisory Committee on Immunization Practices, the American Association for the Study of Liver Diseases, the Infectious Diseases

Society of America, the National Institute for Health and Clinical Excellence, and the World Health Organization. We assessed eligible systematic reviews using the National Institute for Health and Clinical Excellence critical appraisal tool to assess systematicity (the review applied a consistent and comprehensive approach), transparency, quality of methods and relevance. We also assessed relevant guidelines using the Appraisal of Guidelines for Research and Evaluation instrument. We conducted a separate search for hepatitis B and the immigrant population to address population-specific concerns including baseline risk and prevalence in comparison with the Canadian-born population; risk of clinically important outcomes; genetic and cultural factors (e.g., preferences, values, knowledge); and adherence variation (including at the primary care level to search for population-specific burden using the same five databases from 1950 to Dec. 17, 2008). Only articles in English and French were eligible. An updating search, focusing on randomized controlled trials and systematic reviews during the period Jan. 1, 2007–Jan. 1, 2010, was conducted to determine whether any recent publications would change the position of the recommendation.

### *Synthesis of evidence and values*

We compiled evidence from systematic reviews and pertinent cohort studies and clinical trials using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)<sup>7</sup> summary of findings tables (Box 2), which assess both relative and absolute effects of interventions (relative risk and absolute event rate). We also assessed the quality of each outcome using the GRADE quality-assessment tool, which examines study limitations, directness, precision, consistency and publication bias across all studies. The synthesis of data identified both clinically important considerations and implementation issues relevant to our population. Finally, we identified gaps in the research and evidence base.

## Results

In the search for systematic reviews and guidelines in immigrants, 54 records were identified and screened and six met eligibility criteria. All of these were narrative reviews on screening immigrants for hepatitis B and were excluded because none followed a systematic review method.<sup>8-13</sup> A total of 2565 records were identified and screened in the systematic reviews and guidelines for the general population and the Web-based search. Fourteen that met eligibility criteria included two guidelines from the United States on screening for chronic hepatitis B,<sup>14-</sup>

**Table 1:** Global patterns of chronic infection with HBV and hepatocellular carcinoma

Disease characteristic	High	Intermediate	Low
Prevalence of chronic infection with HBV, %	> 8	2–7	< 2
Geographic distribution	Southeast Asia; China; Pacific Islands; sub-Saharan Africa; Alaska; Peru; northwest Brazil	Mediterranean basin; eastern Europe; central Asia; Japan; Amazon basin; Middle East	United States and Canada; western and northern Europe; Australia; New Zealand
Percentage of global population, %	45	43	12
Predominant mode of infection	Maternal–infant, percutaneous or mucosal	Maternal–infant, percutaneous or mucosal, sexual	Sexual, percutaneous or mucosal
Predominant age at acquisition of infection	Perinatal (vertical) and early childhood (horizontal)	All age groups	Adult
Likelihood of developing chronic infection after acute infection with HBV, %*	80–90	30–60	< 5
Mean age of developing hepatocellular carcinoma, yr*	57	57	75
Lifetime probability of infection (immunity), %	> 60	20–60	< 20

Note: HBV = hepatitis B virus.

\*Likelihood of developing chronic infection with HBV after acute infection with HBV is inversely proportional to age of acquisition. The earlier the infection is acquired, the earlier hepatocellular carcinoma will develop.<sup>20,33</sup>

<sup>16</sup> three guidelines addressing treatment of chronic hepatitis B infection,<sup>17–19</sup> one systematic review, one guideline on screening for hepatocellular carcinoma,<sup>20,21</sup> one systematic review and one guideline on preventing hepatitis B infection among neonates,<sup>22,23</sup> one systematic review on adverse effects of hepatitis B vaccination,<sup>24</sup> one systematic review on improving immunization rates,<sup>25</sup> and three guidelines on vaccinating for hepatitis B.<sup>26–28</sup> A flow chart of these combined searches is outlined in Appendix 1. In the immigrant and hepatitis B search, 676 primary articles were identified, of which 148 were relevant and addressed the following areas: epidemiology, screening, knowledge and compliance, treatment, and vaccination in the immigrant population.

### How does hepatitis B virus affect immigrant populations?

Canada is a country with low rates of hepatitis B and an overall seroprevalence of chronic hepatitis B infection of < 0.5%. Over the past 40 years, most immigrants (> 70% of 250 000/yr) who arrived in Canada have originated from countries with intermediate or high rates of endemic hepatitis B (Table 1). These immigrants have an overall seroprevalence of chronic infection with hepatitis B of about 4%.<sup>2,3</sup> People chronically infected with hepatitis B have a 15%–25% lifetime risk of dying from cirrhosis and hepatocellular carcinoma.<sup>1,29</sup> They are typically

asymptomatic until they present with end-stage liver disease or hepatocellular carcinoma several decades after infection. Hepatocellular carcinoma is one of the most fatal types of cancer and has a five-year survival rate of less than 11%, as symptoms usually appear only at an advanced nontreatable stage.<sup>30</sup> The growing pool of asymptomatic, undetected and untreated hepatitis B infection in the immigrant population (8000 to 26 000 new imported infections/yr) is likely why mortality is higher in immigrants than in the Canadian-born population: 1.8–3.8 times higher from viral hepatitis and 2.2–4.9 times higher from hepatocellular carcinoma.<sup>4</sup> The burden of undetected chronic infection with hepatitis B in immigrants is likely also in part responsible for the 8.4-fold increased mortality from chronic infection with hepatitis B and a 2.2-fold increased incidence of hepatocellular carcinoma over the past 30 years in Canada (between 1969 and 1997).<sup>31,32</sup>

Young children living in a household that includes someone with chronic hepatitis B infection have rates of acquiring new infection of 1%–2% per year during the first decade of life.<sup>33–35</sup> Immigrant children therefore, are at risk of acquiring hepatitis B in Canada, as they are more likely to live in a household that includes someone with silent hepatitis B infection. Many immigrant children have not been vaccinated in the universal childhood immunization program because they are too young or arrived after the age of vaccination. This risk was highlighted in a study in which Quebec's school-

**Table 2:** Typical interpretation of serologic test results for HBV infection

Serologic marker				Interpretation
HBsAg	Anti-HBc-IgM	Total anti-HBc	Anti-HBs	
-	-	-	-	Never infected, not immune
+	+	+/-	-	Acute infection with HBV
+	-	+	-	Infection if HBsAg-positive and chronic if present > 6 mo
-	-	+	+	Recovered from past natural infection and immune
-	-	-	+	Immune because of vaccination Immune because of natural infection (rarely)
-	-	+*	-	<ul style="list-style-type: none"> <li>• Natural immunity but with undetectable anti-HBs</li> <li>• Late-phase acute infection with HBV</li> <li>• (Rarely) chronic infection with HBV, with undetectable HBsAg but positive results for HBV DNA</li> <li>• False-positive anti-HBc, thus susceptible</li> </ul>

Note: anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, IgM = immunoglobulin M.

\*Five to ten per cent of people will have isolated anti-HBc and only a minority (4%–13%) have chronic infection with HBV (positive for HBV DNA). When HBV DNA is present, it is usually in low quantities and associated risk of developing progressive liver disease is low.<sup>39, 40</sup>  
Adapted from Plotkin and Orenstein.<sup>33</sup>

based vaccination program (for children in grade 4) was evaluated 10 years after initiation. In this study rates of acute infection with hepatitis B decreased in all age groups except those ten years and younger; 53% of these cases occurred in foreign-born children.<sup>36</sup> This study underscores both the need to provide protection against hepatitis B as early as possible for children (possibly changing to routine infant rather than childhood vaccination programs) and also to provide catch-up vaccination for immigrants.

## Does screening for chronic hepatitis B infection decrease morbidity and mortality?

### Screening tests

Serologic tests to detect hepatitis B are inexpensive, and commercially available tests are sensitive and specific.<sup>37</sup> Antigens and antibodies associated with hepatitis B infection include HBsAg and antibody to HBsAg (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). The most frequently used serologic markers to differentiate acute, resolving and chronic infection are HBsAg, anti-HBc (immunoglobulin M acute, immunoglobulin G chronic or resolved) and anti-HBs; they should be used for initial screening for hepatitis B infection (Table 2).<sup>38</sup> Anti-HBc is a useful marker in the diagnosis of hepatitis B infection, as it appears during the course of acute infection and usually persists for life either in the presence of either chronic

(also HBsAg positive) or resolved infection with or without the presence of concomitant anti-HBs.

### Relative benefits and harms of treatment

Several antiviral agents that suppress chronic hepatitis B infection have become available over the past 10 years. Although follow-up with the newer antiviral agents has not been long enough to show improved clinical outcomes, they have uniformly been shown to decrease surrogate markers of chronic liver disease (normalization of alanine aminotransferase, decreased hepatitis B DNA, loss of HBeAg and even loss of HBsAg etc).<sup>41-43</sup> In a landmark randomized controlled trial, however, of lamivudine versus placebo in patients with advanced liver disease and high-level viral replication, the risk of developing progressive liver failure (hazard ratio 0.45,  $p = .02$ ) and of developing hepatocellular carcinoma (hazard ratio 0.49,  $p = .047$ ) were both decreased in the lamivudine arm after a mean of 32 months of treatment as compared with placebo. (Table 3).<sup>41</sup> Lamivudine is well tolerated, but with prolonged use as a single agent, resistance develops progressively. Since publication of this trial, several other antiviral agents (adefovir, entecavir, telbivudine and tenofovir) have become available that are relatively well tolerated and are more potent than lamivudine.<sup>17-19,44</sup> Treatment of chronic infection with hepatitis B is rapidly evolving and complex; the decision of who should be treated, when to

**Table 3:** Efficacy of lamivudine to decrease mortality in patients with chronic infection with hepatitis B virus

Patient or population: "Adults > 16 yr, positive for HBsAg for at least 6 mo, and either positive or negative for HBeAg, HBV DNA  $\geq 10^5$  IU/mL at screening, who had a liver biopsy showing an Ishak fibrosis score of at least 4 (where 0 indicates no fibrosis and 6 indicates cirrhosis) at screening or during the previous 2 yr."

Settings: Multicentre trial with patients from Taiwan, Hong Kong, China, Singapore, Thailand and Australia

Intervention: Lamivudine treatment

Comparison: Placebo

Source: Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521-31.

Outcomes (follow-up)	Absolute effect		Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
	Risk for control group	Difference with Lamivudine (95% CI)				
Increase in Child-Pugh score (median 32.4 months)	88 per 1000	54 fewer per 1000 (70 fewer to 23 fewer per 1000)	RR 0.39 (0.20–0.74)	651 (1)	Moderate*	NNT 19 (95% CI 15–44)
Hepatocellular carcinoma incidence (median 32.4 months)	74 per 1000	35 fewer per 1000 (54 fewer to 1 more per 1000)	RR 0.52 (0.27–1.01)	651 (1)	Moderate*	NNT 29 (not statistically significant)
Serious adverse events (5 years)	177 per 1000	53 fewer per 1000 (92 fewer to 5 more per 1000)	RR 0.70 (0.48–1.03)	651 (1)	Moderate*	NNT 19 (not statistically significant)

Note: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; GSK = GlaxoSmithKline; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; RR = relative risk; adverse events were considered to be serious if the investigator determined that they jeopardized the patient's health; were life-threatening; or would result in hospitalization, disability or death.

\*Data were analyzed by GSK; article written by committee including GSK employees.

initiate therapy and which medication to use should be made by professionals with expertise in this area.<sup>17</sup>

#### *Effectiveness of surveillance for hepatocellular carcinoma*

Certain people with chronic infection with hepatitis B (i.e., those with cirrhosis, Asian men > 40 years of age, Asian women > 50 years of age, Africans > 20 years of age, and those with a family history of hepatocellular carcinoma) should be screened for hepatocellular carcinoma with ultrasonography and with  $\alpha$ -fetoprotein ( $\alpha$ FP) serologic testing every six months.<sup>18,21</sup> This screening will detect cancer at an earlier stage when it might be amenable to therapeutic intervention resulting in improved survival (five-year disease-free survival of about 50% v. 0%–10%).<sup>19,30</sup> In a randomized controlled trial of screening every six months with ultrasonography and  $\alpha$ FP versus no screening in more than 18 000 Chinese subjects with positive results for hepatitis B markers, those in the screening arm had a 37% reduction in hepatocellular carcinoma–related mortality after a

mean follow-up of five years (Table 4). This was despite suboptimal adherence rates of less than 60% by the end of the study and represents the minimum benefit that can be expected from surveillance.<sup>45</sup>

#### *Effectiveness of screening programs for chronic infection with hepatitis B virus*

*Pregnant women:* Screening for chronic infection with hepatitis B is routinely recommended for pregnant women in Canada and the US.<sup>14,15,23,27,28</sup> There is good evidence that screening and giving immunoprophylaxis to infants born to mothers with chronic hepatitis B infection markedly decreases the transmission of hepatitis B to the newborn. In a recent meta-analysis the risk of transmission of hepatitis B decreased by 92% (95% CI 83%–97%) in infants born to mothers with chronic hepatitis B infection who received hepatitis B vaccine and hepatitis B immunoglobulin within 12 hours of birth compared with placebo.<sup>22</sup>

**Table 4:** Efficacy of screening for hepatocellular carcinoma to decrease mortality in patients with chronic infection with hepatitis B virus

Patient or population: Adults aged 35–59 with chronic infection with hepatitis B virus

Setting: Urban Shanghai

Intervention: Testing for hepatocellular carcinoma with  $\alpha$ FP and abdominal ultrasonography every 6 months

Comparison: No screening

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004;130:417–22.

Outcomes (follow-up)	Absolute effect		Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
	Risk for control group	Difference with screening for hepatocellular carcinoma (95% CI)				
Hepatocellular carcinoma mortality (5 years*)	100 per 1 000 000†‡	37 fewer per 1 000 000 (52 to 17 fewer per 1 000 000)†	RR 0.63 (0.48–0.83)	200 000 (1)	Moderate‡,§	NNT 27 028 (95% CI 19 231–58 824)
Hepatocellular carcinoma incidence $\alpha$ FP (5 years*)	200 per 1 000 000†‡	74 more per 1 000 000 (24 to 135 more per 1 000 000)†	RR 1.37 (1.12–1.68)	200 000 (1)	Moderate‡,§	NNT 13 514 (95% CI 7353–41 667)

Note:  $\alpha$ FP =  $\alpha$ -fetoprotein; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NNT = number needed to treat; RR = risk ratio.

\*5 years of chronological follow-up. Person-years: 38 444 for intervention (screening), 41 077 for control (no screening).

†in person-years.

‡Study population uncertain; cannot determine who the population is. Simple clustering sample, 300 factories, schools or enterprises, but did not specify who within group was chosen. Report suggests all those within group had evidence of hepatitis B virus infection or chronic hepatitis, but is not explicit. Because status is unknown, will give benefit of doubt; have downgraded for “uncertainty about directness.”

§Study included participants aged 35–59 (mean intervention = 42 years old, mean control = 41 years old), but study reported sampling from schools.

*Immigrants:* No studies have directly measured the effectiveness of screening for chronic hepatitis B infection in immigrants, but the indirect evidence is compelling (increased burden of disease that can be decreased with effective treatment). Recent analysis of an adult immigrant population with an HBsAg prevalence of 10% found screening and treating or screening, treating and vaccinating at-risk contacts around the index case were cost-effective strategies to decrease the morbidity and mortality from chronic hepatitis B infection as compared with no strategy. The breakpoint seroprevalence of HBsAg at which screening and treating will remain cost-effective is still to be determined.<sup>46</sup>

### Does vaccination decrease morbidity and mortality from hepatitis B?

Hepatitis B vaccine (around 88% effective in preventing transmission) has been available in Canada since 1982, and a universal childhood hepatitis vaccination program has been recommended and been operating in most

provinces since 1991.<sup>33,47</sup> It is an effective vaccine that substantially decreases the risk of developing acute or chronic hepatitis B and hepatocellular carcinoma. It is well tolerated with only mild and transient adverse events. Additionally, several studies have demonstrated no link between hepatitis B vaccine and multiple sclerosis or other neurologic or rheumatologic disorders.<sup>24,33,48–50</sup>

#### *Effectiveness of hepatitis B vaccination to decrease morbidity and mortality*

*Children:* Several cohort studies in settings where hepatitis B incidence is high have shown the effectiveness of universal infant and childhood vaccination programs in decreasing the incidence of acute hepatitis B, of chronic infection with hepatitis B and of hepatocellular carcinoma. Incidence of acute hepatitis B infection decreased by 93.5% to 1/15th the initial rate (215–14 per 100 000 population) over a four-year period in an Alaskan Native population after 90% vaccine coverage rate of the whole population.<sup>51</sup> The relative risk of chronic infection with hepatitis B in

**Table 5:** Efficacy of universal childhood vaccination to decrease hepatocellular carcinoma

Patients or population: Children aged 6–14 years from Taiwan

Setting: Cases of hepatocellular carcinoma were identified from national cancer registry, major hospitals and tertiary referral centres, and national mortality registry (1981–1984). Baseline was drawn from general population data.

Intervention: Perinatal and childhood hepatitis B virus vaccination launched July 1984\*

Comparison: No hepatitis B virus vaccination

Source: Chang M-H, Chen C-J, Lai M-S, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997;336:1855-9.

Outcomes	Absolute effect		Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
	Risk with placebo or no vaccination	Risk with vaccination				
Liver cancers (except non-hepatocellular carcinoma)	1981–1986: 0.70 per 100 000 (range 0.65–0.78)*	1986–1990: 0.57 per 100 000 (range 0.48–0.62)	RR = 0.81 (0.58–1.15)	3.4 million (1) †,‡	Low	Not possible to calculate NNT
		1990–1994: 0.36 per 100 000 (range 0.23–0.48)	RR = 0.51 (0.35–0.77)	3.4 million (1)	Low	Not possible to calculate NNT
Mortality from hepatocellular carcinoma	1981–1986: 0.80 per 100 000 (range 0.59–1.05)*	1986–1990: 0.58 per 100 000 (range 0.51–0.68)	RR = 0.73 (0.52–1.02)	3.4 million (1)	Low	Not possible to calculate NNT
		1990–1994: 0.34 per 100 000 (range 0.23–0.51)	RR = 0.43 (0.29–0.63)	3.4 million (1)	Moderate§,¶	Not possible to calculate NNT

Note: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NNT = number needed to treat; RR = relative risk

\*“Taiwan’s mass-vaccination program against HBV was launched in July 1984.<sup>10,11</sup> For the first 2 years, the program covered only neonates born to mothers who were HBsAg carriers, but it was extended to all neonates in July 1986, to preschool children in July 1987, to primary-school children in 1988, to middle-school children in 1989, and to adults in 1990.”

†In Taiwan, hepatocellular carcinoma usually develops between age 50–60. These data therefore underestimate the effect of HBV vaccine against hepatocellular carcinoma.

‡Chi-square  $p < .001$ .

§GRADE upgrades 1 for RR < 0.50.

¶Single population-based study using national registers; approximately 3.4 million children aged 6–14 each year.

immunized preschoolers as compared with historical school-aged controls ranged from 0.1 to 0.34 in four South Pacific Islands.<sup>52</sup> Finally a universal infant and childhood vaccination program in Taiwan after 15 years of follow-up showed a dramatic decrease in seropositivity of HBsAg (9.8%–0.7%) and a 49% incidence decrease to just over half the initial rate (0.7 to 0.36 per 100 000 population) of hepatocellular carcinoma (Table 5, Table 6).<sup>53,54</sup>

*Adults:* Hepatitis B vaccination in adults is also effective in decreasing acquisition of acute hepatitis B. A recent meta-analysis of the effectiveness of hepatitis B

vaccination among health care workers (in countries where hepatitis B incidence is low) demonstrated hepatitis B vaccine decreased acquisition of acute hepatitis B infection by 68% (95% CI 35%–84%) as compared with those who were unvaccinated.<sup>48</sup> Because it is uncommon for adults to develop chronic infection with hepatitis B following acute infection (< 5%), we were unable to identify any studies that measured the effectiveness of vaccine to decrease morbidity or mortality associated with chronic infection with hepatitis B in adults.



**Table 6:** Efficacy of universal childhood vaccination to decrease chronic hepatitis B virus infection

Patient or population: Taiwanese children <15 years old born after HBV vaccination program was implemented and adolescents and young adults > 15-20 years old born before HBV vaccination program began

Settings: Measured chronic infection with HBV before and after vaccination program was implemented in Taiwan

Intervention: Perinatal and childhood HBV vaccination\*\*

Comparison: No HBV vaccination

Source: Ni YH, Chang MH, Huang LM, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. *Ann Intern Med* 2001;135:796-800.

Outcomes	Absolute effect		Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
	Risk in control group (1984)	Difference with vaccination (1999; 95% CI)				
HBsAg carriage < 15-year-olds	98 per 1000	91 fewer per 1000 (94 to 85 fewer per 1000)	RR 0.07 (0.04–0.13)	2557 (1)	High*,†	NNT 11 (95% CI 11–12)
Anti-HBc < 15-year-olds	262 per 1000	233 fewer per 1000 (241 to 220 fewer per 1000)	RR 0.11 (0.08–0.16)	2557 (1)	High*,†	NNT 5 (95% CI 5–5)

Note: anti-HBc = hepatitis B core antibody; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; RR = relative risk.

\*Because of uncertainty around sampling method, unclear to which populations these results could be generalized.

\*\*"Taiwan's mass-vaccination program against HBV was launched in July 1984.<sup>10,11</sup> For first 2 years, program covered only neonates born to mothers who were HBsAg carriers, but it was extended to all neonates in July 1986, to preschool children in July 1987, to primary-school children in 1988, to middle-school children in 1989, and to adults in 1990."

†Upgraded two levels for large effect sizes.

*Immigrants:* We were also unable to identify studies that directly measured the effectiveness of hepatitis B vaccination programs among immigrants. If we extrapolate from the data already presented, however, hepatitis B vaccination in immigrants (children and adults) should be both safe and effective. After arrival in Canada, immigrants have a greater likelihood of exposure to hepatitis B than the Canadian-born population; however, the absolute risk of exposure in a setting with low prevalence of hepatitis B is unknown. The increased risk is due to the higher likelihood of living in households of individuals with chronic hepatitis B infection and increased risk of exposure during travel to countries in which endemic rates of infection with hepatitis B are high (travel to visit friends and relatives).<sup>33-35,55</sup> In a recent study of acute cases of hepatitis B infection in the Netherlands, 67% (18/27) of cases were acquired while travelling to countries in which hepatitis B is endemic; all occurred in immigrant travellers visiting friends and relatives (adults and children, age range 2–67 years). The modes of transmission in these cases were through sexual contact, through unsafe medical practices (circumcision and injections) and through inadvertent percutaneous or mucosal contact with blood or infectious fluids

(nonsexual person-to-person contact, i.e., sharing razors, sharing toothbrushes, biting).<sup>55</sup>

#### *Prevaccination screening for prior immunity*

Fifty percent to 80% of adults from countries in which hepatitis B is highly endemic (HBsAg ≥ 8%) and 20%–30% of adults from countries in which hepatitis B is moderately endemic (HBsAg 2%–7%) will have serologic evidence of prior infection with (immunity to) hepatitis B (Table 1). Several cost-effectiveness studies have shown that the “breakpoint seroprevalence” of prior hepatitis B infection, above which prevaccination screening for prior immunity is worth doing, ranges from 17% to 35%.<sup>56-58</sup> It would, therefore, likely be cost-effective to do prevaccination screening for prior infection among adult immigrants originating from countries that are moderately to highly endemic for Hepatitis B. Two studies of refugee children with mean ages of 7 and 10 from several different world regions (Africa, former Soviet Union and Yugoslavia, Asia) had a HBsAg seroprevalence of 6.5% and 4% and prior infection of 30% and 21%, respectively.<sup>59,60</sup> Although these data might not be representative of all immigrants' children, they suggest that it would also be cost-effective to do

serologic testing for prior infection before vaccinating children.

## Clinical considerations

### *Are immigrants screened for hepatitis B?*

All immigrants undergo a preimmigration medical examination, but screening for chronic hepatitis B infection is not performed and hepatitis B vaccination is not given during this assessment. No programs systematically screen for chronic hepatitis B infection nor are there systematic targeted or catch-up hepatitis B vaccination programs outside of the childhood vaccination program for the immigrant population after arrival in Canada.<sup>5</sup>

### *What are the potential implementation issues?*

Studies in several immigrant populations have shown that they have relatively little knowledge (40%–60%) of the importance of hepatitis B infection and its long-term consequences. Low proportions (< 50%) of at-risk immigrants have been screened for hepatitis B.<sup>61-71</sup> Similarly, low proportions of immigrants are vaccinated (24%–76%) against hepatitis B, and rates are lower in adults than in children.<sup>61,64,70,72</sup> Immunization rates can be enhanced by reducing language and cultural barriers, educating immigrant and refugee populations, and improving social supports for using reminder and recall interventions (these being most effective but also most costly).<sup>25,63,73-75</sup> These barriers and limitations need to be considered in order to improve uptake of screening and vaccination programs among immigrants. In general, when provided with the proper education and access, immigrants and refugees seem to accept vaccines with very little “anti-vaccination” sentiment.<sup>72,75-77</sup> No data on how acceptance and compliance rates differ between cultures are available for hepatitis B treatment. Cultural and language barriers might need to be overcome to optimize the clinical impact of antiviral therapy and to minimize drug-resistant hepatitis B mutants.

## Other recommendations

### *Screening for chronic hepatitis B infection*

All pregnant women are screened for chronic hepatitis B infection in Canada and the US to prevent transmission to their neonates.<sup>14,15,23,28</sup> The US Centers for Disease Control and Prevention have also recently recommended screening all immigrants originating from countries in which hepatitis B is endemic (HBsAg  $\geq$  2%).<sup>16</sup>

### *Vaccinating with hepatitis B vaccine*

Hepatitis B vaccination is routinely given to all children (age differs from province to province) as part of the national immunization program in Canada. There are no routine catch-up vaccination programs for immigrants; however, it is recommended that children younger than 7 years whose families have immigrated to Canada from areas where prevalence of hepatitis B is high be targeted for vaccination.<sup>5,28</sup>

## The cases revisited

Ousman is likely to have been infected with hepatitis B since birth or as a young child and was at risk of developing hepatocellular carcinoma at an early age (mean 57 years). If he had been screened for chronic infection with hepatitis B at the time of arrival in Canada, he could have been referred for assessment of the need for treatment and surveillance to prevent death from hepatocellular carcinoma.

Xiu is also likely to have been chronically infected with hepatitis B since infancy. If her two children had not already been infected at birth, they would have had a 1%–2% annual risk of acquiring hepatitis B infection, with a 6% risk of developing chronic hepatitis B and the associated risk of chronic liver disease and hepatocellular carcinoma, as a result of being exposed to a household member with undetected chronic infection with hepatitis B. These risks could have been avoided if, at the time of arrival, the family had been screened for hepatitis B infection and prior immunity and if those found to be susceptible had been given hepatitis B vaccine.

## Conclusion and research needs

Immigrant populations have an increased burden of chronic infection with hepatitis B and would benefit from screening for this infection with targeted treatment and vaccination for those found to be susceptible. A seroprevalence of 2% has arbitrarily been chosen as when to screen for chronic hepatitis B in this population; however, the actual seroprevalence of HBsAg at which it is cost-effective to screen and treat is yet to be determined. We have recommended screening all individuals originating from countries with a seroprevalence of chronic hepatitis B of  $>2\%$ , for prior immunity to hepatitis B and vaccinating those found to be susceptible. The cost-effectiveness however, of vaccinating all adult immigrants who have a low risk of developing chronic infection with hepatitis B if they acquire acute hepatitis B after arrival, is unknown. Detecting all those chronically infected with hepatitis B and vaccinating those who are susceptible would ensure

the control of chronic infection with hepatitis B in Canada.

## Key points

- Newly arrived immigrants and refugees have a prevalence of chronic hepatitis B infection of about 4% as compared with 0.5% in the Canadian-born population.
- Immigrants have increased mortality from chronic and viral hepatitis and hepatocellular carcinoma than the Canadian-born population, likely primarily because of increased prevalence of undetected and untreated chronic hepatitis B infection.
- Immigrants would benefit from screening for chronic hepatitis B.
- Immigrants would benefit from hepatitis B vaccination.

### Box 2: Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org))

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and could change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

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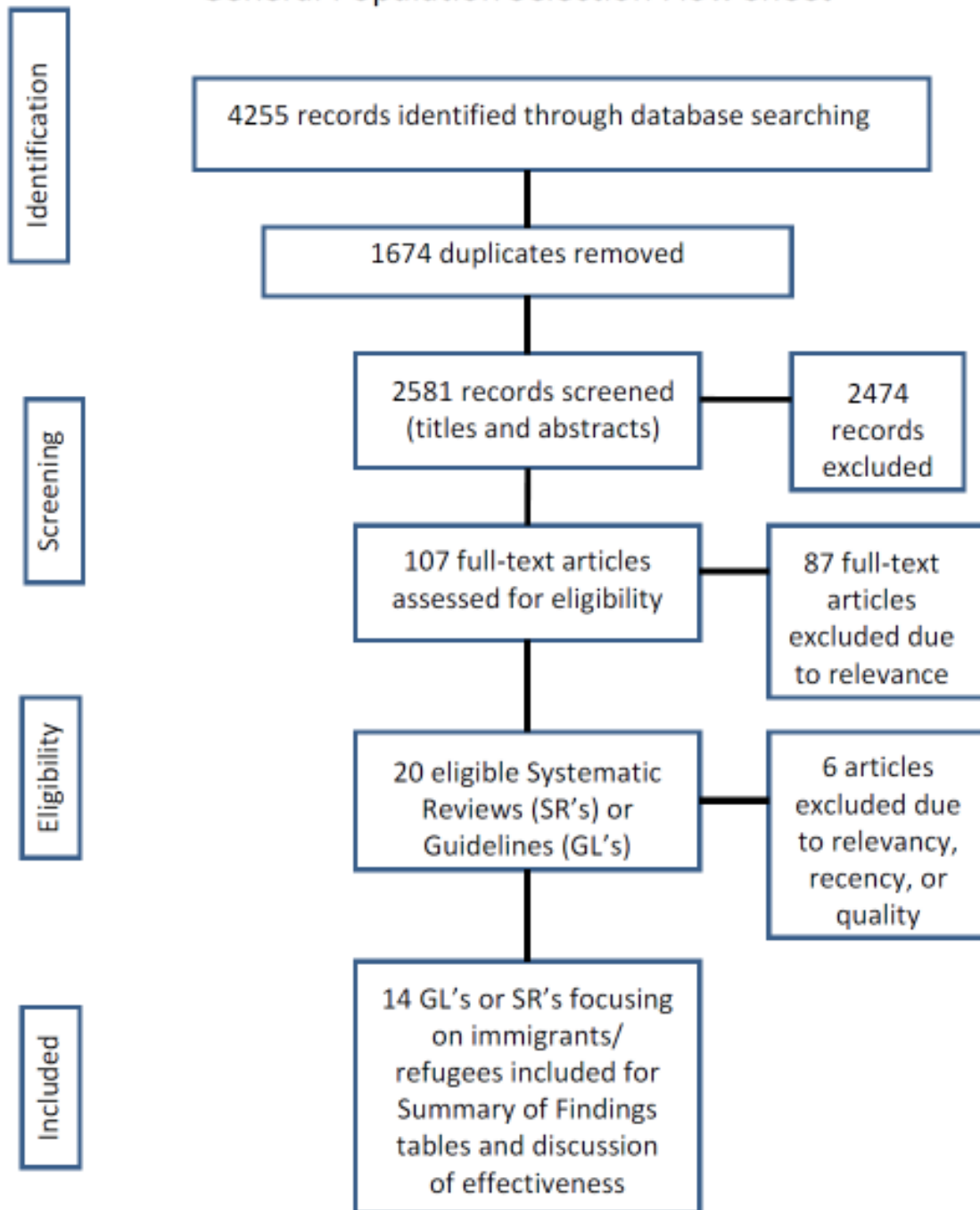
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#### Clinical preventive guidelines for newly arrived immigrants and refugees

This document provides the review details for the CMAJ CCIHR Hepatitis B paper. The series was developed by the Canadian Collaboration for Immigrant and Refugee Health and published at [www.cmaj.ca](http://www.cmaj.ca).

Appendix 1: Figure 1

Figure 1: Hepatitis B Search for Systematic Reviews and Guidelines in the Immigrant/Refugee Population or General Population Selection Flow Sheet



## Appendix 2: Hepatitis B Evidence Based Clinician Summary Table

### ***Screening for Chronic Hepatitis B Infection***

Screen adults and children from countries where chronic hepatitis B virus infection is moderate or high, i.e.  $\geq 2\%$  (HBsAg positive), to decrease disease severity, to possibly reduce incidence of hepatocellular carcinoma, and to decrease transmission of hepatitis B infection. In those found to have chronic infection with hepatitis B, refer for evaluation and assessment of the need for treatment and screen risk groups for hepatocellular carcinoma. Lifelong monitoring is required.

### ***Hepatitis B Vaccination***

Screen adults and children from countries where chronic hepatitis B virus infection is moderate or high, i.e.  $\geq 2\%$  (HBsAg positive) for prior immunity to hepatitis B (hepatitis B core antibody [anti-HBc], hepatitis B surface antibody [anti-HBs]) and vaccinate those found to be susceptible (negative for all three markers of hepatitis B surface antigen, anti-HBc and anti-HBs) to decrease transmission of and morbidity and mortality from acute and chronic hepatitis B.

***Prevalence:*** Canada is a low hepatitis B endemic country with an overall seroprevalence of chronic HBV infection of  $<0.5\%$ . Over the past 40 years, the majority of immigrants ( $>70\%$  of 250,000/yr) that have arrived in Canada have originated from intermediate or high hepatitis B endemic countries and have an overall seroprevalence of chronic HBV infection of  $4\%$ .

***Burden:*** Immigrant populations have increased mortality from chronic viral hepatitis and hepatocellular carcinoma as compared to the Canadian born population likely primarily due to undetected and untreated chronic hepatitis B infection. Immigrants are more likely to be chronically infected with hepatitis B ( $3\%$  vs  $0.5\%$ ) as compared to the Canadian population. Young children living in a household with someone with chronic hepatitis B have rates of acquiring new infection of  $1-2\%$  per year during the first decade of life.

***Access to Care:*** Immunization rates may be enhanced by reducing language and cultural barriers, educating immigrant/refugee populations, improving social supports for using reminder and recall interventions (these being the most effective but also the most costly). Cultural and language barriers may need to be overcome to optimize the clinical impact of antiviral therapy and diminish the emergence of drug resistant HBV mutants.

***Key Risk Factors for Hepatitis B:*** After arrival in Canada, immigrants are likely to be at greater likelihood of exposure to HBV as compared to the Canadian-born population; however, the absolute risk of exposure in a low HBV setting is unknown. The increased risk is due to the increased likelihood of living in the household of a person with chronic HBV infection and increased risk of exposure during travel to high hepatitis B endemic countries (travel to visit friends and relatives- VFR).

***Screening Test:*** Serologic tests to detect hepatitis B are inexpensive, and are sensitive and specific. The most frequently-used serologic markers to differentiate acute, resolving and chronic infection are HBsAg, anti-HBc and anti-HBs. Anti-HBc is a useful marker in the diagnosis of HBV infection as it appears during the course of acute infection and usually persists for life either in the presence of chronic (also HBsAg positive) or in resolved infection with or without the presence of concomitant anti-HBs.

***Screening for Hepatocellular carcinoma:*** Certain individuals with chronic hepatitis B are at increased risk to develop hepatocellular carcinoma (those with cirrhosis, Asian men  $>40$  years of age, Asian women  $>50$  years of age, Africans  $> 20$  years of age, and those with a family history of hepatocellular carcinoma) would benefit from ultrasounds and alpha-fetoprotein (aFP) serologic testing every 6 months to detect hepatocellular carcinoma at an earlier stage when it is more amenable to therapeutic intervention.

***Treatment:*** Lamivudine in patients with advanced liver disease and high level viral replication decreased the risk of developing progressive liver failure and the risk of developing hepatocellular carcinoma. Other more potent antiviral medications have become available in the past few years. Treatment of chronic hepatitis B is a rapidly evolving and

complex area and the decision of who should be treated, when to initiate therapy and with which medication should be made by individuals with expertise in this area.

***Vaccination:*** Immigrants would benefit from hepatitis B vaccination as a large proportion are susceptible to hepatitis B (20-80%) and they are at increased risk of exposure to hepatitis B in their households and during travel to hepatitis B endemic countries.