Title: Economic Impact of Alternative Hepatitis B Vaccination Strategies – Ontario, 2020-2050

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Contributions

Mia Biondi, Chris Estes, Devin Razavi-Shearer, Homie Razavi, and Jordan Feld conceived and designed the study. Mia Biondi, Chris Estes, Devin Razavi-Shearer,

Kanwar Sahdra, Nechama Lipton, and Jordan Feld retrieved the data. Chris Estes and Devin Razavi-Shearer ran the model; supervision by Mia Biondi, Jordan Feld, and Homie Razavi. All authors reviewed the manuscript and approved the final version to be published and agreed to be accountable for all aspects of the work.

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Competing Interests

HLAJ reports serving as a speaker, consultant or advisory board member for AbbVie, Arbutus, Benitec, Bristol Myers Squibb, Gilead Sciences, Glaxo, Janssen, Medimmune, Merck, Roche and Vir Biotechnology, and receiving research funding from AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Medimmune, Merck and Roche. JJF reports receiving research support and/or consulting fees from AbbVie, Enanta, Eiger, Gilead, Janssen, Roche, Arbutus and GlaxoSmithKline. No other competing interests were declared.

Abbreviations

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; WoCBA, women of childbearing age; HBeAg, hepatitis B e antigen; DALY, disability-adjusted life year; CAD, Canadian dollar; UI, uncertainty intervals; ROI, return on investment

Keywords: hepatitis B virus; vaccination; transmission prevention; pediatrics; cost-benefit analysis

Abstract

Background: The World Health Organization recommends universal birth dose vaccination for hepatitis B virus (HBV), yet Ontario continues to vaccinate in adolescence. We recently demonstrated that Canadian-born children in Ontario are acquiring HBV prior to adolescent vaccination. Although there may be clinical benefit to infant immunization, we sought to determine whether this approach was cost-effective.

Methods: A model was constructed to quantify the future disease and economic burden of chronic HBV infection in Ontario from 2020-2050. Four infant vaccination approaches were compared to adolescent vaccination for effectiveness and direct and indirect costs were calculated.

Results: All four infant approaches prevented an additional 550-560 acute and 160 chronic pediatric HBV infections from 2020-2050 in comparison to adolescent vaccination. While birth dose could be cost-effective, incorporating vaccination into a hexavalent vaccine was cost-saving. By 2050 the hexavalent approach led to $428,000 cost-saving per disability-adjusted life years (DALY) averted in comparison to birth dose which led to $103,000 cost-incurred per DALY averted.

Interpretation: Introducing any form of infant HBV immunization in Ontario will prevent acute and chronic pediatric HBV infections. At the current prevalence in Ontario, a switch to birth dose or infant dose will be cost-effective or cost-saving respectively.

Introduction

In Ontario, hepatitis B virus (HBV) ranks 4th on the list of infectious diseases with the greatest burden of illness by years of life lost (1). Health consequences from longstanding infection include cirrhosis and liver failure, or hepatocellular carcinoma. Infants who acquire HBV through vertical or early horizontal exposure have a >90% risk of progression to chronic infection, whereas 99% of immunocompetent adults will clear acute HBV upon infection (2). As a result, the World Health Organization has prioritized HBV birth dose vaccination as a key tenet of the strategy for HBV elimination. Globally, birth dose vaccination has decreased prevalence from 5% to 1% in children under 5 years old (2). However, almost 30 years after the initiation of birth dose vaccination and adoption among 100+ countries (3), only 3 provinces/territories in Canada provide birth dose vaccination, 5 vaccinate in infancy, and 5 in adolescence; including Ontario (4).

We recently demonstrated that children born in Canada, living in Ontario, are acquiring HBV before age 12 (6 cases per 1000); infections likely prevented with universal birth dose vaccination. This number only reflects infections among children who were tested, therefore likely a significant underestimate of Ontario-acquired pediatric infections (5). Children may have been infected through vertical transmission when prenatal screening was missed or horizontal transmission from contacts who may not have been aware of their infection. HBV prevalence is particularly high among newcomers to Canada from HBV-endemic regions (6-8). Although children should be vaccinated at birth if a household contact or caregiver is known to carry HBV, a high proportion of those living

with HBV have not been diagnosed as the infection is largely asymptomatic and is not part of the routine Canadian immigration medical examination (9, 10).

To consider the cost and public health implications of a policy change in Ontario and the other four provinces that immunize in adolescence, we utilized the PRoGReSs model (11), a dynamic HBV model that incorporates population by year, disease stage, sex, and the influence of immigration. We compared vaccination timing based on direct and health outcomes to determine which approaches would be cost-effective or cost-saving compared to current adolescent vaccination over the period 2020 to 2050.

Methods

Data for model inputs were based on literature review, administrative data, institutional internal data, and expert consensus. Ontario population (12), mortality and historical data inputs were entered in the Ontario HBV disease burden and transmission model (PRoGReSs Model) including HBsAg prevalence by age and sex, HBeAg prevalence and rate of high viral load among women of childbearing potential (WoCBP), hepatitis B immune globulin (HBIG) and birth dose for infants born to positive mothers, the annual number of HBV-related liver transplants, and treatment and diagnosis rates (Supplementary Methods) (13).

Scenario development and assessment

HBV disease burden and economic impacts were assessed under five scenarios. A base scenario and four general population vaccination strategies were modeled from 2020-2050 under the following conditions (Table 1): 1) current two-dose adolescent

vaccination (base case); 2) birth dose vaccination, and individual vaccinations at 1 and 6 months; 3) birth dose vaccination, vaccination at 1 month, and a hexavalent 6 month vaccination (DTaP-HB-IPV-Hib); 4) birth dose vaccination, with hexavalent doses at 2 and 6 months; and 5) hexavalent vaccination at 2, 4, 6 months. Scenario details and a description of the calculation of uncertainty are described in Supplementary Methods IV and V.

Economic impact analysis

Cost data were applied to disease burden outcomes to determine the economic impact of each scenario. Direct costs included healthcare, screening, prophylaxis, diagnostic, and treatment costs. Healthcare costs by disease stage were reported previously (14), but were adjusted to remove the reported cost of medications for cases classified as chronic HBV (F0-F3) and compensated cirrhosis, as the treated population was tracked separately. Costs for HBV medication were reported previously (15), and adjusted based on the distribution of patients by treatment regimen at the Toronto Centre for Liver Disease from 2010-2019. Indirect costs were based on the value of a statistical life year (GDP per capita = 62,138 (16); Table 2) and disability-adjusted life years [DALYs] (17) incurred due to years of life lost due to premature mortality and years lived with disability (Table 2). All costs were inflated to 2020 Canadian dollars (CAD) based on the consumer price index for health care (18). Economic outcomes were analyzed to 2050 to account for lag time between the implementation of infant prophylaxis on disease burden effects and economic changes.

Results

Characteristics of the HBV-infected population

Assuming a male to female ratio of 1.38 (5, 7, 19), the impact of immigration, and adjusted for reported HBsAg and HBeAg prevalence among pregnant women (5) including the proportion with high viral load (≥20,000 IU/mL) (20), the HBsAg prevalence in Ontario was estimated at 0.80% in 2017 (Table 2). In that year, there were an estimated 39,623 previously diagnosed cases and 1,878 newly diagnosed cases (21) (19). In 2016, the antiviral treated population was estimated at 11,600 patients, and there were an estimated 25 HBV-related liver transplants performed in Ontario (Table 2).

HBV immunization and post-exposure prophylaxis

Modeling included the impact of diagnostics, treatment, and immunization on disease and economic burden. Ontario introduced universal adolescent vaccination in 1997 (22), and immunization coverage data for Ontario were either directly available from Public Health Ontario or were linearly extrapolated (Supplementary Table 1S). For infants born to HBsAg+ mothers, 93.7% (5) received birth dose coverage within the first 24 hours of life, three dose coverage, and HBIG coverage based on current comprehensive immunization programs (23). 38% of eligible women received third trimester antiviral treatment (5).

Disease Burden

With the current adolescent vaccination strategy, acute HBV infections were projected to decrease from 110 in 2020 to 16 in 2050 (85% decline); largely due to an overall decrease in unvaccinated adults as a result of 70%+ immunization rates in school-based programs since 1997. Despite this, 1500 acute and 520 chronic infections (Table 3) would

still occur over the 30-year time-frame due to infections in the pediatric population under 12, new infections in those who either did not receive or were not eligible for adolescent vaccination and imported cases as a result of immigration. In comparison, all infant scenarios prevented 560-570 acute and 160 and chronic cases by 2050 (Table 3). As a result of those already infected in 2020 and imported cases as well as new adult chronic infections, liver-related deaths increased until 2042 when they peaked at 780 deaths, declining thereafter (Table 3).

Direct Costs

Direct costs included healthcare, screening, prophylaxis, diagnostic, and treatment costs. Both annual costs and cumulative costs (2020-2050) were compared between scenarios. For all proposed scenarios, annual direct medical costs were estimated at $142 M (2020 CAD) in 2020 and were projected to decrease approximately 50%, partially as the result of an annual 3% discount rate, but largely due to a decrease in prevalence with any vaccination strategy. Direct medical costs for adolescent vaccination over 30 years was $3,333M (Figure 1A, Table 3). These costs decreased related to the type of alternative vaccination strategy and in a stepwise fashion depending on whether the HBV vaccine was given as a separate dose, or a part of the hexavalent vaccine. For example, if following the recommended birth dose schedule and delivering all three as separate vaccines, direct costs increased to $3,424M, while as a part of the hexavalent strategy direct costs were less than adolescent immunization at $3,310M (Table 3). Annual cost savings peaked in 2022, with savings ranging from $1.3M-$4.4M.

Immunization Costs

Annual immunization costs were estimated at $2.4M in 2020 under all scenarios and declined by 65% for adolescent vaccination to $0.91M in 2050, due to the application of a standard 3% discount rate. Costs were incurred during the 12-year catch-up period for all infant vaccination scenarios (Figure 1B). Annual costs for the two strategies which include birth dose and 1-month dosing had greater costs every year from 2020-2050, leading to cumulative immunizations costs increasing by up to 160% (from $46M to $119M). However, the two strategies that had at least two of three doses as a part of the hexavalent immunization had costs below the current adolescent costs by 2030 (**Error! Reference source not found.**B). The hexavalent strategy also decreased cumulative costs by 50%, from $46M to $23M. Cumulative immunization costs represented 1.4% of direct medical costs for adolescent vaccination and between 0.70% (3 hexavalent immunizations) and 3.5% (3 individual doses including birth dose) of costs under the infant vaccination scenarios.

Indirect and Total Costs

Indirect costs were based on the value of a statistical life year ($62,138) applied to DALYs incurred by each scenario. Indirect costs accounted for 75% of total (direct and indirect) costs in 2020 ($600M), peaking at 85% of annual total costs in 2045 under all scenarios. Total indirect and direct costs were $18.43B for adolescent vaccination, increased to $18.52B for 3 individual doses, and were $18.41B when using the three-dose hexavalent approach (Figure 2A). As compared to adolescent vaccination, total cumulative costs were $62M higher with three individual doses, while three-dose hexavalent led to cost savings of $23M by 2050 (Figure 2B).

Disability-Adjusted Life Years (DALYs) and Cost-Effectiveness

Approximately 3% of all DALYs were incurred as a result of years lived with disability, and 97% were incurred due to years of life lost (liver-related death). In 2020, there were an estimated 9,650 annual DALYs incurred due to HBV, increasing to 11,100 annual DALYs by 2050 with the current adolescent strategy, an increase of 15%. This increase is largely the result of the impacts of the liver-related disability and death for the current chronically infected population, as well as chronic infections among newcomers to Canada between 2020 and 2050. Total cumulative DALYs using adolescent vaccination were estimated at 360,000 during 2020-2050, and by 2050, all four infant scenarios had averted the same number of DALYs (≥54 DALYs) (Table 3). As the model did not use a lifetime horizon, the major contributor to DALYs averted is immunization costs from 2020-2050. Cost per DALY incurred ranged from $104,000 to $1.68M (birth dose plus separate individual vaccines at 1 and 6 months), while hexavalent dosing at 2, 4, and 6 months was cost-saving at $428,000 per DALY averted (Figure 3B, Table 3). Sensitivity analysis was conducted for the cost per DALY averted in the hexavalent approach as compared to adolescent vaccination (Supplementary Methods V). HBsAg prevalence, the cost of HBV treatment and the prevalence of HBeAg+ among HBsAg+ WoCBA were the key drivers of uncertainty, accounting for 95% of variation (Figure 4). Prevalence alone accounted for >80% of observed uncertainty (Supplementary Material Section III).

Discussion

We recently demonstrated that there is epidemiologic evidence to reconsider the current adolescent HBV vaccination strategy in Ontario (5). Here, we demonstrate that incorporating infant immunization into our current vaccination schedule would prevent

acute and chronic infections. Incorporating immunization into a hexavalent vaccine given at 2, 4, 6 months would also be cost-saving by 2050.

We evaluated 5 scenarios for HBV vaccination strategies. The impact of immigration, especially as it relates to immigration to Canada from high prevalence countries of HBV, was included. While infant vaccination does not eliminate the impact of imported cases, it would prevent early childhood transmission from caregivers who may have acquired HBV prior. All vaccination strategies led to an overall decline in chronic cases by 2050. However, switching to any form of birth or infant vaccination, would prevent 37-38% of acute and 30-31% of chronic cases in Ontario by 2050. All models include continuation of HBV screening of pregnant women (~94%), and universal birth dose and HBIG for children born to known HBsAg-positive mothers.

To switch from two-dose adolescent to three-dose infant vaccination, there would be a 12-year period where vaccination was occurring both groups to ensure all children were vaccinated. A single birth dose strategy was cost-effective, as the cost per DALY was less than the standard willingness-to-pay threshold of two times GDP per capita ($124,000) (24). In this approach the hexavalent vaccine at 2 and 6 months would replace our current pentavalent strategy which does not include HBV, costing less per year than the adolescent strategy after the 12-year catch-up period after 2032. However, as shown in Figure 1B, switching now to a hexavalent approach at 2, 4, and 6 months would not lead to additional immunization costs, and thus no additional costs during the catch-up period.

Visits for pediatric immunizations are typically incorporated into well-baby visits in primary care/pediatrics, or at local health units, whereas school-based adolescent vaccination require additional infrastructure. Nonetheless, adolescent immunization coverage is suboptimal and much lower than infant. Both national and provincial reports published in 2020 demonstrate an uptake of other 3-dose infant programs of 90% (25), while HBV adolescent coverage in Ontario in recent years has been as low as 67% (Table 1S). Not only would incorporating HBV vaccination into well-baby visits reduce the number of injections children would receive, and be cost-saving, but this approach would follow the provincial strategy for primary care providers to administer the majority of immunizations in Ontario (26).

There is existing evidence that birth dose or infant immunization reduces both acute and chronic HBV in children; yet adoption varies greatly by province. British Columbia has been immunizing children in infancy for 20 years (27), and early analysis of the impact of infant vaccination showed benefit (28). Nunavut, a region known to have a high prevalence, has also been providing birth dose and infant vaccination for over 20 years. The first serosurvey results in the post-vaccination era were recently described, documenting a reduction in hepatitis B core antibody (a marker of exposure) prevalence from 19.8% to 1.8%, and a decrease in HBsAg prevalence from 2.5% to 0.3% (29).

Limitations

Estimates of HBV prevalence for foreign-born Ontario residents were assumed to be similar to the prevalence in country of origin (30), however this assumption may not be

accurate in some populations(31). The model likely underestimates the cost of disease burden, as it does not account for HIV/HBV, HBV/HCV and HBV/HDV co-infections; all of which can lead to faster disease progression. Although hepatocellular carcinoma can still develop following HBsAg clearance (32, 33), the current model does not account for the small amount of older chronically infected individuals who clear HBsAg (34-37). As a result of the short timeframe, HBV-related deaths and end-of-life care is not accounted for. Although not evaluated in this model, additional cost-savings are very likely, including eliminating the logistics, supplies and personnel for the school-based HBV vaccination program; the likely higher cost of adult vs pediatric vaccine doses; and the buying power of Ontario, potentially benefitting other provinces which use the hexavalent vaccine in Canada.

Conclusion

Transitioning from adolescent HBV vaccination to infant immunization would be cost-effective and could be cost-saving. These cost-savings and decreases in case numbers would almost certainly apply to other provinces where adolescent vaccination continues to be the standard of care, and therefore it may be reasonable to suggest a national shift to infant HBV vaccination.

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Supplementary Material

Methods

I. Literature search

The literature review was conducted by searching PubMed and Embase for peer-reviewed studies reported HBsAg prevalence using the terms: "[Ontario] AND [(hepatitis B) or HBV] AND [prevalence]" AND "[Ontario] AND ('prevalence'/exp OR prevalence) AND ('hepatitis B'/exp OR 'hepatitis B' OR 'HBV'/exp OR 'HBV')". Studies published between Jan 1, 1985, and March 1, 2016 and without language restrictions were assessed. Grey literature, ministry of health reports, conference presentations, local journals, and personal communications with local experts were included in the data review. Studies conducted in non-representative populations (e.g. blood donors, hemophiliacs, and patients on hemodialysis) were excluded. Per Delphi process protocol, two in-person meetings were held with Ontario experts who reviewed and approved epidemiologic inputs or provided improved data sources to finalize the model.

II. The HBV PRoGReSs Model

The HBV Progress Model is a dynamic Markov disease burden and transmission model that tracks the distribution of HBsAg prevalence by sex, age (1-year age cohorts), year (1950-2050), disease stage (acute, chronic, cirrhosis, decompensated cirrhosis, HCC, and death), and viral load (categorical), while accounting for background mortality, disease progression rates, spontaneous viral clearance, and fulminant hepatitis. Disease transmission was calculated both horizontally and vertically (by vertical transmission rates). Data from Statistics Canada (12) and the United Nation's Department of Economic and Social Affairs, Population Division (42) were used for annual background population

and mortality estimates by sex and 1-year age cohort from 1950-2050. Epidemiologic estimates for HBV (Table 2), were applied to the background Ontario population.

III. HBV prevalence estimate

HBsAg prevalence in Ontario may vary by birth cohort due to changing vaccination policies and immigration over time (23). Therefore, 2016 HBsAg prevalence estimates based on recorded clinical data, adjusted based on two age distributions: reported cases by age group and population data for Ontario, with additional adjustment for the impact of immigration (5, 7). Among native-born Canadians, prevalence rates were modified to account for a declining prevalence in older Ontario residents (due to mortality rate and low infection rate). National surveillance data estimating a higher prevalence in men than women (13.2 vs. 9.6 per 100,000) (19), was applied to the distribution of cases by age group. While prevalence data do not exist for the immigrant population, estimated HBsAg prevalence based on Toronto data was considered in the baseline estimate for Ontario as a whole. For ten high prevalence countries with sizable immigrant populations (China, Hong Kong, India, Iran, Jamaica, Pakistan, Poland, Philippines, Sri Lanka, Vietnam) annual entrance data by age and sex were available from 1980-2016 (43). The Polaris Observatory has previously published country specific PRoGReSs Models for all ten of these countries (13). Utilizing these models and the annual country-specific entrance data by age and sex the estimated annual number of HBsAg+ immigrants by age, sex, and disease stage were added to the Ontario model. For years in which no published data were currently available (2017 onwards), the number of immigrants by country of birth and distribution by age and sex were assumed to remain constant into the

future. It was estimated that 70% of cases in Ontario in 2017 were among first generation migrants.

IV. Scenario development: Additional criteria

In all scenarios, it was assumed that patients between ages 15-85, that had a high viral load or were cirrhotic, were eligible for treatment and that treatment efficacy was 90%. Prophylaxis coverage rates were varied in 3 waves (2021, 2022-2023, 2024-2050). Prevalence was also estimated for infants and 5-year-olds to assess the impact of intervention on disease outcomes in children.

V. Sensitivity analysis

Sensitivity analysis was calculated for high-level disease burden and economic impact outcomes using Crystal Ball release 11.1.2.3.500. β-PERT distributions were used for all uncertainty intervals. We used a Monte Carlo simulation to estimate key drivers of uncertainty for the cost per DALY averted for Scenario 5 as compared to the Base Scenario, with input ranges based on published estimates and expert input (Table 1) (13). The key drivers of uncertainty (Figure 4) account for >99% of the variation around cost per DALY averted when comparing the hexavalent approach to the adolescent vaccination.

Figure 1S. HBsAg prevalence and case count for the adolescent vaccination, Ontario, 2020-2050.

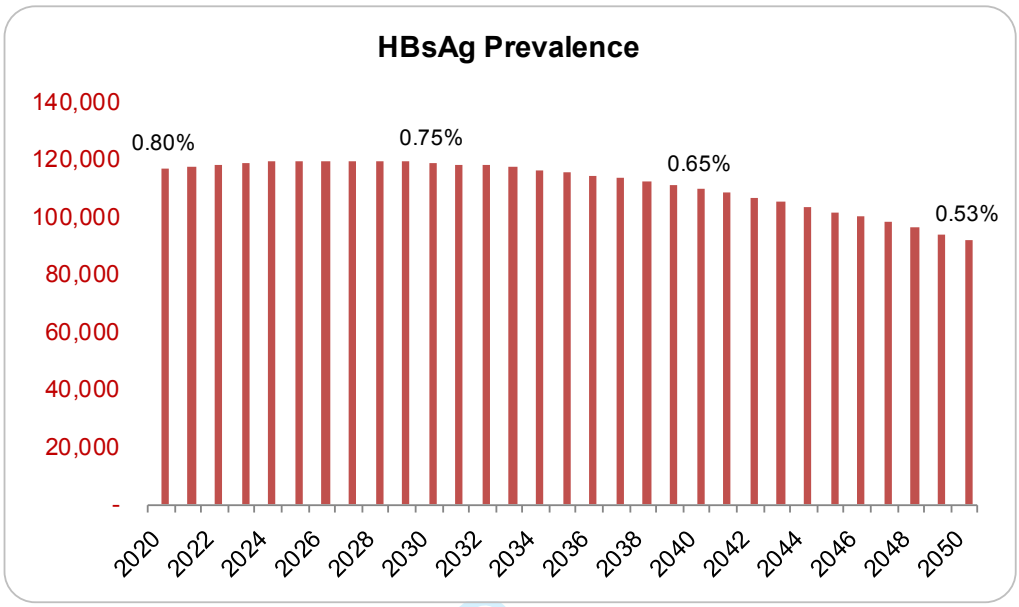

Figure 2S. HBsAg prevalence by sex and age group for the adolescent vaccination, 2020 and 2035.

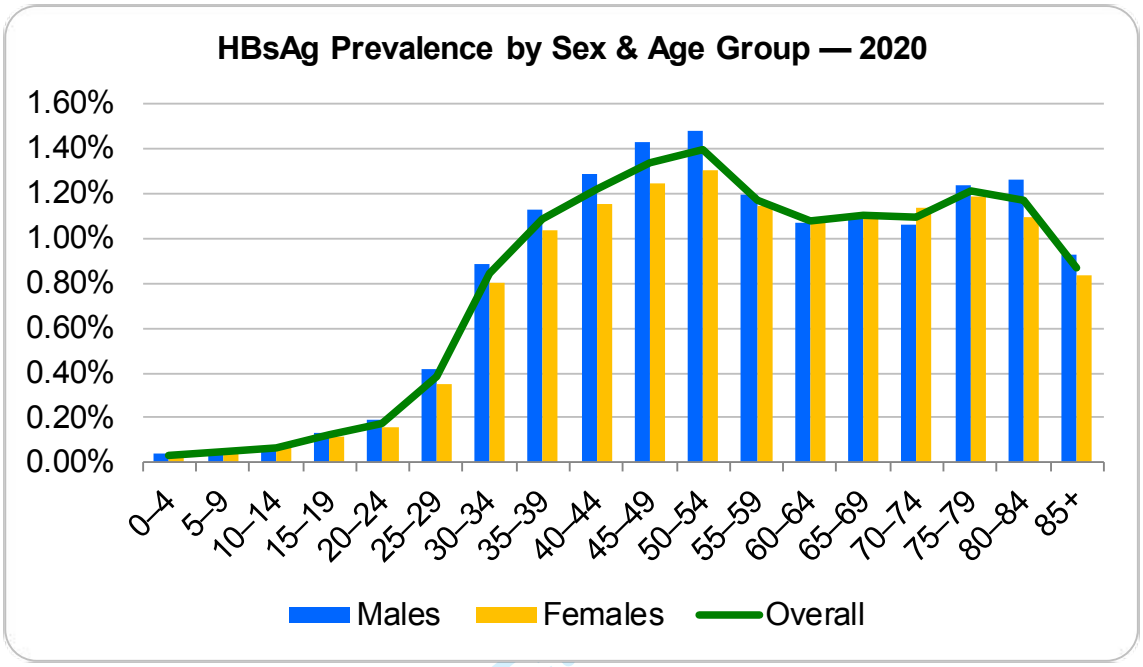

Table 1S. Vaccination Rate in Grade – Ontario, 1994-2016.

Year	Value
1994-1995	86.6%
1995-1996	88.7%
1996-1997	93.6%
1997-1998	86.5%
1998-1999	85.9% *
1999-2000	85.2% *
2000-2001	84.6% *
2001-2002	83.9% *
2002-2003	83.3% *
2003-2004	82.6% *
2004-2005	82.0% *
2005-2006	81.3% *
2006-2007	80.7% *
2007-2008	80.0%
2008-2009	78.1%
2009-2010	74.2%
2010-2011	76.6%
2011-2012	86.6%
2012-2013	86.9%
2013-2014	71.7%
2014-2015	70.7%
2015-2016	69.9%

* Not reported, data linearly interpolated

TABLES

Table 1. General Population Intervention Scenarios – Ontario

	Scenario	Administration	Predicted Immunization Coverage					
			2021	2022-2023	2024-2050	2021	2022-2023	2024-2050
1	Base Scenario (current adolescent schedule)	Two pediatric HBV doses in Grade 7	0%	0%	0%	0%	0%	0%
2	3 individual doses (0, 1, 6 months)	Three pediatric HBV doses in the first year of life	75%	90%	95%	75%	90%	95%
3	2 individual, 1 combined (0, 1, 6 months)	Two pediatric HBV doses, final dose hexavalent on the same schedule as current pentavalent	75%	90%	95%	75%	90%	95%
4	1 individual, 2 combined (0, 2, 6 months)	One dose of pediatric HBV, two doses of hexavalent on the same schedule as current pentavalent	75%	90%	95%	75%	90%	95%
5	3 combined (2, 4, 6 months)	Three doses of hexavalent on the same schedule as current pentavalent	0%	0%	0%	75%	90%	95%

Table 2. Model Parameters

Disease Burden Inputs			Low	High
Item	Year	Value (Source)		
HBsAg+ prevalence	2017	0.80% (determined)	0.29%	1.6%
HBsAg+ prevalence: Male to female ratio	2017	1.38 (1)	—	—
HBeAg+ among HBsAg+ WoCBA	2012-2016	18.9% (2)	9.1%	24.0%
Viral load ≥20,000 UI/mL among HBeAg+	2002-2008	90% (3)	—	—
Viral load ≥20,000 UI/mL among HBeAg-	2002-2008	13% (3)	—	—
Total diagnosed	2003-2013	39,623 †	—	—
Newly diagnosed	2017	1,878 (1)	—	—
Total treated	2018	6,520 (1, 4) ‡	—	—
Annual liver transplants	2016	264 *	—	—
Liver transplants due to HBV	2016	9.3% *	—	—
HBV vaccination timely birth and three dose coverage rates for infants born to HBsAg+ mothers	2016	93.7% (5) †	—	—
HBIG coverage rate for infants born to HBsAg+ mothers that also receive timely birth dose	2016	93.7% †	—	—

Economic Inputs			Low	High
Category	Item	2020 Value (Source)		
Disability Weight	Disability weight – decompensated cirrhosis	0.178 (6)	—	—
	Disability weight – HCC	0.466 (6)	—	—
	Disability weight – liver transplant	0.024 (6)	—	—
Value of a statistical life year (2020 CAD)	GDP per capita	62,138 (7)	—	—
Screening and lab costs per test (2020 CAD)	HBsAg	10.25 §		
	HBeAg	10.25 §		
	Viral load testing	100.00 †		
	ALT testing	10.00 §		
	CBC / Creatinine / Bilirubin	29.00 §		
	Abdominal Ultrasound	135.9 (8) ¶	68.39	271.8
HBV Treatment and prophylaxes costs (2020 CAD)	Treatment (annual)	5,770 (9)	3,509	8,031
	HBV Vaccination – children	11.16 †	10.92	11.40
	Vaccination – adult	7.44 †	7.28	7.60
	HBIG	287 (10)	230	344

Annual health state costs (2020 CAD)	Chronic HBV	1,150 (11)	1,048	1,341
	Compensated cirrhosis	2,517 (11)	2,013	3,760
	Decompensated cirrhosis	15,113 (11)	11,184	22,059
	Hepatocellular carcinoma	17,970 (11)	14,279	23,134
	Liver transplant	133,346 (11)	126,969	143,801
	Post-liver transplant	51,475 (11)	45,015	62,035

ALT, alanine transaminase; HBeAg, hepatitis B e-antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; CAD, Canadian dollar

* Unpublished data: Internal analysis conducted at London Health Sciences Centre & Toronto General Hospital
† Expert consensus
‡ Treatment rate for British Columbia applied to Ontario with adjustment for population and prevalence rate ratio
§ Provincial reimbursement
¶ Adjusted: 67% of infected population receives abdominal ultrasound based on age guidelines (≥40 years for men and ≥50 years for women)

Table 3. General Population Intervention Scenarios – Ontario

	Scenario	Cumulative Burden 2020-2050				
		Acute HBV	Chronic HBV	Cumulative Direct Costs (M)	DALYs Averted	Cost per DALY Averted
1	Base Scenario (current adolescent schedule)	1,500	520	3,333	–	–
2	3 individual doses (0, 1, 6 months)	940	360	3,424	54	1,675,000
3	2 individual, 1 combined (0, 1, 6 months)	940	360	3,370	54	671,000
4	1 individual, 2 combined (0, 2, 6 months)	940	360	3,339	54	103,000

FIGURES

Figure 1A

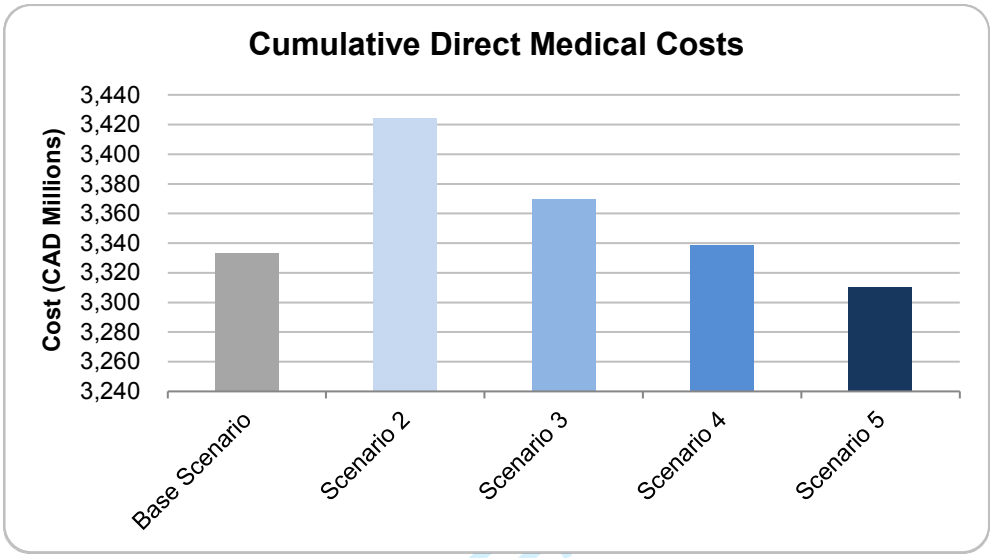

Figure 1B

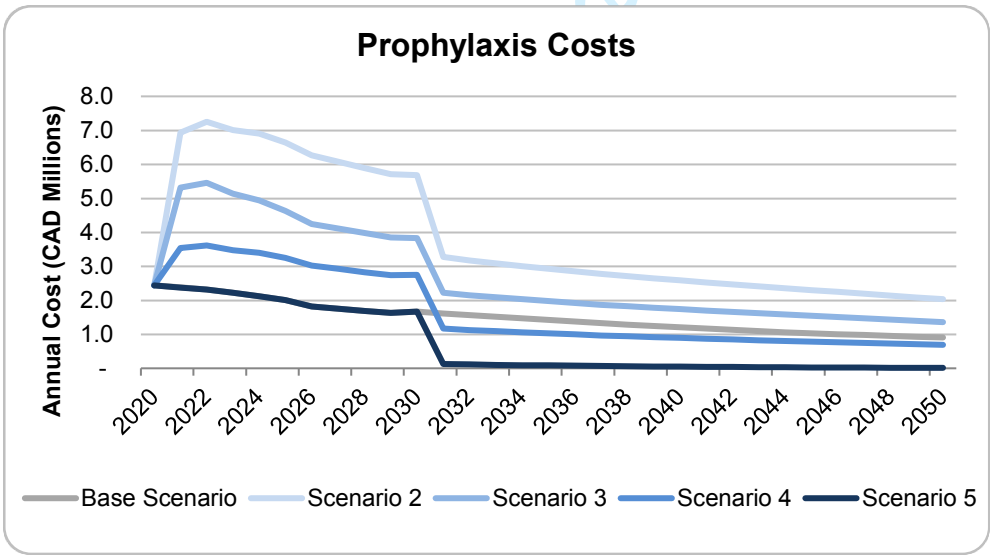

Figure 1. HBV-related direct A) medical costs of HBV management and B) immunization costs by scenario 2020-2050, Ontario.

Figure 2A

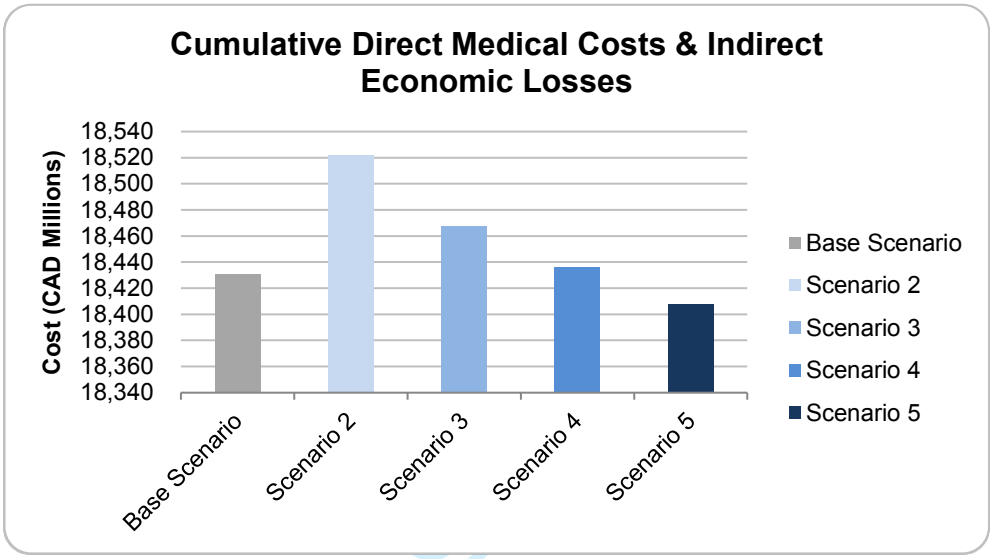

Figure 2B

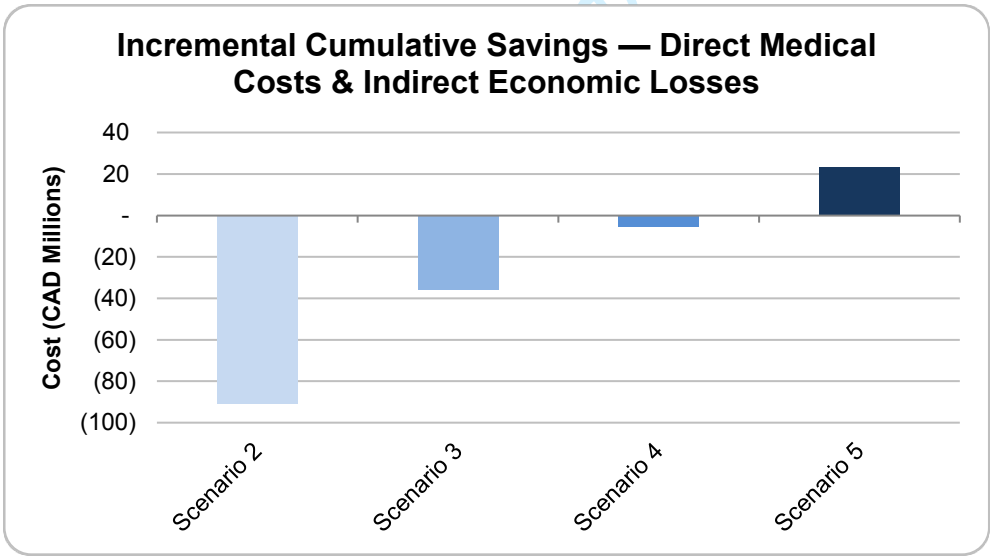

Figure 2. HBV-related direct A) HBV management and economic loss due to disease, and B) incremental cumulative savings as of 2050 as compared to adolescent.

Figure 3A

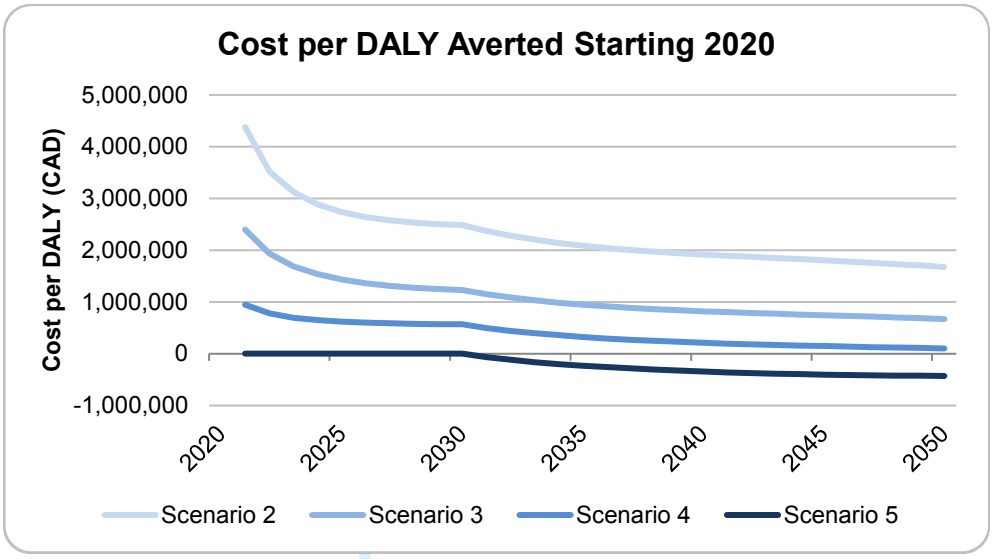

Figure 3B

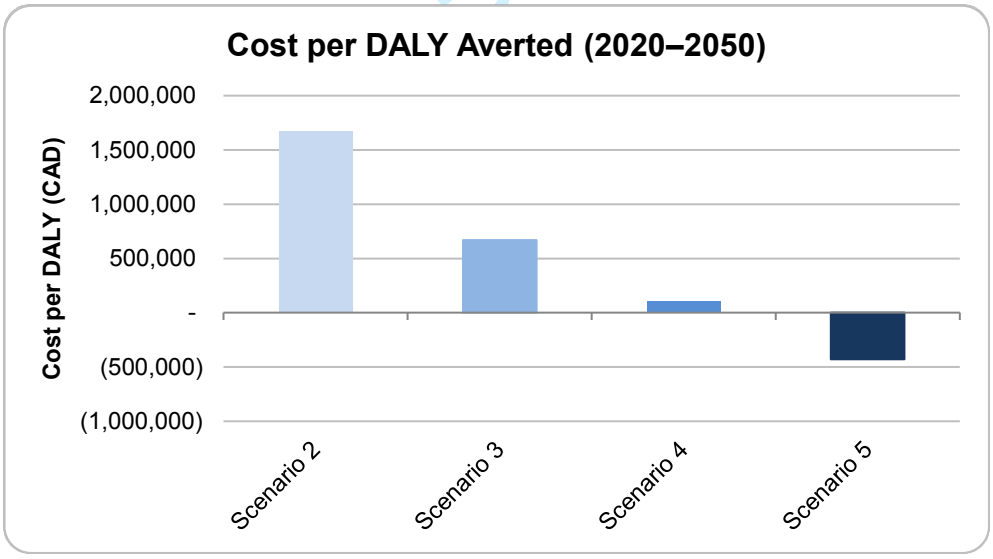

Figure 3. Cost per daily averted from A) 2020-2050 and B) as of 2050.

Figure 4

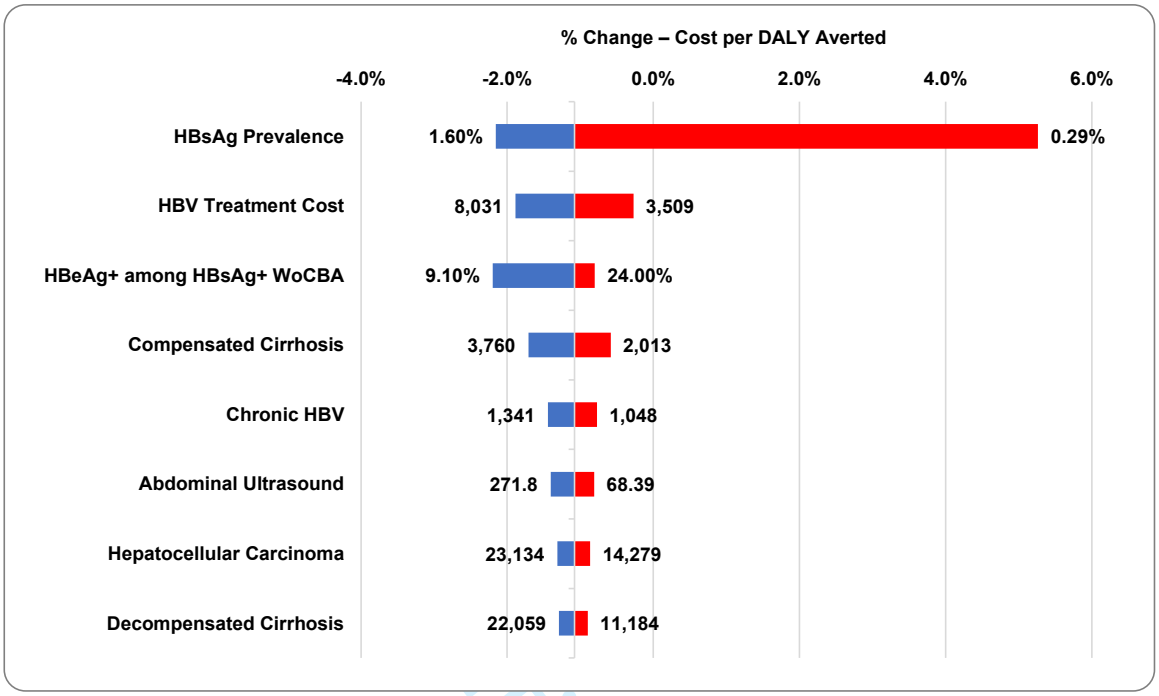

Figure 4. Key Drivers of Uncertainty – Cost per DALY Averted comparing vaccines at 2, 4, 6 months as a part of the hexavalent approach to adolescent vaccination.