Should Hepatitis B Screening Be Added to the United States Immigration Medical Exam? A Cost-Utility Model

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science
Health Policy, Management and Evaluation
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Abstract

Hepatitis B virus (HBV) infection is a global leading cause of death as a result of its role in the development of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). In industrialized nations such as the United States, chronic hepatitis B infection represents a significant and disproportionate disease burden among the foreign-born population. A Markov cohort decision model was developed to determine the cost-effectiveness of HBV screening among new immigrants for the purposes of early detection and treatment, as compared to usual care. The incremental cost-effectiveness ratio for the screening strategy was $45,570 per quality-adjusted life year saved. Given the potential for health gains for the immigrant cohort as well as the economic attractiveness of the intervention, some consideration should be given to the addition of a universal HBV screening program to U.S. immigration policy.
Acknowledgments

I would like to thank Dr. Hoch and Dr. Khan for supervision and guidance, as well as the University of Toronto and CIHR for grant support.

I also wish to acknowledge input from Dr. Audrey Laporte, Dr. Jenny Heathcote, and Kednapa Thavorn, as well as assistance from Jean Yong, Ying Di and Jun Wang.
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Chapter 1
Background and Literature Review

1.1 Introduction

Hepatitis B virus (HBV) infection represents a significant global disease burden, estimated to affect two billion people worldwide, with more than 350 million people chronically infected (Lavanchy 2004). Within industrialized nations, the prevalence of infection is low and levels of transmission are on the decline as a result of effective universal vaccination programs; since a safe and effective vaccine and associated universal vaccination strategy was introduced to the United States in 1982, incidence of acute cases of hepatitis B has fallen from over 11.5 to 1.6 per 100,000 in 2006 in the general population (Weinbaum et al. 2008). While incidence of new cases has dropped dramatically in the past few decades, this has not translated to equally diminished prevalence or disease burden, and the country has actually experienced increases in health care utilization, liver transplant waitlist registrations, and mortality from HBV infection (Kim 2009). The recent rise in globalization and population mobility has introduced a new disease burden concentrated among select groups that often differ markedly from the general population (Gushulak and MacPherson 2000). The influx of new immigrants means that chronic illnesses such as chronic hepatitis B continue to exert considerable financial strain and consume significant resources even if transmission is limited among the general population.

Management of hepatitis B is debated, and there are a number of guidelines updated annually from such organizations as the American Association for the Study of Liver Diseases (AASLD), the Centre for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and the European Association for the Study of the Liver (EASL) to keep up with new treatment options and an expanded knowledge base (Lok and McMahon 2009; Weinbaum et al. 2008; Sorrell et al. 2009; The EASL Jury 2009). The main focus of the body of hepatitis B research is on treatment options and disease sequelae. However, a major factor that impacts the value of this information is detection of illness. The majority of the time, chronic hepatitis B is a silent infection, asymptomatic until irreparable liver damage has occurred or cancer has developed. It is vital that the affected population be identified in order to benefit from rapidly improving treatment and management options (Lok and McMahon 2009). Current guidelines have recently been updated to recommend screening in all high-risk groups, most notably the foreign-born
population from regions where HBV prevalence is intermediate or high (>2%) (Weinbaum et al. 2008; Sorrell et al. 2009). Regions with intermediate or high HBV prevalence include all of Asia and the Pacific Islands, Africa, much of Eastern Europe, the Middle East, and parts of the Caribbean and South America (Weinbaum et al. 2008). However, screening practices are not universally implemented by health departments and community centres or at the provider level. This raises the question as to whether it would be worthwhile to screen all individuals entering the U.S. from these areas of the world for HBV infection during the immigration process, upstream of current screening practices, in order to identify and manage chronic HBV infection effectively in the foreign-born population. This paper considers the possibility of introducing HBV screening to the immigration medical exam, in order to address high-risk populations at their point of entry to the country, through the study of the cost and health outcomes associated with such a screening intervention. More specifically, it considers whether upfront screening and treatment costs associated with a mass-screening program would be outweighed by the long-term gains in health outcomes and reduction in costly long-term disease complications of the chronic disease, for both the entering cohort and the health care system in the United States. In order to address this question, this thesis reviews the HBV infection literature and conducts an economic analysis of such a screening program.

1.2 HBV Infection

1.2.1 Background on HBV infection

HBV infection is a global leading cause of death as a result of its role in the development of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). In the United States, it is estimated that over 1.25 million residents (0.4% of the population) are chronically infected with HBV, of which 47-70% were born outside the U.S. (Sorrell et al. 2009). An estimated 4,000 patients die each year from complications and cost upwards of $1 billion annually in hospitalizations alone (Kim 2009). The public health burden of the illness is almost entirely a result of the long-term effects on liver function (Sorrell et al. 2009).

HBV is transmitted through exchange of blood and bodily fluids, most commonly perinatally (from mother to newborn) in developing regions of the world, and also horizontally through sexual intercourse, sharing of needles or even sharing of toothbrushes or razors within households (Lavanchy 2004). Acute illness may present with jaundice, fatigue, nausea or
abdominal pain, which may last up to six months before the infection clears. However, a proportion of individuals will not be able to clear the infection and will subsequently develop chronic hepatitis B. Chronically HBV infected individuals become lifetime carriers of the virus and can transmit the virus to babies and sexual and household contacts that have not been vaccinated (Weinbaum et al. 2008). The risk of chronic infection is inversely proportional to the age at infection; over 90% of affected infants will develop chronic infection, while the risk is only 5-10% among adults (Lok 2002). Thus, the majority of morbidity and mortality from cirrhosis and liver cancer related to CHB is concentrated among those who acquire HBV infection at the youngest age (Keeffe et al. 2008). Perinatal transmission is believed to be the major route by which infection is perpetuated in regions of high prevalence, leading to a disproportionate burden of chronic infection among endemic populations (Fattovich 2003). Clinical signs or symptoms of acute illness do not frequently accompany infection at a young age, and the infected individual is often unaware of their disease condition until clinically apparent liver damage develops (Stevens et al. 1975).

1.2.2 Natural history

The clinical course of chronic HBV infection is highly variable and dependent on the complex interaction of virus, hepatocyte and host immune response (Keeffe et al. 2008). The disease has four distinct phases, which patients typically pass sequentially through, although the path can vary. The initial stage, known as immune tolerance, is characterized by high levels of viral replication, but with minimal inflammation or injury to the liver. Among those infected at birth or in early childhood, the disease typically remains asymptomatic in this stage for the first few decades of life, whereas those infected in adulthood remain in this phase for much shorter periods (Fattovich 2003). In this stage, the immune system does not appear to actively fight the infection (Shepherd et al. 2006). The second stage of chronic HBV infection is referred to as immune active, where the host immune system appears to activate and attempts to clear infected hepatocytes. In addition to detectable HBV DNA in serum, there is elevation of liver enzymes in the blood, suggesting liver inflammation and possible fibrosis (scarring). In this stage, there is greater risk of disease progression and liver damage, particularly with prolonged duration or acute flares of inflammation (Chen et al. 2009). The transition to the third stage is marked by clearance of hepatitis B e antigen (HBeAg), and often seroconversion to anti-HBe-positive status, which is accompanied by a reduction in viral load to low or undetectable levels,
normalization of liver enzymes in serum, and reduced liver inflammation. Seroconversion occurs spontaneously among carriers with elevated alanine aminotransferase (ALT) levels at an average annual rate of 8-12% (Lok and McMahon 2009). This phase, known as the inactive carrier state, is associated with an improved prognosis and remission of liver injury. However, it has been suggested that those infected at birth may continue to experience disease progression in the inactive state (Shepherd et al. 2006; Sorrell et al. 2009).

It is often described that patients without HBeAg have improved outcomes, which refers to the initial loss of HBeAg from a patient in the immune active state and transition to inactive or non-replicative state; it is well known that inactive carriers have lower rates of disease progression than those with chronic active hepatitis, regardless of HBeAg status (Taylor et al. 2009). When HBeAg loss, along with ALT normalization and reduction of viral load, is sustained, it is associated with excellent long-term prognosis. However, carriers may also experience a reactivation of disease following HBeAg seroconversion, progressing into HBeAg-negative chronic hepatitis B. This is marked by a reappearance of HBV DNA replication and ALT levels in serum and is associated with progression of disease and necro-inflammation on histology (Fattovich 2003). Reactivation can happen directly from the immune active state in a small proportion (1-5%) of patients, after which it occurs at a rate of 3% annually, such that up to 30% of inactive carriers will subsequently experience reactivated infection (Shepherd et al. 2006; Chu and Liaw 2009). The reactivated state is a later and more advanced stage in disease progression, occurs in patients of older age, and occurs more frequently in males (Fattovich 2003).

About 0.5% of chronically infected persons will spontaneously resolve their illness annually (by loss of hepatitis B surface antigen and development of antibodies to HBsAg), which has a benign prognosis unless cirrhosis has already developed (Weinbaum et al. 2008; Fattovich 2003). All of these stages tend to be clinically asymptomatic and have minimal impact on quality of life (Shepherd et al. 2006).

1.2.3 Disease sequelae

Patients with chronic hepatitis B are at increased risk of developing cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC). It is estimated that 25-35% of chronically infected patients will die of liver complications (Feld et al. 2009). These disease complications can take decades to develop, but are associated with considerable morbidity and mortality.
Disease complications occur more frequently in males than females, and among those who have experienced a longer period of active liver inflammation.

Hepatitis B is the leading cause of cirrhosis worldwide (Kanwal et al. 2006). Among those with chronic active hepatitis who develop cirrhosis, the five-year survival rate is approximately 55% (Weissberg et al. 1984). Liver cirrhosis, or permanent scarring of liver tissue, is the end stage of the natural history of chronic HBV infection. As it initially develops, the remaining liver tissue will compensate for the reduced function, and the injury will often remain asymptomatic or present as non-specific symptoms, such as fatigue or mild discomfort (Liang 2009). Decompensation of liver function and liver failure can occur with the development of ascites, portal hypertension, encephalopathy, jaundice, peripheral edema or gastrointestinal bleeding, or a combination. Five-year survival for patients with decompensation of the liver is only 14% (Fontana 2003). Patients are also at risk of acute exacerbations of hepatitis, known as flares. These reflect immune-mediated lysis of infected hepatocytes and are especially dangerous in end-stage liver disease because of the risk of fulminant liver failure and death (Fattovich 2003).

Patients with hepatitis B are 100 times more likely to develop liver cancer than matched uninfected individuals (Fattovich 2003). HBV infection accounts for over 50% of cases of hepatocellular carcinoma around the world (Heathcote 2008). The risk for liver cancer and subsequent mortality are increased dramatically with the presence of cirrhosis, high viral load, older age and male gender (Taylor et al. 2009). However, hepatitis B-related HCC can develop in the absence of cirrhosis, and there is some risk associated with all stages of HBV infection, including the inactive carrier state (Fattovich 2003; Bruix and Sherman 2005). HBV-related HCC has an extremely poor prognosis, with median survival less than 16 months (Nguyen et al. 2009). The incidence and mortality from HCC is increasing in the U.S. despite the decline in incidence of HBV infection and overall decline in cancer deaths, and this is likely due to the long latency period in the development of HBV-related HCC among the pool of those infected prior to the implementation of vaccination programs (Nguyen et al. 2009). It is believed that the HBV-related HCC incidence will continue to rise over the next two decades due to this prolonged latency of HCC in the unvaccinated cohort (Nguyen et al. 2009).
1.2.4 Biomarkers of disease and disease progression

A number of viral antigens and their antibodies are associated with HBV infection. Chronic hepatitis B is marked by persistent presence of hepatitis B surface antigen (HBsAg) in serum for greater than 6 months. Its presence in serum is indicative of viral replication occurring in the liver (Weinbaum et al. 2008). Those who have been acutely exposed to the hepatitis B virus and resolved illness, as well as those vaccinated against HBV will have developed antibodies (anti-HBs) to the surface antigen. Presence of anti-HBs is indicative of immunity against HBV and recovery from infection.

Early stages of infection are characterized by the presence of HBeAg, along with high viral replication and infectivity (Liang 2009). HBeAg will often persist in high titres for years in perinatally acquired infections, resulting in prolonged immune tolerant and immune active phases. HBeAg will clear over time in a majority of CHB patients, either spontaneously or through treatment, accompanied by a marked reduction in disease activity, viral load, and histological improvement over time. Sustained remission is observed in up to 60% of patients, whereas the rest will continue to experience viral replication despite the presence of anti-HBe.

Antibody to hepatitis B core antigen, anti-HBc, appears at the start of infection and persists in the majority of persons for life (Weinbaum et al. 2008). It can be used to distinguish between acute infection and chronic infection. Immunoglobulin M class (IgM) anti-HBc is associated with acute infection and will be replaced by immunoglobulin G (IgG) class during chronic infection (Weinbaum et al. 2008).

Serum HBV DNA concentrations are highly correlated with levels of total intracellular HBV DNA, and reflect level of hepatocellular viral replication. High viral loads are excellent predictors for disease progression. It has been observed in several prospective cohort studies that high viral loads are associated with cirrhosis and HCC, and the relative risk can be as high as 60 for high vs. undetectable levels (Chen et al. 2006; Wursthorn et al. 2008). During HBeAg-positive active hepatitis, viral loads are commonly above $10^5$ copies /ml. During reactivated CHB, lower levels are still considered high risk, above $10^4$ copies/ml. Suppression of viral load is one of the main targets of pharmaceutical drug therapy.
Hepatocellular injury is mediated by host immune response to viral antigens on infected hepatocyte cells (Wursthorn et al. 2008). Indications of the immune response include serum levels of liver enzymes alanine and aspartate aminotransferases (ALT and AST, respectively). ALT and AST are elevated consistently or intermittently when active (>1.5 ULN) and are commonly associated with disease progression. However, particularly in reactivated CHB, disease activity can occur while ALT levels are normal, and on their own, aminotransferase levels are not reliable indicators for disease severity (Feld et al. 2009).

There are eight distinguishable genotypes, from A to H, that differ in geographical distribution (Wursthorn et al. 2008). Among Asians, genotypes B and C are most prevalent, while Alaskans have a distribution of A, B, D and F. It is believed that the genotype has an influence on the natural history of the disease, with certain genotypes being associated with more rapid or progressive illness (McMahon 2009). However, these data are preliminary, and the role of genotype in the natural history and in clinical management requires further research. Genotypes are currently not typically determined outside of academic or clinical settings (Smith and Bruno 2008; Rotman et al. 2009). Genotypic differences in natural history and treatment response are beyond the scope of the model presented in this paper.

Finally, there are several mutant DNA variants that persist, most notably those in pre-core and core promoter regions that produce an HBeAg-negative form of CHB and those that confer drug resistance. HBeAg-negative CHB is derived from naturally-occurring variant HBV strains carrying mutations that limit or prevent production of HBeAg, which may develop during seroconversion or at an earlier stage (Shepherd et al. 2006; Fontana 2009). They are rarely tested for outside of academic settings, as they do not provide independent prognostic information (Fontana 2009). Drug-resistant mutations are often selected for with the use of pharmaceuticals, and can be inferred with the re-emergence of high viral loads.

### 1.3 Management of HBV Infection

#### 1.3.1 Clinical considerations

The identification of a chronic carrier is essential to proper disease management and offers the best chance for survival from long-term disease sequelae. Chronic carriers, regardless of disease state, require lifetime monitoring with a liver specialist to assess damage to the liver, eligibility
for drug intervention, and progression to serious conditions such as hepatocellular carcinoma (Weinbaum et al. 2008).

The initial evaluation of a patient should attempt to establish the stage and severity of illness in relation to the known natural history of the disease. An initial visit to a hepatologist would include a medical history and focused physical examination, as well as blood tests including a complete liver panel (alanine and aspartate aminotransferases, alkaline phosphatase, albumin, bilirubin, prothrombin time) and white blood cell count, measurement of HBV viral load, antigens and antibodies (HBsAg, anti-HBs, HBeAg, anti-HBe, total anti-HBc). Subsequent monitoring, particularly of ALT and AST levels, would be used to assess the progression of liver damage, and should occur 6 months to annually, depending on the disease state of the individual. In addition, screening for HCC is typically done with assessment of alpha-fetoprotein (AFP) as well as abdominal ultrasonography, particularly among Asians over 40 years old and patients with cirrhosis (Rotman et al. 2009).

Persistently or intermittently elevated levels of the marker ALT, and active replication of HBV DNA (above $10^5$ copies/ml for HBeAg-positive and above $10^4$ copies/ml for HBeAg-negative CHB) can prompt imaging with an abdominal ultrasound, or infrequently, a biopsy of the liver. Liver biopsy is the gold standard for assessing necro-inflammatory activity (grade) and degree of fibrosis (stage), but its role in the management of a patient is controversial, particularly due to its invasive nature, small sample of overall liver histology and lack of definitive indication for its use (Fontana 2009; Rotman et al. 2009). Even most large clinical trials are unable to collect biopsy results from all participants and will rely on ultrasound results to detect cirrhosis (Taylor et al. 2009). Laboratory results may also be used as noninvasive biomarkers that might suggest advanced disease. Low albumin, prolonged prothrombin time, and increased bilirubin are evidence of hepatic decompensation, and persistently elevated levels of AFP are associated with HCC (Rotman et al. 2009).

Patients infected with HBV can be co-infected with hepatitis C, hepatitis D, or human immunodeficiency virus, as they are associated with shared modes of transmission typically seen in adult-acquired infections (Shepherd et al. 2006). These patients are likely to experience more severe liver disease and more rapid progression, and as such they require special management (Fattovich 2003). These complications are beyond the scope of the model presented in this paper.
1.3.2 Treatment options

Therapy is indicated for patients with evidence of active liver inflammation, advanced fibrosis and cirrhosis. Pharmaceutical therapy is prescribed to suppress viral load and minimize or delay the onset and progression of complications (Shamliyan et al. 2009). While there is no one ideal biomarker for therapy, surrogate biochemical, virologic, serologic and histologic markers are examined in combination to assess treatment effect (Feld et al. 2009). The goal in therapy also varies depending HBeAg status. For HBeAg-positive patients, the serological endpoint is HBeAg seroconversion, after which treatment is continued for 6-12 months of consolidation to produce a sustained serologic response. For HBeAg-negative patients, treatment goals are less clear but focus on suppression of viral load.

Pharmaceutical therapy is a rapidly changing area of clinical practice. A large body of research exists to assess treatment options alone or in combination, as well as a number of consensus statements elucidating guidelines and treatment algorithms to help identify which patients should be treated, with which treatments, for how long, and with monitoring of which serological outcomes (Rajendra and Wong 2007; Weinbaum et al. 2008; Keeffe et al. 2008; Sorrell et al. 2009). Despite these rigorous research initiatives and international focus on the management of CHB patients, to date there exists no clearly optimal treatment option or therapeutic course (Sorrell et al. 2009; Shamliyan et al. 2009). Treatment decisions are highly complex, made on the basis of HBeAg status, HBV DNA viral load, ALT, stage of liver disease, age of patient and other factors (Weinbaum et al. 2008). The AASLD and EASL recommend treatment be administered when ALT concentrations are greater than 1.5 times the upper limit of normal (ULN) (30 IU/L) and HBV DNA concentrations are high (>10^4 copies/ml) (Lok and McMahon 2009; The EASL jury 2009).

Currently, seven treatment options approved by the FDA include subcutaneously injected interferons (interferon alfa-2b and pegylated interferon alfa-2a) and orally administered nucleoside and nucleotide analogues lamivudine, adefovir dipoxil, entecavir, tenofovir disoproxil fumarate and telbivudine (Weinbaum et al. 2008). These drugs vary in their usage, effectiveness, resistance profiles, and side effects.
1.3.2.1 Interferons

Interferons are administered by injection for a finite duration of 16 to 48 weeks. They have dual action, both immunomodulatory and antiviral activity, and the response to treatment is sustained in 90% of HBeAg-positive patients after 4-6 months of treatment 3 times weekly (Lavanchy 2004). The pegylated derivative requires fewer injections and is associated with more sustained response compared to interferon-alfa and early nucleoside analogues (Shepherd et al. 2006). They are most efficacious in HBeAg-positive, immune active patients. However, interferon-based therapies are poorly tolerated and associated with systemic side effects, such as headache, nausea, flu-like symptoms, depression, and some hematological abnormalities, and cannot be tolerated in the long term (Shepherd et al. 2006; Sorrell et al. 2009). According to meta-analysis, dose modifications were required for nearly 50% of patients as a result of adverse effects, and withdrawal from studies was 24% higher than with no treatment (Shamliyan et al. 2009). The use of interferon is also limited by cost, inconvenience, and risk of liver failure due to hepatic flare in cirrhotic patients.

1.3.2.2 Nucleos(t)ide analogues

Nucleoside and nucleotide analogues are oral agents taken daily, often for long-term maintenance therapy (Shepherd et al. 2006). They are associated with more profound HBV DNA suppression than interferons and fewer systemic side effects. However, pre-mature discontinuation is associated with a resurgence of HBV DNA levels and severe rebound of disease, and there is risk of development of resistance, as well as renal toxicity, myopathy and mitochondrial toxicity in a small number of patients (Sorrell et al. 2009). HBeAg-negative patients rarely experience sustained remission off therapy and must be continued on oral antivirals indefinitely (Gish 2008).

Introduced in 1998, lamivudine was the first oral antiviral therapy approved for use against HBV infection. It has since been a viable treatment option for chronic hepatitis B because it is effective, easy to administer and well tolerated (Lok 2002). However, long-term usage is associated with virological breakthrough through the emergence of lamivudine-resistant mutations in up to 70% of patients after 5 years (Shepherd et al. 2006). It may still be used once resistance is established, for a minimal treatment effect, or replaced with salvage therapy with newer antiviral agents (Shepherd et al. 2006). It is no longer recommended as first-line therapy,
though still prescribed in a significant minority of patients because of its low cost (Nguyen and Keeffe 2009).

More recently, adefovir was used both as salvage therapy and in monotherapy, as it has improved efficacy as an antiviral for both HBeAg-positive and –negative patients, as well as a lower resistance profile than lamivudine. Cumulatively, however, it exhibits 30% resistance after 5 years (Nguyen and Keeffe 2009). Telbivudine is a more potent, but structurally similar drug to lamivudine. It is associated with high rates of resistance after the first year of therapy and as a result, the AASLD recommends that it not be used as monotherapy (Lok and McMahon 2009). The recommended first-line, most efficacious therapies available are entecavir and tenofovir (Keeffe et al. 2008). Clinical trials show that these new classes of drugs demonstrate much lower resistance profiles and greater potency as antivirals. The first trials demonstrating long-term effects show 1-2% cumulative resistance rates over 5 years for entecavir in treatment-naïve patients, and negligible resistance profiles for tenofovir (Tenney et al. 2009; Nguyen and Keeffe 2009). Economic analyses demonstrate that the newest antivirals are likely to be both more costly and more effective for CHB patients, and that cost-effectiveness estimates tend to be favourable from third-party payer perspectives (Spackman and Veenstra 2008; Veenstra et al. 2007; Yuan et al. 2008).

### 1.3.3 Management of disease sequelae

Treatment is indicated for patients experiencing cirrhosis and rapid deterioration of liver function. Though there are limited clinical trials in these patient populations, clinical experience supports a reduction in adverse outcomes with the use of antiviral therapy (Sorrell et al. 2009). Decision analyses have shown that antivirals are particularly cost-effective for the treatment of patients with disease complications, as opposed to less advanced HBV infection, and that newer antivirals are favoured despite their added costs in light of their potency and lower resistance profiles (Kanwal et al. 2006). Treatment options for patients with decompensated cirrhosis are limited to nucleoside analogues, because interferons are contraindicated due to risk of fatal exacerbations of liver damage.

Regular screening for HCC with AFP and ultrasonography is widely practiced and for high-risk groups, and there is recent evidence that routine screening of is a cost-effective and beneficial strategy (Bruix and Sherman 2005; Thompson Coon et al. 2007). Historical detection of HCC
after the onset of symptoms is associated with extremely low survival rates (0-10% after 5 years), while due to major advances in treatment options, small tumours detected early can be cured through resection, RFA, ethanol injection or liver transplantation with reasonable success, >50% survival after 5 years (Bruix and Sherman 2005). Prospective screening of high-risk groups, particularly those with HBV-related cirrhosis, allow for the identification of patients eligible for curative treatment and increase chances for long-term survival and mortality from HCC (Thompson Coon et al. 2007; Gannon et al. 2009).

Patients with end-stage liver diseases, including decompensated cirrhosis and HCC, are also eligible for liver transplantation. Historically, patients with HBV-related liver complications have not been prioritized for transplantation due to high rates of graft re-infection post-transplant (Zoulim et al. 2008). With advances in immunosuppression, surgical technique and intensive care, liver transplants have become an effective treatment option for liver failure and HCC, with 5-year survival above 75% (Kim et al. 2004). It is recommended that patients are continued on oral nucleoside antiviral therapy along with hepatitis B immune globulin (HBIG) prophylaxis leading up to and following transplantation to minimize liver injury while on the waitlist and to prevent recurrence of hepatitis in the new transplant (Zoulim et al. 2008).

1.4 Screening in the United States

1.4.1 Rationale for HBsAg screening

Currently, routine screening recommendations from the National Institute of Health, the AALSD, and the CDC for all high-risk groups has been expanded to include individuals originating from regions of both intermediate (2-8%) and high prevalence (>8%). However, this has not been implemented in any universal or mandatory screening program, and thus there is no strategy in place to guarantee adherence to these guidelines. Approximately 45% of all people worldwide live in regions of high prevalence, and a further 43% live in regions of intermediate endemicity (Weinbaum et al. 2008). For example, the lifetime risk of infection in East Asia is over 90% (Shepherd et al. 2006). While the United States is a region of low endemicity itself, it receives over 1 million immigrants annually. Recent data from the U.S. National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of HBV infection among U.S.-born individuals is merely 0.14% of the population, whereas the prevalence is 7 times greater among the foreign-born population (0.97%, 95% CI: 0.64-1.48%). Considering the
elevated risk for chronic infection among endemic regions, there is clearly a concentration of illness among the foreign-born population that must be addressed. In addition, studies of programs conducting testing among Asian-born persons in the United States have suggested one-to two-thirds of infected persons were unaware of their infections (Lin et al. 2007).

Population movements that increase the disease burden in low prevalence countries necessitate active measures to identify, monitor and treat this pool of chronically infected patients (Gushulak and MacPherson 2000; Heathcote 2008). The WHO and public health authorities have established criteria for screening programs (Wilson and Jungner 1968). Among other things, the condition sought must be an important health problem, there should be accepted treatments available, a recognizable latent or early symptomatic stage, a suitable, acceptable and economically feasible test to detect the condition, as well as some understanding and agreement around the natural history and treatment of the condition (Wilson and Jungner 1968). Hepatitis B testing is relatively reliable and inexpensive, and can be established prior to the presentation of symptoms. Its purpose is to identify a serious disease for which patients can gain years of life with early medical intervention, and thus it is deemed that testing for hepatitis B largely meets these established guidelines for screening programs (Weinbaum et al. 2008). The economics of case-finding, including the diagnosis and treatment of patients, remains to be assessed fully.

Identification of infected persons also allows for patient education and primary prevention of HBV transmission. Chronically infected new immigrants can serve as a reservoir for new infections in the United States, and their identification can complement vaccination strategies in order to limit HBV transmission (Weinbaum et al. 2008). The behavioural modifications and added management options that can accompany knowledge of chronic infection, such as limiting alcohol intake, engaging in less risky sexual behaviours, as well as testing and vaccination of susceptible close contacts, are added benefits to a screening program in addition to medical management of the infected individual. It has also been proposed by the CDC that a surveillance registry for case management could be established for chronic HBV infection, as it has been done as part of disease control programs for HIV and TB, as well as for tracking cancers and identifying disease trends and treatment outcomes by public health agencies historically (Weinbaum et al. 2008).
1.4.2 Immigration policy

The Immigration and Nationality Act (2009) and the Public Health Code of Federal Regulations (Scope of Examinations 2003) stipulate the requirements for the medical examination of aliens seeking immigration to the United States. The examination is comprised of a physical examination, serologic tests, chest radiography, mental health assessment, and review of vaccination records, and aims to address serious health-related conditions; in particular, communicable diseases of public health significance and vaccine-preventable diseases.

Currently, hepatitis B is on the Centre for Disease Control and Prevention’s list of nationally notifiable infectious diseases; an infected person must be reported to state public health departments, and the CDC collects data from states for surveillance purposes. However, for the immigration medical exam, only evidence of vaccination to hepatitis B must be provided. Vaccination does not confer any benefit to an individual once they have been infected. Thus, someone who has been infected at birth has a high probability of being a chronic virus carrier regardless of any subsequent vaccination. It may be argued that proof of vaccination is thus not sufficient from a public health standpoint, particularly if those with chronic infection are largely unaware of their status and may in fact believe themselves to be immune as a result of vaccination. Since vaccination status may not be informative among individuals originating in intermediate and high prevalence regions due to the risk of infection prior to their vaccination, it would be practical to test for HBV infection.

1.4.3 Previous studies and economic analysis

No previous studies exist to comprehensively examine the impact to cost or health outcomes for hepatitis B screening among immigrant populations entering the United States. Previous work by Hutton et al. (2007) examined the potential public health options associated with screening, including vaccination efforts and ring vaccination and monitoring of close contacts among Asian and Pacific Islanders in the U.S. and found the screening strategies likely to be cost-effective and produce added life-years for the population. An unpublished study has demonstrated that the cost of a HBV screening program in a population with a 2% prevalence of infection would range from $750 to $3,752 per infection detected, and would be less costly per case identified among populations with higher prevalence (as cited in Weinbaum et al. 2008). The authors reporting this data conceded the difficulty in calculating the cost-effectiveness of a full screening program as a
result of rapidly evolving treatment options that constantly enhance years of disease-free life, at widely variable cost (Weinbaum et al. 2008).

There is a limited availability of evidence-based practice guidelines to direct screening programs (Fowler 1998). Typical clinical trials to assess the benefits or costs associated with screening programs for the purposes of informing immigration policy would not be feasible. There is a trade-off with any screening program between the upfront costs and the downstream reduction in morbidity and mortality. A model-based approach is our best and most practical approach to aid decision-making in this previously unexplored area, as it allows both the long term costs and health outcomes to be compared and provides an overview of evidence for decision-makers to evaluate whether added costs of screening might be worth investing.

1.5 Objectives and Hypothesis

1.5.1 Objectives of study

The objectives of this study are to a) describe the current body of knowledge available on epidemiology, natural history and treatment options in chronic hepatitis B research; b) estimate the cost, health outcomes, and the cost-effectiveness of screening for hepatitis B virus infection among new immigrants to the United States; c) ascertain the effect of key parameters on cost-effectiveness estimates of a screening program, such as prevalence of infection among the targeted population; and d) identify important gaps in knowledge and needs of future research.

1.5.2 Hypothesis

It is hypothesized that the introduction of a mass-screening program for hepatitis B virus infection as part of the immigration medical exam will be cost-effective through identification and management of chronic infection, minimization of disease complications and production of additional years of life for a cohort of new immigrants to the United States.
Chapter 2
Methods

2.1 Overall description

A Markov decision analytic model was developed to project clinical and economic outcomes of screening potential new immigrants for chronic HBV infection from a U.S. health care system perspective. The screening strategy included mandatory testing for hepatitis B surface antigen (HBsAg) for all new immigrants and treatment for individuals with active HBV infection, and the no screening (or usual care) strategy followed individuals with chronic hepatitis B over the natural course of disease progression. Cost-utility analysis and probabilistic sensitivity analysis using Monte Carlo simulations were performed to capture the impact of screening on quality of life, hepatitis B-related disease outcomes and cost over a twenty-year horizon for an immigrant cohort with an elevated risk of CHB.

2.2 Population

A hypothetical cohort of new entrants was established based on the typical influx of new entrants to the United States in any given year (Department of Homeland Security [DHS] 2009). The cohort was assumed to have an average age of 30, in accordance with the approximate average age of immigrants to the U.S. (DHS 2009). Among those testing positive for HBsAg, the population was also assumed to demonstrate no cirrhosis nor clinically evident liver disease, no other comorbidities, nor any infection with other viruses that cause hepatitis. Recent nation-wide data from the National Health and Nutrition Examination Survey (NHANES) collected from 1999-2004 suggest that the prevalence of CHB among foreign-born individuals in the United States is approximately 1%. However, since the prevalence of HBV is higher in many regions from which new entrants immigrate, as well as in additional studies in recent U.S. immigrant populations (Lin et al. 2007; CDC 2006), this value was varied from 0-20% in sensitivity analysis. The population was followed for a period of 20 years, a sufficient time horizon for the development of clinically relevant disease complications, which also balances the diminishing impact of future illness due to time preference, as well as limitations in the forecasting of new pharmaceutical and diagnostic developments.
2.3 Perspective

Direct medical costs to the health care system of the U.S. were examined to assess the cost-effectiveness of a screening program. A societal perspective is not easily applicable in this case. In accordance with the American immigrant policy and health care system, applicants are solely responsible for costs of all required medical tests outside the United States prior to their admission, except in specific instances for refugees and landed immigrants applying for permanent residency (Scope of Examinations 2003). Since costs of screening are borne by applicants prior to their acceptance to the U.S., they may not be included in the U.S. society as usually defined. In addition, the additional cost of the HBsAg screening test is not likely to be prohibitive to applicants because it is minimal in comparison to the cost of the rest of the immigration medical exam and of relocation in general. Since there are numerous governmental and non-governmental perspectives specific to the U.S. health care system, we will adopt a perspective considering all direct medical costs regardless of payer, and we will examine the effects of including the costs of the screening test into the model or excluding them.

2.4 Model structure

A Markov process decision analysis model that compared screening and usual care strategies was constructed with the use of Microsoft Excel spreadsheet software. A Markov decision model assumes that a patient is always in one of a finite number of health states, and events occur each cycle as transitions between these health states (Sonnenberg and Beck 1993). The major health states associated with CHB disease progression are diagrammed in Figure 1. The length per cycle was one year.

The proportion of the immigrant cohort that is HBsAg-positive entered the model in age-appropriate proportions into either the HBeAg-positive active CHB or inactive CHB states. In the no-screening strategy, patients followed the natural history of illness and usual rates of disease progression. Patients could move sequentially through the early stages of CHB, which included active HBeAg-positive, inactive, and active HBeAg-negative CHB states. Patients could also spontaneously recover with loss of HBsAg or could move into disease sequelae, which include cirrhosis (CC) or cancer (HCC).
Only patients in active CHB states were eligible for treatment, in addition to any individuals already in response or on-treatment states. Treated patients in the HBeAg-positive state received one year of consolidation therapy after transition to the inactive state before being removed from treatment, and HBeAg-negative patients were kept on long-term maintenance therapy, in accordance with current guidelines (Lok and McMahon 2009; Sorrell et al. 2009).

Patients could only move backwards in the model if they stopped responding to treatment and returned to the reactivated CHB state from the response state. Patients experienced benefit from treatment by slowing their progression to further disease states. Treatment acted to 1) push patients more rapidly into the inactive state from the active HBeAg-positive state; 2) induce a low replicative state, denoted as ‘response’ among HBeAg-negative active CHB patients, which was associated with similar risk of disease progression as the inactive state; and 3) reduce the risk of decompensation, HCC and death for cirrhotic patients. We estimated this reduction in risk to be 50%, to reflect evidence from a placebo-controlled study that CHB patients with fibrosis or cirrhosis treated for up to five years with the less potent antiviral lamivudine experienced a 50% decrease in disease progression (Liaw et al. 2004). We allowed the value to vary from 0-100% in sensitivity analysis.

End-stage liver disease was assumed to be symptomatic and thus managed the same way in both branches. Complications associated with decompensation, including ascites and encephalopathy, were collapsed into one disease state for simplicity. Patients were unable to move backwards once end-stage disease states developed and could only experience improved outcomes through successful liver transplantation following decompensation or HCC. There was added mortality risk associated with all disease sequelae.
2.5 Major model assumptions

The major model assumptions are outlined below:

- Those infected were infected at birth in their country of origin, since prevalence in the general population of the U.S. is low.

- At the average age of entry, 30 years, the infected cohort will have progressed from immune tolerant stage and have active CHB (i.e., have elevated ALT, actively replicating HBV, increased risk of developing HCC and cirrhosis, and be considered for treatment) unless they have progressed further to inactive CHB.

- Nearly half (45%) of the population will have seroconverted to anti-HBe at the average age of entry and will enter in the inactive carrier state.

- Screening will be universal and mandatory as a part of the immigrant medical exam.
Those who seroconvert to anti-HBe will not move directly into the reactivated state, but we make the conservative estimate that they must spend at least one cycle in the inactive carrier state, nor will they revert back to the HBeAg-positive active state.

Patients who undergo HBsAg seroconversion have normal life expectancy and are considered recovered.

Intermediate biomarkers such as HBeAg seroconversion and HBV DNA suppression are predictive of long-term outcomes of disease progression and mortality.

Antivirals with minimal resistance profiles will be prescribed as first-line therapy. In the future, additional drugs with comparable cost and effects will replace current therapies, particularly in the event of resistance or primary treatment failure.

70% compliance with interventions to recognize that not all persons will be willing to follow up with physicians and complete drug treatment regimens.

Annual probability for voluntary screening and detection is 2%, to compound to 33% over the analytic horizon, in accordance with studies that suggested up to 2/3 of infected immigrants were unaware of their disease status, as well as NHANES data (unpublished) that indicated 15% of HBsAg-positive individuals reporting having a liver condition.

Complications of liver transplantation besides death are not explicitly considered, instead resource utilization and quality of life are incorporated into costs and utility measures for post-transplant patients.

Those who survive liver transplantation do not experience recurrence of HBV infection, accomplished with regimen of antiviral maintenance.

2.6 Outcomes

The main outcome was reported in terms of quality-adjusted life years (QALYs). In addition, we included both discounted and undiscounted estimates of life years, QALYs, and costs. The analysis reports the incremental cost per QALY or life year gained for the screening strategy compared to usual care, as well as simulation results for the cost-effectiveness of screening based on 1,000 simulated trials (see Section 2.8 Sensitivity Analysis for details).
2.7 Data sources

2.7.1 Literature review

The database MEDLINE was searched according to the search strategy for hepatitis B-related studies employed in systematic reviews by the NIHR Health Technology Assessment Program (Shepherd et al. 2006). We included randomized controlled trials of drug effectiveness, retrospective cohort studies for natural history, economic evaluations of treatment and screening interventions, and reviews and guidelines for hepatitis B management. We also reviewed bibliographic references of key papers, particularly of previous economic evaluations and their data sources. We were directed to additional literature through contact with appropriate experts. The grey literature was also evaluated, and key websites, such as the Centre for Disease Control (CDC), Food and Drug Administration (FDA) and the Department of Homeland Security were consulted for technical information.

2.7.2 Probabilities

Disease progression data and annual transition probabilities were derived from a review of the existing literature: previous cost effectiveness analyses and long-term studies of the natural history of CHB (Shepherd et al. 2006; Hutton et al. 2007; Crowley et al. 2000; Wong et al., 1995; Toy et al. 2009; Kanwal et al. 2005; Kanwal et al. 2006; Fattovich 2003; Fattovich et al. 1995; Fattovich et al. 2008; Liaw et al. 1991; de Jongh et al. 1992; Iloeje et al. 2006; Chen et al. 2006; Chu and Liaw 2007; Hsu et al. 2002; Yuen et al. 2001). Data from key economic models were extracted into a spreadsheet and sources were compared. Studies that used or reported markedly differing values were investigated. Wherever possible, original data was used to estimate transition probabilities. Where progression and mortality rates were reported, annual transition probabilities we calculated from the standard formula:

\[ P(t) = 1 - e^{-k \cdot t} \]

where \( t \) is time, \( k \) is the annual rate and \( e \) is the base of the natural logarithm (Miller and Homan 1994). When disease progression differed among population subgroups, the rates associated with Asian populations were chosen to reflect the most common epidemiological characteristics of foreign-born chronically HBV-infected persons in the United States. For probabilistic sensitivity analysis, beta distributions were established for each probability variable using the total sample
size of the original data, or the 95% CI of the probability where summary data were available, in accordance with standard economic modeling guidelines (Briggs et al. 2006). Beta distributions were chosen to reflect the dichotomous nature of decision probabilities and their logical constraint between 0 and 1. Where probabilities were unknown or assumed, uniform distributions were chosen so that any number across the plausible range could be selected at random with equal chance. Relative risk values are often modeled with a lognormal distribution, however, without a 95% confidence interval for our data, we elected to use a conservative approach that the value was unknown and thus, applied a uniform distribution over the entire 0-1 range of possible values. Data are summarized in Table 1.

The prevalence of CHB infection among the immigrant cohort was summarized from foreign-born persons in the National Health and Nutrition Examination Survey (NHANES). We estimated approximately half of the cohort to be HBeAg-negative by their age of entry, in accordance with average annual progression rates for seroconversion from HBeAg-positive to HBeAg-negative, inactive CHB.

In light of the variety of pharmaceutical options available for the treatment of CHB, we chose to focus on the outcomes from the two drugs currently recommended as first-line treatment for both HBeAg-positive and -negative patients, entecavir and tenofovir. It is rationalized that their tolerability for both short- and long-term treatment, limited adverse effects, equal or superior effectiveness and their drastically limited resistance profiles compared to other available options suggest that these drugs will be most likely to be utilized in the present and near future for the treatment of CHB. We estimated the average rate of HBeAg seroconversion as 21% in accordance with the phase three clinical trials for several of the available antivirals for HBeAg-positive individuals, including entecavir and tenofovir (Nguyen and Keeffe 2009). We took a conservative estimate of response rate for HBeAg-negative treated individuals as 70%, although both entecavir and tenofovir suppress viral load in >90% in this population, because the ideal indicator of successful therapy is less clear among HBeAg-negative patients. The minimum improvement in ALT, histology, and HBV DNA suppression among most antivirals is 70% for HBeAg-negative patients (Nguyen and Keeffe 2009). We estimated the average resistance (i.e., patient stops responding to treatment) with a conservative estimate of entecavir’s 5-year resistance profile, since long-term data for tenofovir are not available.
Table 1. Input parameters for Markov model, range for one-way sensitivity, and distribution used for simulation.

<table>
<thead>
<tr>
<th>Annual transition probabilities</th>
<th>Value</th>
<th>Range</th>
<th>Source</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>From HBeAg+ to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>0.040</td>
<td>0 – 0.20</td>
<td>Yuen et al. 2001</td>
<td>Beta</td>
</tr>
<tr>
<td>CC</td>
<td>0.026</td>
<td>0 – 0.20</td>
<td>Iloeje et al. 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>HCC</td>
<td>0.012</td>
<td>0 – 0.20</td>
<td>Chen et al. 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>From Inactive to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactivated</td>
<td>0.011</td>
<td>0 – 0.20</td>
<td>Chu and Liaw 2007</td>
<td>Beta</td>
</tr>
<tr>
<td>CC</td>
<td>0.005</td>
<td>0 – 0.01</td>
<td>Iloeje et al. 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>HCC</td>
<td>0.003</td>
<td>0 – 0.01</td>
<td>Chen et al. 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>HBSAg SC</td>
<td>0.008</td>
<td>0 – 0.10</td>
<td>Liaw et al 1991</td>
<td>Beta</td>
</tr>
<tr>
<td>From Reactivated to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>0.700</td>
<td>0 – 1.00</td>
<td>Nguyen and Keeffe 2009</td>
<td>Beta</td>
</tr>
<tr>
<td>CC</td>
<td>0.026</td>
<td>0 – 0.20</td>
<td>Iloeje et al. 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>HCC</td>
<td>0.011</td>
<td>0 – 0.20</td>
<td>Chen et al. 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>HBSAg SC</td>
<td>0.005</td>
<td>0 – 0.01</td>
<td>Liaw et al 1991</td>
<td>Beta</td>
</tr>
<tr>
<td>From Response to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>0.002</td>
<td>0 – 0.10</td>
<td>Tenney et al. 2009</td>
<td>Beta</td>
</tr>
<tr>
<td>CC</td>
<td>0.005</td>
<td>0 – 0.01</td>
<td>Same as Inactive to CC</td>
<td>Beta</td>
</tr>
<tr>
<td>HCC</td>
<td>0.003</td>
<td>0 – 0.01</td>
<td>Same as Inactive to HCC</td>
<td>Beta</td>
</tr>
<tr>
<td>HBSAg SC</td>
<td>0.008</td>
<td>0 – 0.10</td>
<td>Same as Inactive to SC</td>
<td>Beta</td>
</tr>
<tr>
<td>From CC to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DC</td>
<td>0.052</td>
<td>0 – 0.20</td>
<td>Fattovich et al. 1995</td>
<td>Beta</td>
</tr>
<tr>
<td>HCC</td>
<td>0.036</td>
<td>0 – 0.20</td>
<td>Fattovich 2008</td>
<td>Beta</td>
</tr>
<tr>
<td>Death</td>
<td>0.029</td>
<td>0 – 0.20</td>
<td>Fattovich 2008</td>
<td>Beta</td>
</tr>
<tr>
<td>From HCC to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.036</td>
<td>0 – 0.20</td>
<td>Same as CC to HCC</td>
<td>Beta</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>0.033</td>
<td>0 – 0.20</td>
<td>Toy et al. 2009</td>
<td>Beta</td>
</tr>
<tr>
<td>Death</td>
<td>0.325</td>
<td>0 – 1.00</td>
<td>de Jongh et al. 1992</td>
<td>Beta</td>
</tr>
<tr>
<td>From HCC to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>0.012</td>
<td>0 – 1.00</td>
<td>Toy et al. 2009</td>
<td>Beta</td>
</tr>
<tr>
<td>Death</td>
<td>0.315</td>
<td>0 – 1.00</td>
<td>Natl Cancer Institute 2006</td>
<td>Beta</td>
</tr>
<tr>
<td>From Liver T to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.056</td>
<td>0 – 1.00</td>
<td>OPTN 2008</td>
<td>Beta</td>
</tr>
<tr>
<td>From Post LT to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.056</td>
<td>0 – 0.20</td>
<td>OPTN 2008</td>
<td>Beta</td>
</tr>
</tbody>
</table>

| Probabilities                   |       |       |        |              |
| HBsAg+                          | 0.010 | 0 – 0.20 | NHANES | Beta |
| HBeAg+                          | 0.55  | 0 – 1.00 | Assumed(see text) | Uniform |
| Annual probability of detection | 0.02  | 0 – 0.20 | Assumed | Uniform |
| Compliance with intervention    | 0.70  | 0 – 1.00 | Assumed | Uniform |
| Effect of treatment on HBeAg+ SC| 0.21  | 0 – 1.00 | Nguyen and Keeffe 2009 | Beta |
| Relative risk of progression on treatment | 0.50 | 0 – 1.00 | Liaw et al. 2004 | Uniform |
| Sensitivity of screening test   | 0.80  | 0.70-0.90 | Black et al. 1999 | Uniform |
| Specificity of screening test   | 0.97  | 0.95-0.99 | Black et al. 1999 | Uniform |

| Annual costs (2008 USD)         |       |       |        |              |
| Screening                       | 26    | 0-150 | CMS 2008 | Gamma |
| Treatment                       | 9,380 | 4,000-15,000 | Johns Hopkins 2008 | Gamma |
| CHB (non-drug costs)            | 740   | 400-1,200 | BLS 2007; CMS 2008 | Gamma |
| CC                              | 800   | 100-1,000 | BLS 2007; CMS 2008 | Gamma |
| DC                              | 16,000| 10,000-20,000 | Lee et al. 2004 | Gamma |
| HCC                             | 10,520| 5,000-15,000 | Lee et al. 2004 | Gamma |
| Liver transplant                | 120,820| 90,000-150,000 | Lee et al. 2004 | Gamma |
| Post liver transplant           | 17,520| 10,000-20,000 | Lee et al. 2004 | Gamma |

| Utilities (distributions formed around utility decrement from 1) |       |       |        |              |
| Active CHB                     | 0.95  | 0.8 – 1.0 | Wong et al. 1995 | Gamma |
| Inactive CHB                   | 0.99  | 0.9 – 1.0 | Wong et al. 1995 | Gamma |
| HBSAg seroconverted            | 0.99  | 0.9 – 1.0 | Same as inactive CHB | Gamma |
| CC                              | 0.80  | 0.7 – 0.9 | Chong et al. 2003 | Gamma |
| DC                              | 0.60  | 0.5 – 0.7 | Chong et al. 2003 | Gamma |
| HCC                             | 0.73  | 0.5 – 0.8 | Chong et al. 2003 | Gamma |
| Liver Transplant                | 0.86  | 0.7 – 0.9 | Chong et al. 2003 | Gamma |
| Post Liver Transplant           | 0.86  | 0.7 – 0.9 | Chong et al. 2003 | Gamma |

BLS=U.S. Bureau of Labor Statistics; CMS=Centers for Medicare and Medicaid Services; OPTN=Organ Procurement and Transplantation Network
2.7.3 Cost parameters

For the early stages of CHB, the direct health care costs were incorporated, including physician visits and diagnostic tests. Wages were estimated from national data on median salaries available from the U.S Bureau of Labor Statistics (BLS) for nurses, physicians and medical technicians (2007). Median costs for laboratory tests were derived from the Centers for Medicare and Medicaid Services (CMS) Laboratory Fee Schedule (2008). The cost of treatment was estimated from the costs of the low-resistance profile drugs entecavir and tenofovir from the Johns Hopkins Antibiotic Guide (2008). Physician visit, laboratory test, diagnostic test and drug unit costs were totaled according to current guidelines addressing the frequency of follow-up visits, monitoring and treatment schedules (Lok and McMahon 2009; Sorrell et al. 2009; Weinbaum et al. 2008).

Cost estimates for disease sequelae, including decompensation, HCC, liver transplantation and post-liver transplantation were obtained from a published resource utilization study of annual U.S. costs of care for CHB (Lee et al. 2004). It was assumed that these were inclusive of all hospitalization and drug treatment costs, and thus, no additional costs were incorporated into these states. When applicable, costs from previous years were adjusted to 2008 USD with use of the Consumer Price Index from the U.S Bureau of Labor Statistics (2009). Costs were discounted at a rate of 3% per annum, and this value was varied from 0-5%.

Cost estimates tend to be positively skewed as a result of a relatively smaller number of high costs within a sample contributing to a mean that is greater than the median. Cost estimates are also constrained to non-negative values. For the probabilistic sensitivity analysis, gamma distributions were established around the point estimates, with standard error equal to the mean, to reflect the positive skew of cost data and constraint on the interval 0 to positive infinity (Briggs et al. 2006). The cost estimates used are reported in Table 1.

2.7.4 Morbidity and mortality

Health state utilities found in the literature were used to adjust for quality of life detriment associated with disease states. Since early stages of CHB are largely asymptomatic, there is little utility decrement associated with these states; only the symptomatic disease states with significant liver damage, i.e., decompensated cirrhosis and hepatocellular carcinoma are associated with considerable utility decrement. Patients in the active HBeAg-positive and
HBeAg-negative states experience slightly lower utility than those in inactive and response states. In the absence of definitive utility measures for CHB patients, the best estimates from literature and previous cost-effectiveness estimates were used (Wong et al. 1995; Chong et al. 2003). The utilities for less progressive disease states were based on results of an expert panel, as well as other studies that suggest there is little difference between early stages CHB and healthy individuals, since these stages largely asymptomatic (Wong et al. 1995; Shepherd et al. 2006). For disease sequelae such as cirrhosis, DC, HCC and transplantation, since there is no reason to suggest that quality of life decrements vary by underlying cause (Kanwal et al. 2005), the utility estimates were collected from a study that elicited utilities from chronic hepatitis C patients through standard gamble techniques (Chong et al. 2003). For probabilistic sensitivity analysis, gamma distributions were also established for the utility decrement associated with each disease state (Briggs et al. 2006). The utility estimates used are listed in Table 1. Effects were also discounted at a rate of 3% per year, and this value was varied in sensitivity analysis.

Age-specific mortality rates were obtained from life tables of the general U.S. population from the National Vital Statistics Report prepared by the Centers for Disease Control and Prevention’s National Center for Health Statistics (NCHS 2006). Excess mortality rates were converted to transition probabilities as described in section 2.7.2 Probabilities.

2.8 Sensitivity Analyses

One-way sensitivity analyses were performed for each of the parameters across their plausible range (Table 1). For the probability values that were assumed by the authors, we varied the parameter across the entire possible range (0-1). The ranges of plausible values for utilities and costs were obtained from previous studies (Wong et al. 1995; Chong et al. 2003; Lee et al. 2004). The change in incremental cost-effectiveness ratio was plotted for each one-way sensitivity analysis. A tornado diagram was created to depict the impact of varying each input parameter while holding the remaining values constant. Selective two-way sensitivity analyses were performed on those variables that had the greatest impact in one-way sensitivity analysis, and the results were tabulated. Probabilistic sensitivity analysis was also performed by randomly sampling from a distribution of values associated with each variable for all relevant parameters over 1,000 Monte Carlo simulations. The distributions used for each parameter are listed in Table 1. The results were used to calculate incremental cost-effectiveness ratios for each
simulation, and these values were plotted on an incremental cost-effectiveness plane. Finally, plots of the cost-effectiveness acceptability curve (CEAC) and the cost-effectiveness acceptability frontier (CEAF) were constructed to visualize the uncertainty around the cost-effectiveness of the screening and usual care strategies.
Chapter 3
Results

3.1 Base-case results

The results of the analysis are presented in Table 2. The screening strategy was more effective and more expensive than usual care. The incremental cost-effectiveness ratio for screening over usual care was $45,570 per quality-adjusted life year (QALY) gained. The undiscounted incremental cost-effectiveness ratio for screening over usual care was $37,880 per quality-adjusted life year gained. The estimates of the ICER without adjustment for quality-of-life were higher, as there was a much greater improvement in quality-adjusted life compared to the difference in total life years. Subsequent analyses were performed on discounted, quality-adjusted incremental cost-effectiveness ratios.

Table 2: Results of the base-case analysis, including the discounted and undiscounted incremental costs and outcomes for an immigrant cohort of 1.2 million individuals and 1% HBsAg+ prevalence receiving screening or usual care.

<table>
<thead>
<tr>
<th></th>
<th>Discounted</th>
<th>Undiscounted</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔC</td>
<td>$276.5 million</td>
<td>$342.2 million</td>
</tr>
<tr>
<td>ΔE</td>
<td>4,500</td>
<td>6,068</td>
</tr>
<tr>
<td>ICER</td>
<td>$61,460</td>
<td>$49,570</td>
</tr>
</tbody>
</table>

3.2 One-way sensitivity analyses

3.2.1 Influential variables

The model was most influenced by variables that impacted the early stages of chronic hepatitis B (CHB), including the probability of being HBeAg-positive at entry, the probability of transition from HBeAg-positive to compensated cirrhosis (CC), inactive CHB, and hepatocellular carcinoma (HCC), as well as the effects of treatment and the probability of treatment in the screening branch. A tornado diagram was created to illustrate the magnitude of the impact of these variables across their plausible range of values on the ICER, presented in Figure 2. These model drivers are further analyzed below. Influential variables were defined as those that changed the model outcome by more than $30,000 per quality-adjusted life year when varied over their plausible range of values.
Figure 2. Tornado diagram depicting each input variable and its corresponding effect on the ICER estimate across the plausible range of values for each variable.
3.2.2 Probabilities

The variables with the greatest impact on the cost-effectiveness of the screening program were those related to the early stages of CHB infection. When varied over a range of plausible values, the proportion of the cohort initially HBeAg-positive had a large impact on the cost-effectiveness of screening. It was evident that the larger the proportion of HBeAg-negative patients in the cohort, the smaller the gain in quality-adjusted life years with the screening strategy (Figure 3). Thus, we observed a large and unfavourable ICER estimate when the cohort was predominately composed of HBeAg-negative individuals.

Figure 3. The change in a) total cost and b) total quality-adjusted life years for each strategy across a range of values for the proportion of HBeAg-negative patients at entry.

The variable for the effect of treatment on inducing the inactive CHB state in active HBeAg-positive CHB individuals also had a large impact on the cost-effectiveness of the screening intervention, when varied over a plausible range of values. The value for the natural transition from HBeAg-positive active CHB without treatment was 0.04 (Table 1). Treatment-related transition rates below this value were associated with exponentially increasing costs and diminishing gains in quality-adjusted life years (Figure 4). It is clear from Figure 4 that for
values for the treatment effect at or below the natural rate of transition from active HBeAg-positive CHB to inactive CHB (0.04), screening strategy costs were large compared to usual care and gains in quality-adjusted life years were minimal. Larger treatment-related transition rates from active HBeAg-positive CHB to inactive CHB, particularly values surrounding the base-case estimate of 0.21 and beyond, were associated with both smaller cost differences and larger QALY gains, and therefore, improvement in the cost-effectiveness of the screening intervention as well.

Figure 4. The change in a) total cost and b) total quality-adjusted life years for each strategy across a range of values for treatment-induced transition from HBeAg-positive active CHB to inactive CHB.

The probability of treatment in the screening branch was another variable that greatly impacted our estimate of cost-effectiveness. Values for treatment compliance in the screening branch below 5% were associated with worse outcomes than usual care (Figure 5), which would result in a negative ICER, as the screening strategy would be dominated by the usual care strategy. Above this threshold value, larger values for treatment compliance were associated with larger total costs as well as larger total quality-adjusted life year estimates, with a greater incremental increase in outcomes compared to incremental costs. Thus, more favourable ICER estimates were observed at higher probabilities for treatment compliance in the screening branch. At the
far end of the spectrum, if 100% compliance were observed in the screening branch (compared to our 70% base case estimation), the ICER for the screening intervention would be lower than the base-case value, at $39,180 per QALY gained.

Figure 5. Change in a) total costs and b) total quality-adjusted life years for each strategy across a range of values for treatment compliance among those in the screening branch of the model.

Other influential probability variables included the transition from active HBeAg-positive CHB to compensated cirrhosis, hepatocellular carcinoma, and inactive CHB, as well as the transition from inactive CHB to reactivated HBeAg-negative CHB. The first two of these variables are transitions to disease sequelae, and larger values for these transition rates were associated with more favourable cost-effectiveness estimates for the screening strategy. The latter two probabilities, for the natural transition from active to inactive CHB, and from inactive to reactivated CHB, exhibited less favourable cost-effectiveness estimates for the screening strategy at higher transition probability values.

The relative risk of progression due to treatment was also influential to the cost-effectiveness estimate, due to its impact on quality-adjusted life years. Lower values, associated with reduced
transitions to disease sequelae, were associated with larger total quality-adjusted life years, and this impacted the screening strategy dramatically more so than the usual care strategy (Figure 6).

Figure 6. Changes in total quality-adjusted life years for each strategy across a range of values for relative risk of progression due to treatment.

The prevalence of HBsAg in the cohort was not as influential as is implied by its placement in the tornado diagram in Figure 2. At extremely low prevalence values, due to the small difference in total life years produced between the strategies, the ICER becomes exponentially large, after which the changes in cost and changes in outcomes are proportional and there is minimal impact in the resulting ICER for greater prevalence values (Figure 7). When the prevalence rate was zero, the ICER was not defined, with no difference in total life years between the two strategies. The ICER for the screening strategy quickly dropped below $50,000 per QALY gained and remained consistent for values greater than 0.5%. At the far end of the plausible range (20%), the ICER had decreased only slightly to $39,600 per QALY gained.

Figure 7. Change in incremental cost-effectiveness ratio across a range of values for the prevalence of HBsAg in the immigrant cohort.
Of note, though the impact was not as great as some of the key variables discussed above, there was an interesting relationship between the probability of incidental screening/detection and the incremental cost-effectiveness ratio. Near zero, both the costs and outcomes demonstrated rapid increases for the usual care strategy, and increased to a smaller extent for the screening strategy (Figure 8). The changes were not exactly proportional, such that at zero incidental detection, the ICER was actually slightly higher than the base case at $48,620 per QALY gained, despite the poorer outcomes associated with this scenario. At the high end of the range, the screening and usual care strategies were nearly identical in both costs and outcomes.

Figure 8. Change in a) total costs and b) total quality-adjusted life years for each strategy across a range of values for the probability of incidental screening and detection as a CHB patient among those not identified at entry into the United States.
3.2.3 Utilities

The most influential utility values were the utilities of active and inactive CHB; the rest of the variables had minimal impact on the ICER across their range of values. Considered an influential variable, changes in the utility of inactive, suppressed and HBsAg seroconverted (“recovered”) CHB made the largest impact on the cost-effectiveness of screening. Values closest to one produced the largest incremental gain in quality-adjusted life years, and consequently, the most favourable ICER values. Changes to utility variables did not impact costs, for logical reasons.

3.2.4 Costs

The most influential cost variables were the costs of treatment and screening; the rest of the cost variables had negligible impact on the ICER. Increasing treatment costs increased total costs in both branches, but impacted the screening branch more so than the usual care branch. Larger treatment costs were associated with larger ICER values. Changes to all cost variables did not impact life years, for logical reasons.

As discussed previously, the base case analysis was compared with the exclusion of screening costs in order to address the third-party payer cost as confined to the United States. When the cost of screening was zero, the incremental cost-effectiveness was $40,360. This value was lower than the base-case estimate, reflecting the reduction in upfront costs of the screening strategy. However, the decrease was only a small fraction of the total cost, and thus was not the major cost driver in the screening branch. As in the case of treatment costs, an increase in the screening cost would have an unfavourable effect on the ICER.

3.3 Two-way sensitivity analysis

Select two-way sensitivity analyses were performed between the most influential variables in the model, according to one-way sensitivity analysis. Both the proportion of HBeAg-negative CHB patients at entry and the transition rate from active HBeAg-positive CHB to inactive CHB on treatment were varied simultaneously, and the resulting ICER values were calculated (Table 3). The combinations of the two variables that produced non-dominated, cost-effective ICER values, below $50,000 per QALY gained, were identified. Screening was cost-effective for combinations with fewer proportions of HBeAg-negative patients initially in the cohort and higher treatment-related transitions to inactive CHB.
Table 3. Two-way sensitivity analysis, with ICER estimates rounded to the nearest hundred, for proportion of HBeAg-negative patients vs. treatment effect. Base case combination of variables is most closely represented with bolded text. Combinations in white text are cost-effective below a $50,000 per QALY gained threshold.

<table>
<thead>
<tr>
<th>Proportion of HBeAg-negative patients at entry</th>
<th>0</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
<th>0.8</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition from HBeAg-positive to inactive CHB due to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
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<tr>
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<td>22700</td>
<td>32100</td>
<td>54600</td>
<td>180500</td>
</tr>
</tbody>
</table>

The proportion of HBeAg-negative CHB patients at entry and the variable for treatment compliance in the screening branch were varied simultaneously and the resulting ICER values were calculated (Table 4). The combinations of the two variables that produced non-dominated, cost-effective ICER values, below $50,000 per QALY gained, were again identified. Several negative ICER values were observed for very low values of treatment compliance, as a result of a negative incremental effect when comparing the screening strategy with usual care. For these values, the screening strategy is dominated by the usual care strategy, as they fall in the upper left (north-west) quadrant of a cost-effectiveness plane and represent an intervention that is more costly and less effective than its comparator. Screening was cost-effective for combinations with fewer proportions of HBeAg-negative patients initially in the cohort and higher values for treatment compliance amongst screened individuals.

Table 4. Two-way sensitivity analysis, with ICER estimates rounded to the nearest hundred, for proportion of HBeAg-negative patients vs. treatment compliance. Base case combination of variables is most closely represented with bolded text. Combinations in white text are cost-effective below a $50,000 per QALY gained threshold.

<table>
<thead>
<tr>
<th>Treatment compliance in the screening branch</th>
<th>Proportion of HBeAg-negative patients at entry</th>
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<th>0.4</th>
<th>0.6</th>
<th>0.8</th>
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</tr>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

3.4 Probabilistic sensitivity analysis

The robustness of the ICER estimate was assessed using probabilistic sensitivity analysis. All input parameters were varied according to their selected distributions simultaneously and the
results of 1,000 simulations were recorded and plotted on an incremental cost-effectiveness plane (Figure 9).

![Figure 9](image)

Figure 9. Results of 1,000 Monte Carlo simulations plotted on an incremental cost-effectiveness plane. Each point represents the incremental cost-effectiveness ratio obtained from an individual simulation. The solid lines represent commonly used societal threshold willingness-to-pay ICER values ($\lambda$) of $50,000/QALY gained and $100,000/QALY gained. ICER estimates below and to the right of the solid line are considered cost-effective at that willingness-to-pay threshold level.

The resulting distribution of ICERs was used to generate a cost-effectiveness acceptability curve (CEAC) from the formula for incremental net benefit

\[ INB = \lambda \cdot \Delta E - \Delta C \]

at varying levels of $\lambda$, willingness-to-pay. The incremental net benefit is a simple rearrangement of the ICER to explicitly incorporate valuation of benefits with the threshold willingness-to-pay. If a strategy is cost effective when $\Delta C/\Delta E < \lambda$, then it is cost-effective when $\lambda \cdot \Delta E - \Delta C > 0$ at that threshold willingness-to-pay value. The incremental net benefit represents the difference in strategies, valued in dollars, for a given willingness-to-pay threshold. A positive value for INB
indicates that the screening strategy provides larger net monetary benefit than usual care, and is the optimal or cost-effective option at that willingness-to-pay level (Fenwick et al. 2001). All positive values of INB among the 1,000 simulations at various levels of $\lambda$ were tabulated and the proportion of the total number of simulations that were cost effective was plotted as a function of $\lambda$ (Figure 10).

![Cost-effectiveness acceptability curve of screening and usual care strategies](image)

Figure 10. Cost-effectiveness acceptability curve of screening and usual care strategies. Results are based on 1,000 Monte Carlo simulations, with all variables varied simultaneously according to distributions outlined in Table 1.

From this figure, the likelihood of cost-effectiveness for the screening program can be determined at any particular willingness-to-pay value. At the commonly used threshold value of $50,000/QALY gained, it was observed that the chance that the screening intervention is cost-effective based on the simulation was just under 50%. At $100,000/QALY gained, the proportion of cost-effective trials for the screening intervention was slightly below 67%.

CEAC curves describe the probability that each option is cost-effective at any given willingness-to-pay threshold, but it alone cannot be used to identify the optimal strategy (Fenwick et al. 2001). A cost-effectiveness acceptability frontier (CEAF) was also plotted to demonstrate the uncertainty around the optimal strategy for any given level of willingness-to-pay (Figure 11). The optimal strategy was determined by the formula for incremental net benefit (INB). For any given willingness-to-pay level, the optimal decision is always determined by the strategy with
the highest expected net benefit (Fenwick et al. 2001). The screening strategy had the highest expected net benefit, i.e., a positive INB, for all values greater than the ICER. At our ICER estimate, 45% of the distribution of ICERs were cost-effective, and the proportion of cost-effective ICERs increased with higher levels of maximum willingness-to-pay.

Figure 11. Cost-effectiveness acceptability frontier depicting the probability that the optimal strategy is cost-effective. The optimal strategy was selected by maximum net benefit for each threshold level. Vertical dotted line represents the point at which the optimal strategy switches from usual care to screening strategy, equal to the ICER estimate. Results are based on 1,000 Monte Carlo simulations.
4.1 Summary of model findings

We assessed the cost-effectiveness of screening for HBV infection among immigrants entering the United States compared to usual care over a 20-year horizon. Our analysis indicates that a strategy of screening immigrants for chronic hepatitis B at the time of their entry into the United States may be cost-effective, with a base case estimated incremental cost-effectiveness ratio of $45,570 per QALY gained. According to our results, screening is cost-effective if we are willing to pay $50,000 per QALY gained. Medical interventions that cost less than $50,000 per QALY gained are commonly considered acceptable (Winkelmayer et al. 2005). The results of this model are comparable to those of Hutton et al. (2007), who developed a cost-effectiveness model for HBV screening in Americans originating from Asia and the Pacific Islands, and found incremental cost-effectiveness ratios of approximately $38,000 per QALY gained for screen-and-treat and screen, treat and ring vaccination strategies.

Probabilistic sensitivity analysis has highlighted that our estimate for the incremental cost-effectiveness of a screening program has a wide range of possible outcomes, due to uncertainty in several variables of the model. The analysis has found that the probability that the screening strategy is cost-effective using common values of $50,000 per QALY and $100,000 per QALY thresholds was just below 50% and 67%, respectively. The cost-effectiveness acceptability frontier (Figure 11) demonstrated the uncertainty around the optimal decision given any particular willingness-to-pay threshold. For a threshold just above the base-case estimated incremental cost-effectiveness ratio, there is a 45% chance of screening being cost-effective. The probability increases as the maximum willingness-to-pay increases.

4.2 Variables of importance

Our model differs from existing cost-effectiveness analyses in chronic hepatitis B research in that it considers a hypothetical screening strategy that encompasses both case identification and subsequent treatment and management strategies. Other economic evaluations in the literature have only rigorously addressed one of these two factors at a time, in the form of decision
analyses assessing the impact of various immunization or treatment strategies. While the primary objective of this model was to elucidate the economic and disease impact of identifying chronic hepatitis B carriers, this could be comprehensively achieved only by including disease management, treatment options and a complete natural history of CHB. We recognize the complexity of managing this highly individualized and long-term condition, and concede that simplifications, while not ideal, are required in order to make a reasonable estimate for the cost-effectiveness of a screening intervention. The decision to treat a chronically infected patient is in itself an appropriate scenario for an economic evaluation, as evidenced in the literature by the numerous analyses surrounding the available pharmaceutical therapies (Wong et al. 1995; Kanwal et al. 2005; Shepherd et al. 2006; Veenstra et al. 2007; Spackman and Veenstra 2008; Yuan et al. 2008; Toy et al. 2009). We did not examine all possible outcomes of an infected individual entering the U.S. from admission to death, nor include all clinical characteristics of disease progression and options for therapies, as incorporating this much decision-making into one model would only serve to further obscure the true result; however, this model has provided numerous insights into the areas that most impact the decision to screen individuals, highlighted the areas of greatest uncertainty, and identified aspects of CHB natural history and disease management that would benefit most from further research or expansion of the model to refine the results.

It can be observed from the model that the early stages of CHB have the greatest impact to the cost-effectiveness of screening for CHB patients, even without incorporating discounting to account for time preference. Sensitivity analysis shows that the more active HBeAg-positive infection that exists in the population, the more cost-effective screening would be for the cohort. This suggests that a screening strategy would be cost-effective for a relatively young population of active infection, such as that generally seen in new immigrants, since an older population would be more likely to have either transitioned naturally to inactive CHB, and not require treatment, or into disease sequelae, which would be more likely to be detected incidentally through symptomatic illness. The rates of transition from active HBeAg-positive CHB to inactive CHB, compensated cirrhosis (CC), and hepatocellular carcinoma (HCC) also had a large impact on the cost-effectiveness of screening. This is an optimal area for expansion of the model through meta-analysis of natural history studies in the literature.
In addition, the use of treatments that more rapidly induce the transition to an inactive CHB or more dramatically reduce the risk of developing disease sequelae would also make the screening strategy more favourable from a cost-effectiveness standpoint. As discussed in detail in the upcoming section of this paper, the choice of pharmaceutical agent used for treatment is currently an important and rapidly evolving area of research. The newest antiviral medications available in the treatment of HBV infection are highly potent, with extremely low resistance profiles. While we have not modeled specific medications and have used a wide range for treatment-related parameters in sensitivity analysis, it is important to recognize that the characteristics of newly developed therapeutic agents are not subject to some of the limitations of the early pharmaceuticals. It is also not unreasonable to believe that future developments will include pharmaceuticals with greater potency in terms of the surrogate biomarkers used, such as viral suppression and transition to inactive CHB through HBeAg-seroconversion. We did assume that drugs with similar efficacy and cost will replace current drugs in the future, which is reasonable since new drugs would only be expected to enter the market if they are comparable or improved upon in relation to the current standard therapy.

4.3 Model scenarios

In order to make the model closer to a realistic comparison of real-world options, we incorporated random detection in the usual care strategy. Decision models often make unrealistic comparisons between all-or-none options. In this case, we acknowledged that the usual or standard care option does result in the detection and treatment of a number of CHB patients over the course of their lifetime, which can occur at any stage of the natural disease history. We have included our best estimate for an annual rate of detection and subsequent treatment, as well as recognition of possible noncompliance or loss in the screening strategy, in order to model what it would be like in the real world upon implementation of either strategy. By looking at idealistic situations, such as when the probability of treatment in the screening strategy is 1.0, or the probability of incidental detection in the usual care branch is non-existent, we can observe the result in more theoretical conditions. As mentioned in the previous chapter, 100% compliance with treatment in the screening branch produces a slightly more attractive ICER estimate of $39,180 per quality-adjusted life year gained compared to the base case estimate. As well, a negligible probability of incidental detection among undetected CHB patients, representing the more idealistic “do nothing” scenario, produced a slightly higher ICER estimate than the base
case ($48,620 per QALY gained), owing to the impact of this variable to both lower costs and poorer outcomes. For our attempt to determine the most accurate estimate of cost-effectiveness compared to what currently occurs, we acknowledge that it is not possible to ascertain the exact value for the annual rate at which CHB patients are detected. We based our estimate on studies assessing the knowledge amongst immigrants with CHB regarding their disease status (NHANES unpublished; Lin et al. 2007), and allowed the value to vary widely in sensitivity analysis to account for this uncertainty, as well as to gain an understanding of the impact of the variable should a more precise estimate become available in the future.

Another unique aspect of our model was its use of large-scale U.S. study for the estimate of HBsAg prevalence among foreign-born residents. It gives an accurate picture of the current burden of illness for chronic hepatitis B in the higher-risk subpopulations of the U.S., of which there are varied estimates in the literature, ranging from 7-15% (CDC 2006; Hutton et al. 2007; Ma et al. 2007). Interestingly, the model was not particularly sensitive to the prevalence of HBsAg in the population cohort, as the added costs of early therapeutic intervention and monitoring balanced the added gains in quality-adjusted life years over the vast majority of the range of values. The impact of the variable remained consistent at values well below the lower end of the range for intermediate prevalence of HBV infection (2-7%), for which screening is currently recommended (Weinbaum et al. 2008). Thus, for population cohorts from regions of either intermediate or high prevalence, including the estimates for population subgroups found in the literature, the cost-effectiveness estimate is very likely to remain consistent.

4.4 Limitations of the model

Our analysis has several limitations. As previously discussed, it was necessary to make simplifying assumptions in order to estimate the cost-effectiveness of screening for such a long-term and complex condition with numerous treatment strategies available. We assumed only two possibilities for initial entry into the model, mono-infection of HBV with either HBeAg-positive active infection or inactive CHB, assuming all patients had surpassed the immune tolerant phase at entry. We considered a full spectrum of ratios of HBeAg positive:negative patients, which had a large impact on the cost-effectiveness. We did not include any patients in an immune tolerant stage of infection, who would not immediately be eligible for treatment, but would be regularly monitored, and thus might incur additional costs without receiving immediate benefit. A large
number of immune tolerant patients would presumably make the cost-effectiveness of screening less favourable compared to usual care; however, given the decades of time since infection at birth, the most common mode of transmission in regions of intermediate and high endemicity, we believe it is reasonable to assume that the average patient has progressed in the natural disease history to active infection or beyond. The epidemiology of CHB, particularly the stage of infection among new immigrants, or alternatively, the average time from infection to various stages of infection, is an area that would benefit greatly from further research. Additionally, it is beyond the scope of this paper to address the increased severity of illness and special management required for the small proportion of chronically HBV infected individuals that are co-infected with HIV or other hepatitis-causing viruses, particularly HCV and HDV. However, we believe this may bias the model results in favour of usual care, since detecting a more severe and rapidly progressing HBV infection in persons with HIV would only result in greater benefits from early intervention. Further analysis might be warranted in these special populations or among different age groups in order to acquire a more accurate estimate of the cost-effectiveness of screening in these populations.

There were limits to the amount of detail that could be included in the management of chronic HBV infection for an identified individual, in either branch of the model. We chose to make the conservative assumption that patients with end-stage illnesses are managed identically in both branches. This may not accurately reflect reality, particularly in the event of routine screening for hepatocellular carcinoma amongst detected CHB cases. As mentioned previously (see section 1.3.3), recent evidence has shown that there is benefit to routine screening for evidence of liver cancer, and that the detection of small tumors improves survival rates compared to the more advanced stages of cancer that have developed once the disease becomes clinically evident (Bruix and Sherman 2005). However, it would add too much complexity to the analysis to also model the management of hepatocellular carcinoma, which in itself is a multifaceted and evolving area of clinical practice. Thus, we simply allowed those patients who develop hepatocellular carcinoma to be managed identically in either branch, and acknowledge that this may bias the result toward the usual care strategy.

Furthermore, there has historically been debate around the timing for the initiation of drug therapy in CHB management. Several of the early treatment options, including interferon, lamivudine, and adefovir, were associated with either harsh negative side effects or high rates of
drug resistance, and thus were not tolerated in the long term. As a result, treatment was reserved for late stages of liver disease and highly active infection only. However, recent progress has led to the development of effective and highly potent nucleoside analogues that do not appear to be limited by drug resistance in their ability to provide long-term disease control, such as entecavir and tenofovir (McMahon 2008). It is suggested now that the potential for long-term viral suppression and subsequent improvement in outcomes with these newer agents is valid reason not to delay treatment and provide long-term maintenance therapy against active infection (Khokhar and Afdhal 2008). It is conceded that treatment of active infection with first-line drug therapies, including use of long-term maintenance therapy, is assumption of the model that is based on evidence-based guidelines, but may not reflect the current spectrum of clinical practice. We included wide sensitivity analysis for both costs and effects of drug treatments in order to limit the introduction of any bias, should less potent and less costly drugs be prescribed instead.

More broadly, we could not possibly incorporate all possible outcomes for the clinical management of an individual identified with HBV infection, beyond treatment options or time of detection for disease sequelae. It is possible that a person with CHB identified through screening could still be lost to follow-up, as it is well documented that immigrants new to a country have lower health service utilization compared to the general population, whether it be due to the healthy immigrant effect, socio-economic factors (e.g., lack of insurance), language barriers or inadequate disease knowledge or awareness of available resources (Ma et al. 2007). It is also quite plausible that a patient would be unwilling to undergo long-term treatment, particularly in light of the asymptomatic nature of chronic HBV infection. Barriers to effective management also include the possibility that providers are not equipped or aware of the proper management of CHB, due to its low prevalence in the United States (Gushulak and MacPherson 2000). There are many variables associated with chronic disease management that extend beyond the scope of this analysis, and we acknowledge that factors that limit the management of chronic HBV infection would reduce the impact of the screening strategy and make it a less attractive option.

Finally, the model was designed only to capture the direct cost and outcomes associated with screening, and failed to capture a number of indirect costs and benefits. For example, we have not included the indirect costs due to lost productivity for CHB patients, as this consideration was not explicitly mentioned in the study from which the utility estimates were elicited and to include them would have possibly resulted in double counting. The model does not capture any
effects of primary preventative measures, such as ring vaccination for sexual or household
contacts or babies of pregnant carriers, nor does it capture benefits associated with behavioural
modifications and patient education in reducing transmission and limiting other risk factors for a
CHB patient, such as alcohol use. It is believed that the additional benefits are externalities that
not easily captured in cost-effectiveness analysis, but which ought to be kept in mind, as it
suggests that estimates of cost-effectiveness may be conservative.

4.5 Policy Implications

The results of this analysis have implications in policy at the national level for immigration and
public health. While the issue of mandatory screening is controversial, the potential for improved
health outcomes for new immigrants make it worthy of consideration for new policy. According
to the model, early detection and subsequent treatment of CHB through a mass-screening
program among high-risk populations can impact both health outcomes and health service
utilization, allowing new immigrants with CHB to begin effective treatment prior to the onset of
symptoms and development of severe liver complications. The strategy is intended to facilitate
access to care for individuals and the families of those affected by CHB, not serve as cause for
exclusion or facilitate any form of stigmatism.

Screening for hepatitis B is not currently implemented anywhere in the world at the level of
national immigration policy. The current approach for chronic hepatitis B management is
suboptimal, in that recommendations for screening at the provider level are not universally
followed and many cases go undetected until complications have already developed. The
findings of our analysis in the U.S. context may be relevant to other immigrant-receiving
countries, who face many of the same pressures and challenges surrounding CHB management
in their foreign-born population, including detection, progression to end-stage complications and
premature death. While we used the United States as a prime example for the movement of a
chronic disease of high prevalence in many regions of the world to a region of low prevalence, it
is conceivable that a number of industrialized nations with similar immigration patterns would
experience comparable results for such an analysis. The introduction of a mass-screening
program for HBV infection to the immigration medical exam of the United States and potentially
other nations appears to warrant consideration.
The current analysis assessed the impact of screening among the immigrant cohort as a whole, and thus the next step might be to consider the cost-effectiveness of a screening program for specific subgroups of immigrants based on region of origin. There is potential for greater efficiency through geographically directed screening, a practice currently implemented for other diseases with geographical variation; for example, Canadian immigration requires screening for immigrants from a list of designated countries that is based on tuberculosis endemicity (Public Health Agency of Canada 2001). It is plausible that such a strategy would be more economically attractive, by limiting the budget impact and upfront costs to those with the highest risk of having chronic infection. By focusing on new immigrants specifically from regions of intermediate or high HBV endemicity, the absolute cost of the intervention and any additional costs to monitor and track chronically infected patients would be minimized.

4.6 Future Research

Probabilistic sensitivity analysis suggested that due to uncertainty in several parameters, the proportion of simulations that were cost-effective at a more conservative threshold of $50,000/QALY gained was just below 50%, and was 67% at a threshold willingness-to-pay of $100,000/QALY gained. The wide range of values observed from probabilistic sensitivity analysis suggests that further research would be useful, particularly to obtain better estimates of the proportion of HBeAg-positive CHB individuals at entry, the effects of first-line treatments on transitions to inactive CHB and disease sequelae, and the rates of incidental detection and treatment compliance in current clinical settings, in order to make a more precise estimate of the cost-effectiveness of the intervention. Since the early stages of infection are particularly influential for our estimates, the model would be strengthened by long-term, comparative data on both the natural history and effect of treatment on disease path.

4.7 Conclusions

Our model has produced an incremental cost-effectiveness ratio for the screening strategy of $45,570 per quality-adjusted life year saved, which may indicate a cost-effective strategy for the management of chronic hepatitis B in the United States. Given the potential cost-effectiveness of the strategy, some consideration should be given to new policy that would expand the scope of diseases screened for as part of the U.S. immigrant medical exam to include HBV infection.
This analysis has provided insight into a potential new strategy for CHB management with important health and economic implications to both new immigrants and their receiving country as a whole. Chronic hepatitis B infection is a significant health issue with risk for a number of costly and debilitating disease complications. The CDC and other prominent health organizations have recommended screening for all persons originating from regions of intermediate or high HBV endemicity, but currently this is not well implemented at the provider or community level. According to our model, a universal screening program, moved upstream to the immigration process in order to capture the incoming high-risk population in its entirety, appears to be economically attractive from the perspective of the U.S. health care system, as well as to substantially impact the health and well being of new immigrants and their subsequent ability to meet their potential in their new country. Our analysis has also identified key areas of uncertainty in the epidemiology and management of chronic HBV infection, as well as the need for further research in order to better define parameters associated with the cost-effectiveness of screening. These results can be used to direct discussion and inform decision-making regarding national immigration policy in the United States and potentially other immigrant-receiving countries, along with meaningfully contribute to the literature surrounding the identification and management of chronic HBV infection.
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