



Economic evaluation of a publicly funded hepatitis A travel vaccination program in Ontario, Canada



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ARTICLE INFO

Article history:

Received 12 September 2018

Received in revised form 11 January 2019

Accepted 23 January 2019

Available online 13 February 2019

Keywords:

Hepatitis A
Economic evaluation
Travel vaccine
Cost-effectiveness

ABSTRACT

Background: Hepatitis A virus (HAV) causes acute liver infection and is spread through the fecal-oral route. Travel to countries in HAV-endemic regions (e.g., Asia and Latin America) is a well-described risk factor for infection. Currently, Ontario publicly funds hepatitis A vaccination for some populations at high risk of HAV infection but not for all travellers to endemic countries. The objective of this study was to determine the cost-effectiveness of expanding publicly funded HAV vaccination to people planning travel to HAV-endemic regions, from the Ontario healthcare payer perspective.

Methods: We conducted a cost-utility analysis comparing an expanded high-risk publicly-funded hepatitis A vaccination program including funded vaccine for travellers to endemic regions to the current high risk program in Ontario. A Markov state transition model was developed, including six possible health states. Model parameters were informed through targeted literature searches and included hepatitis A disease probabilities, utilities associated with health states, health system expenditures, and vaccine costs. Future costs and health outcomes were discounted at 1.5%. Primary outcomes included cost, incremental cost-effectiveness ratio (ICER) and quality adjusted life years (QALYs) over a lifetime time horizon. We conducted one-way, two-way, and probabilistic sensitivity analysis.

Results: The expanded high risk HAV vaccine program provided few incremental health gains in the travel population (mean 0.000037 QALYs/person), at an incremental cost of \$124.31. The ICER of the expanded program compared to status quo is \$3,391,504/QALY gained. The conclusion of the model was robust to changes in key parameters across reasonable ranges.

Conclusions: The expanded vaccination program substantially exceeds commonly accepted cost-effectiveness thresholds. Further research concerning possible cost-effective implementation of high-risk travel hepatitis A vaccination should focus on a more integrated understanding of the risk of acquiring hepatitis A during travel to endemic regions (e.g., purpose, length of stay).

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1. Background

Hepatitis A virus (HAV) causes acute liver infection and is spread through the fecal-oral route, for example through consumption of contaminated food or drink, or close contact with a person with hepatitis A while they are infectious (including sexual contact) [1]. HAV pre-exposure vaccination is 90–97% effective in pre-

venting illness [2]. Disease severity increases with age; 70% of adult cases present with jaundice, and older adults experience increased morbidity, but young children are often asymptomatic [3]. It has been estimated that 25% of symptomatic cases require hospitalization, and those with chronic liver disease, including hepatitis B and C, experience a greater risk of fulminant hepatitis and acute liver failure [4]. Canadian estimates of direct healthcare costs per symptomatic HAV case range from \$1140 to \$1923, depending on age [5]. Immunity, either following infection or vaccination, is considered to be lifelong [3].

A region's HAV endemicity is typically defined by the estimated age-related seroprevalence of anti-HAV antibodies in the

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population [6]. In a Canadian systematic review of HAV surveillance, high endemicity was defined as more than 90% of individuals younger than 10 years old having HAV immunity, while low endemicity was defined as less than 50% of individuals younger than 30 years old having anti-HAV antibodies [7]. Travel to countries in HAV-endemic regions (including Asia, Africa, the Middle East, and Latin America) is a significant risk factor for infection [8–10]. Travel-related cases constitute a large proportion of incident HAV infections reported in non-endemic countries, such as Canada [11]; between 1998 and 2004, 43% of 1381 reported cases in Ontario were travel-related [12]. Travel-associated HAV incidence is expected to grow due to increased migration to Ontario from HAV-endemic countries, and accompanying travel to and from these regions (e.g., to visit friends and relatives) [13]. Low HAV seroprevalence within Canada, a low endemicity setting in which most provinces and territories offer high risk rather than universal hepatitis A vaccination programs [2], results in substantial population susceptibility to travel-related acquisition [7,14,15]. Moreover, being infectious in the latter part of the comparatively long 15- to 50-day incubation period (typically, 28 days) and the potential to transmit in the absence of symptoms, increase the likelihood of secondary transmission to close contacts. Sporadic, travel-acquired HAV cases also have the potential to lead to community outbreaks following return home [16]. The potential importance of expanded HAV vaccination programs in non-endemic countries as a strategy for targeting travel-associated transmission has been previously identified [17].

Currently, Ontario provides publicly-funded, pre-exposure hepatitis A vaccination for some populations at high risk of HAV infection or severe hepatitis A infection— i.e., persons who inject drugs, men who have sex with men, and those with chronic liver disease (e.g., hepatitis B and C) – but not for travellers to endemic countries who do not meet other eligibility criteria [18]. The Canadian Immunization Guide recommends pre-exposure hepatitis A vaccination for all people aged 6 months and older traveling to hepatitis A endemic countries [2]. However, in Canada provinces and territories are responsible for immunization program decisions and most jurisdictions, including Ontario, do not offer publicly-funded pre-exposure hepatitis A vaccination based on travel alone. Given the public health impact of travel-associated HAV in Ontario, it is useful to investigate the cost-utility of a publicly-funded vaccination program that includes all travellers to endemic countries. This expanded vaccination strategy will be compared to existing privately-purchased access.

2. Methods

A cost-utility analysis was conducted to evaluate two alternative HAV vaccination programs in Ontario: (1) an ‘expanded high-risk’ program that includes travellers to endemic regions, and (2) the existing status quo as a comparator, where HAV vaccination is privately purchased by travellers that do not meet the one of the current Ontario high risk eligibility criteria. The analysis was conducted using the provincial healthcare payer perspective (Ontario Ministry of Health and Long-Term Care). Principal outcomes included quality-adjusted life years (QALYs), program costs (2017 Canadian dollars), and the incremental cost-effectiveness ratio (ICER). Costs and outcomes were discounted at 1.5% (0% and 3% in sensitivity analysis) annually [19]. Cost-effectiveness was assessed using the commonly accepted cost-effectiveness threshold of \$50,000 per QALY gained.

2.1. Model

A Markov state transition model was developed using the 2016 Ontario travel population as a cohort [20,21], with TreeAge Pro

2017 software (Williamstown MA). Possible health outcomes considered within the model included HAV infection, symptomatic illness, physician visits and hospitalization, and complications (fulminant hepatitis and acute liver failure, liver transplant), mortality (due to HAV as well as unrelated causes), and QALYs. A lifetime time horizon was used, with a Markov cycle length of one year. Costs of vaccination, public health contact tracing, and disease treatment were considered.

2.2. Structural assumptions

Modelling was based on HAV disease history, and included six possible health states: well (susceptible to HAV), well (immunity from HAV vaccine), well (unknown natural immunity), well (known natural immunity), post-liver transplant, and dead (Fig. 1). The four well states were included in order to capture varying susceptibility to HAV and their subsequent vaccination decisions; well (susceptible to HAV) includes those with no prior vaccine or past HAV infection and who may choose to be vaccinated prior to travel, well (immunity from HAV vaccine) includes those with vaccine-induced immunity, well (unknown natural immunity) includes those who are protected against HAV infection due to past asymptomatic infection but are unaware of their immunity and thus may still choose to be vaccinated, and well (known natural immunity) includes those with known past infection and who we assumed would not choose to be vaccinated. Informed by general seroprevalence data as a conservative estimate of immunity (corresponding to greater vaccine demand), the majority of the population (95%) started in the well (susceptible to HAV) health state, with the rest (5%) starting in an immune well state [4]. For each of the four well states, events included: receipt of HAV vaccine, travel to an endemic region, infection with HAV, development of symptomatic illness, hospitalization, and liver transplant (Fig. 2). Post-liver transplant, possible transitions included remaining in the post-transplant state, or death. It was assumed that individuals opting to get an HAV vaccine (for travel purposes) would travel within one year. It was also assumed that anyone with known immunity would not receive the HAV vaccine, and that it was not possible to develop hepatitis A more than once, given the lifelong persistence of anti-HAV antibodies following infection [4]. Regarding those infected with r HAV, it was assumed that only symptomatic cases would result in either a physician visit or hospitalization; it was also assumed that hospitalized cases were the only ones at risk of experiencing severe outcomes (e.g., acute liver failure).

2.3. Model inputs and data assumption

Data regarding probabilities, utilities, health system costs, and vaccination were obtained from relevant targeted literature sources. Parameter estimates and sources are summarized in Table 1.

2.3.1. Probabilities

The probability of infection with HAV was estimated to be 0.033% for travellers to HAV-endemic regions [15], and 0.0009% for those who do not travel to an endemic region [22]. Likelihood of travelling to an endemic location was derived from international travel patterns of Canadians [21]. Assuming similar sociodemographic characteristics between travellers from Canada and the U.S., the probability of privately-purchased HAV vaccine uptake was drawn from a U.S. study where 26.6% of participants reported seeking HAV vaccination before travelling to a location of high or intermediate endemicity [23]. To estimate the likely increase in vaccine uptake resulting from public financing, Canadian data regarding the increase in human papillomavirus (HPV) vaccine

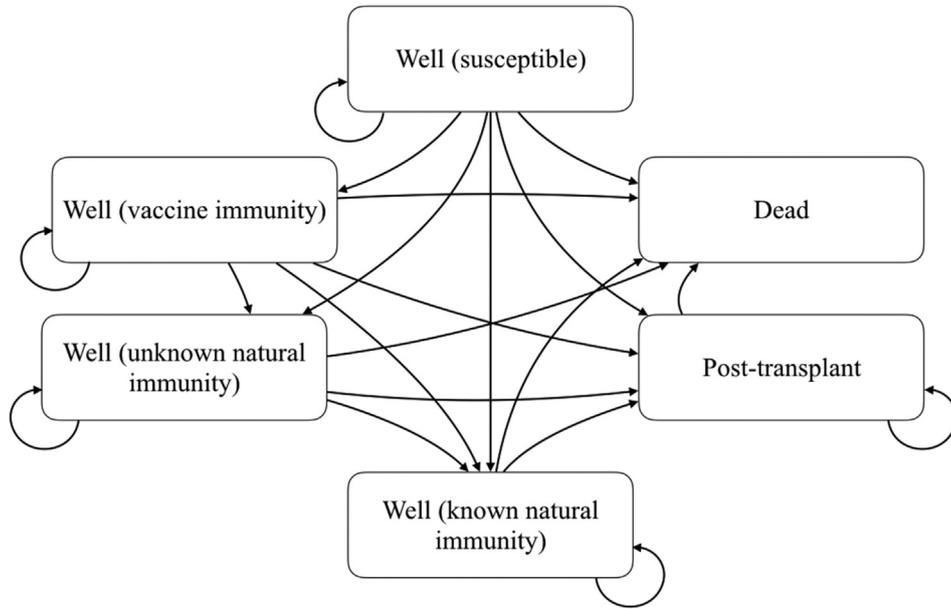


Fig. 1. State transition diagram. This figure depicts the health states included in the model and possible transition paths between states.

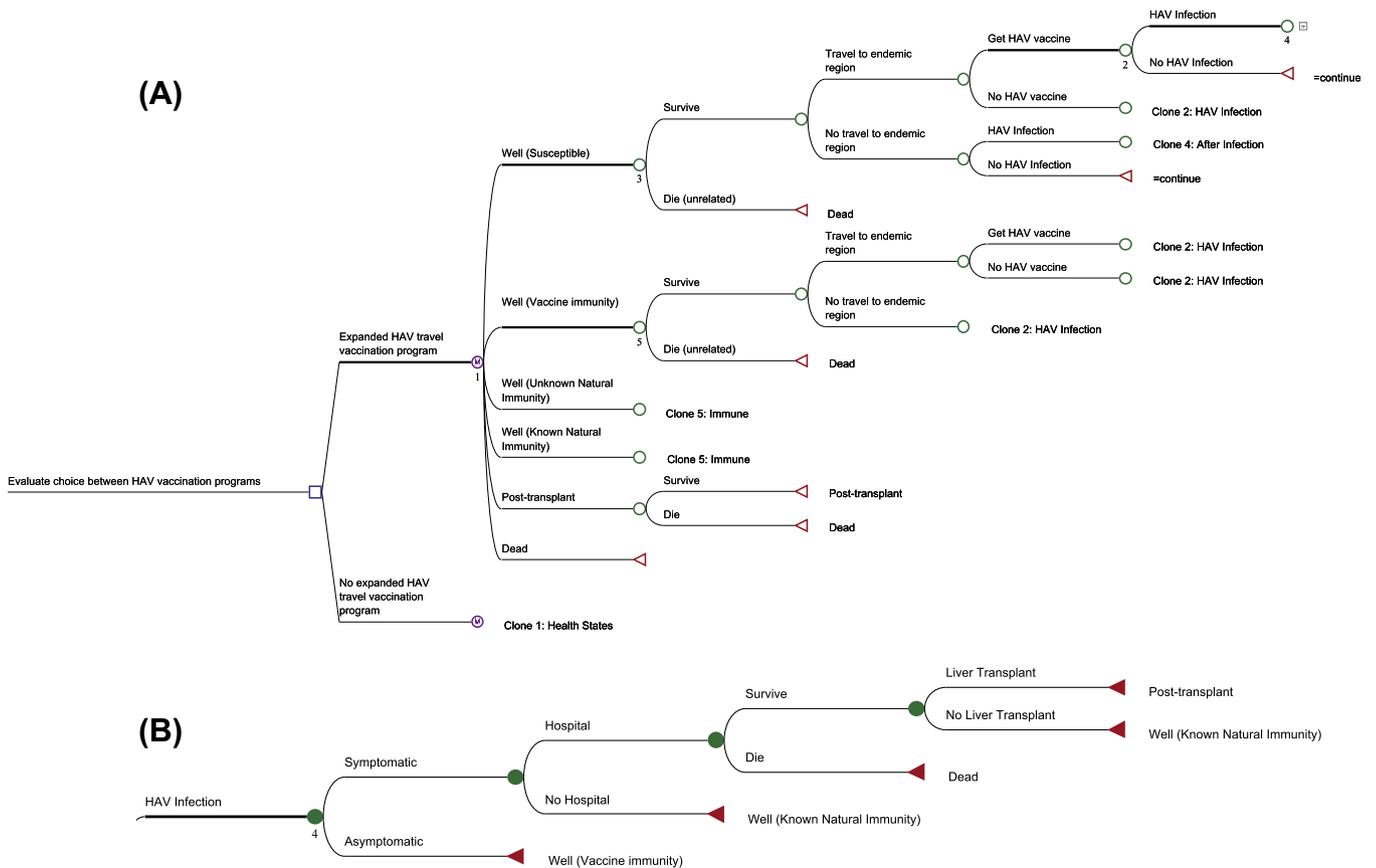


Fig. 2. Schematic of hepatitis A model. The schematic represents the two strategies under consideration: (1) Expanded HAV travel vaccination program, and (2) No expanded HAV travel vaccination program. The model structure for each strategy is the same. The 'HAV Infection' subtree is displayed in Panel B. The Markov model has a cycle length of one year and a lifetime horizon.

uptake following a switch from private to public funding (53% increase) were applied as a proxy [24]. Age-specific disease probabilities were included for the likelihood of developing symptomatic illness (range from 11% in children to 81% adults), visiting

a physician (67–85%), being hospitalized (16–23%), hospital length of stay (three to seven days), and dying from HAV (0.3–1.8%) [5,25,26]. The risk of requiring a liver transplant following acute liver failure, and post-liver transplant mortality were included as

Table 1
Input parameters to cost-utility model.

Variable	Baseline value	Range	Ref.
Probabilities			
Probability of contracting HAV			
If have travelled to an endemic region	0.033%	0.003%–0.069%	[15]
If have not travelled to an endemic region	0.0009%	0.00085%–0.003%	[22]
Probability of travelling to an endemic region	50%	20%–90%	Assumption based on [21]
Probability of getting HAV vaccine			
If privately purchased	26.6%	10%–50%	[23]
If publicly funded	79.9%	60%–90%	[24]
Probability of symptomatic illness			
<4 years	11%	8%–14%	[5]
5–9 years	34%	26%–42%	
10–19 years	70%	53%–88%	
20–29 years	81%	61%–100%	
30–39 years	81%	61%–100%	
40–59 years	81%	61%–100%	
≥60 years	81%	61%–100%	
Probability of physician visit			
<4 years	80%	40%–100%	[5]
5–9 years	80%	40%–100%	
10–19 years	82%	41%–100%	
20–29 years	67%	34%–100%	
30–39 years	83%	42%–125%	
40–59 years	79%	40%–100%	
≥60 years	79%	40%–100%	
Probability of hospitalization			
<4 years	21%	11%–32%	[5]
5–9 years	21%	11%–32%	
10–19 years	21%	11%–32%	
20–29 years	17%	9%–26%	
30–39 years	17%	9%–26%	
40–59 years	23%	12%–35%	
≥ 60 years	16%	8%–24%	
Probability of acute liver failure requiring a transplant	0.7%	0.018%–2.56%	[27]
Long-term probability of death post-transplant	5.7%	2.0%–10.6%	[29]
Probability of death from HAV			
<50 years	0.3%	0.15%–0.45%	[25]
≥50 years	1.8%	0.9%–2.7%	
Probabilities of unrelated mortality	Life table		[30]
HAV hospital length of stay			
<20 years	3 days	1–5 days	[26]
20–39 years	4 days	2–6 days	
40–59 years	5 days	3–8 days	
≥60 years	7.5 days	4–11 days	
Utilities			
Utility of being healthy			
<40 years	0.94		[31]
40–49 years	0.93		
50–59 years	0.92		
60–79 years	0.91		
≥80 years	0.88		
Utility of having symptomatic HAV (if not hospitalized)	0.556	0.1–1	[33]
Utility if hospitalized	0.364	0.1–1	[33]
Utility of acute liver failure	0.364		[33]
Utility of living post-liver transplant	0.750	0.63–0.80	[32]
Vaccine Variables			
Vaccine doses per person	2		[2]
Vaccine effectiveness	93.5%	90.0%–97.0%	[2]
Vaccine cost per dose	\$45.50		[43]
Public health clinic administration cost	\$44.26		[5]

Table 1 (continued)

Variable	Baseline value	Range	Ref.
Costs			
Public health costs per case for follow-up of contacts	\$997.19	\$332.4–\$3,323.97	[36]
Physician visit	\$77.20	\$30.00–\$130.00	[38]
Hospitalization (per day)	\$954.93	\$722.47–\$1,188.14	[5]
Acute liver failure	\$37,150.73	\$21,435.59–\$57,161.57	[41]
Liver transplant	\$127,278.81	\$43,592.84–\$986,653.03	[42]
Post-liver transplant (annual)	\$25,907.79	\$19,539–\$32,265	[40]
HAV serology	\$32.87	\$21.44–\$42.87	[41]
Discount rate			
	1.5%	0–3%	[19]

* Costs adjusted for inflation to 2017 Canadian dollars; ranges used the point value as a mean, with 12.5% of total cost as a standard deviation.

parameters [27–29]. Age-related probabilities of unrelated mortality were also considered [30].

2.3.2. Utilities

Age-specific utilities for the well state were drawn from Health Utilities Index-Mark III (HUI-Mark III) scores obtained through a Canadian National Population Health Survey (NPHS) [31]. Healthy utilities ranged from 0.88 for those 80 years of age and older to 0.94 for those under 40 years of age. Post-liver transplant utilities were drawn from a study that evaluated quality of life in hepatitis C patients in Vancouver, Canada using the Health Utilities Index Mark 2/3 and the Hepatitis Quality of Life Questionnaire [32]. Disutilities associated with developing symptomatic HAV infection, and HAV-associated hospitalization (for the duration of time spent in hospital) were drawn from a cost-effectiveness analysis conducted in Belgium that elicited relevant utilities as part of their study [33].

2.3.3. Health system costs

All costs are expressed in 2017 Canadian dollars (equivalent to 2017 USD 0.77) [34]; where necessary, costs were adjusted for inflation using the Consumer Price Index (CPI).

Public health costs were included to reflect spending by public health organizations to follow up with possible contacts of any confirmed HAV cases – i.e., communication with the contact, assessing history of exposure, and offering/administering HAV vaccine as post-exposure prophylaxis for susceptible household and close contacts within 14 days of exposure [35]. Additional costs of post-exposure prophylaxis with immune globulin (e.g., for contacts with underlying liver disease, immunocompromising conditions or older adults) were not included. HAV-associated public health costs for contact tracing were derived from cost-per-contact estimates from the 2015 measles outbreak in Toronto [36]. An average of three contacts per case was assumed, since HAV transmission may occur among residents sharing a household [4]. This estimate is slightly higher than the average Ontario household size of 2.6 persons, to allow for possible wider transmission induced by a high-risk case (e.g. food handler) [35]. Public health costs were estimated at \$997.19 per case (three contacts × \$332.40 per contact); costs were assumed to apply to all hospitalized HAV cases, and 70% of cases that consulted a physician due to underreporting of HAV infection [37].

Health care costs included health services costs (physician visits, hospitalization, HAV serology testing), and treatment costs for HAV-associated acute liver failure, liver transplant, and post-transplant care [5,38–42]. Publicly-funded vaccine prices are not available in Ontario, therefore \$45.50 per dose was assumed based on the commercially reported price [43], and considering the bulk purchasing discount that the Ontario Ministry of Health and Long Term Care may reasonably achieve. Costs of vaccination included

vaccine administration costs, assuming administration at a public health clinic [5].

2.3.4. Vaccination

Mean HAV vaccine effectiveness was 93.5% with a lower and upper limit of 90 to 97% [2]. Optimal HAV immunity requires two doses of vaccine administered six months apart, although a single dose is sufficient to induce immunity for at least two years following vaccination [44]. For this reason, it was assumed that individuals receiving at least a single dose of HAV vaccine in advance of travel (within the same year) experienced immunity. For those receiving two doses, lifelong immunity – comparable with natural immunity induced following infection – was assumed [45].

2.4. Analyses

A base-case analysis was performed, using mean parameter values, and a mean start age of 30 years. Parameter uncertainty was assessed through sensitivity analyses. One-way sensitivity analyses were performed on all uncertain parameters. Two-way sensitivity analysis was performed on vaccine program cost (combined cost of vaccine product and administration) and the probability of HAV infection while traveling in an endemic region. Probabilistic sensitivity analysis with 100,000 simulations was performed. Distributions were estimated for all uncertain parameters in the model. Beta distributions were used for probabilities and utilities, and normal distributions were used for costs.

3. Results

3.1. Base-case results

Table 2 summarizes health outcomes, costs, and incremental cost-effectiveness ratios for the base-case analysis, comparing an expanded publicly-funded HAV vaccination program for travellers to existing privately purchased vaccination. The expanded HAV vaccination program provided 32.76636 QALYs (48.08204 undiscounted) at a cost of \$126.41 (\$129.58 undiscounted), compared to 32.76633 (48.08199 undiscounted) and \$2.10 (\$2.69 undiscounted) QALYs and costs of the status quo, respectively. The expanded HAV vaccination program provided a mean incremental health gain of 0.000037 QALYs (0.000053 undiscounted) for an incremental cost of \$124.31 (\$126.89 undiscounted) relative to the status quo comparator. The ICER of the expanded HAV vaccination program is \$3,391,504 per QALY gained (\$2,403,144 undiscounted) (Table 2).

Table 2

Base case results for publicly-funded HAV travel vaccination versus existing private purchase (status quo), undiscounted, discounted at 1.5%, and discounted at 3%.

	Expanded Program	Status Quo	Difference
Mean QALYs Per Person			
Undiscounted	48.082044	48.081991	0.000053
Discounted at 1.5%	32.766364	32.766327	0.000037
Discounted at 3%	23.760166	23.760139	0.000027
Mean Cost Per Person (CS)			
Undiscounted	129.58	2.69	126.89
Discounted at 1.5%	126.41	2.10	124.31
Discounted at 3%	123.60	1.72	121.88
ICER (CS/QALY)			
Undiscounted			2,403,144
Discounted at 1.5%			3,391,504
Discounted at 3%			4,469,975

Acronyms: QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

3.2. Sensitivity analysis

The model was most sensitive to the probability of HAV infection when travelling to an endemic region, the proportion of the population obtaining the vaccine in the private purchase scenario, and the probability of liver transplant (Fig. 3). Overall, the conclusions of the model were robust to all parameters tested across reasonable ranges in one-way sensitivity analyses. Two-way sensitivity analysis – on the probability of HAV infection when traveling to an endemic region and the vaccine program cost – demonstrated few combinations (i.e., when probability of HAV infection is at least 0.00035 and the cost of vaccination is at most \$90) of these variables in which the expanded program would be

considered cost effective (Fig. 4). Probabilistic sensitivity analysis found that at a \$50,000 cost-effectiveness threshold 100% of simulations would not be considered cost-effective (Fig. 5).

4. Discussion

The results of the cost-utility analysis demonstrate that expansion of publicly-funded HAV vaccination to include travellers to endemic regions results in a mean incremental gain of 0.000037 QALYs, with an incremental cost of \$124.31. With an incremental cost-effectiveness ratio of \$3,391,504 per QALY gained, this health intervention would not be considered cost-effective at a threshold of \$50,000 per QALY gained.

This is the first analysis to investigate the cost-effectiveness of including travellers as a high-risk population eligible for publicly-funded HAV vaccination in Ontario. This analysis has several limitations. First, analysis was done from a healthcare payer perspective. This perspective was chosen to accord with recent CADTH guidelines [19]. However, this viewpoint excludes societal costs – i.e., productivity losses (days of work, earnings, leisure time), time costs, informal caregiving resources, underestimating the impact of the publicly-funded program. The publicly funded costs associated with hospitalization may also be underestimated as hospitalization rates may be higher than the rates used in the model [4], however, extensive sensitivity analyses tested uncertainty around this parameter. Second, due to lack of data, uptake of HAV vaccine when publicly-funded is based on a surrogate estimate, using human papillomavirus (HPV) vaccine uptake in Canada – following a switch to public funding – as a proxy. HPV vaccine uptake as a surrogate was chosen due to similarities with the proposed HAV intervention: a change from private to public funding,

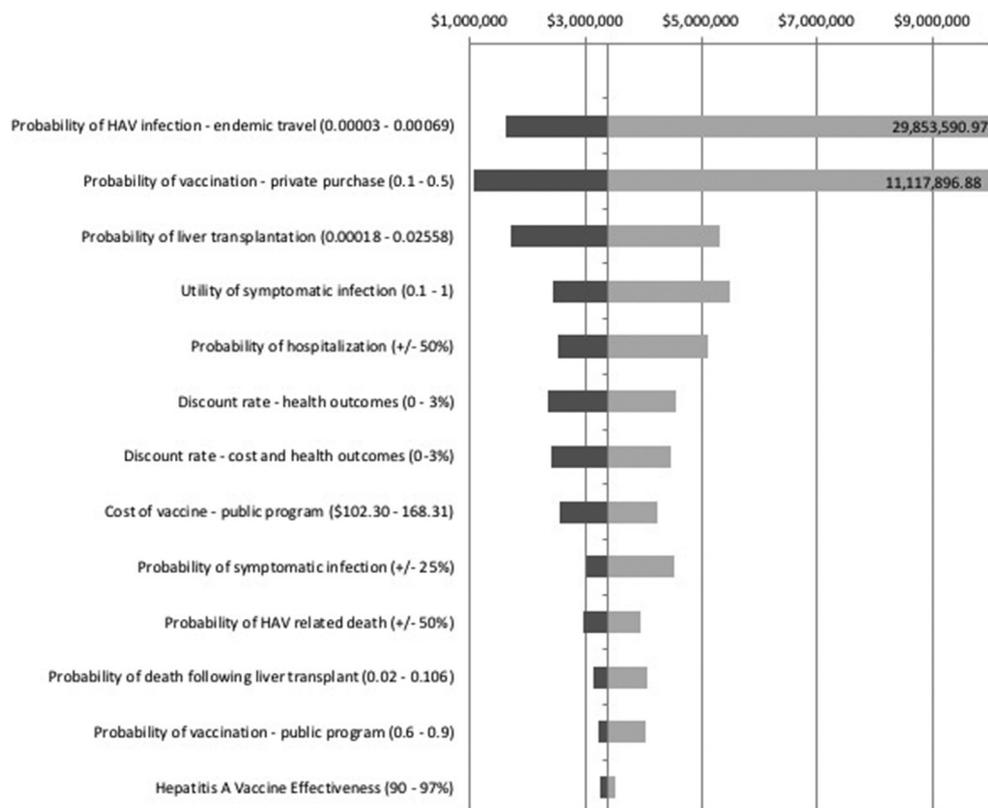


Fig. 3. Tornado diagram showing one-way sensitivity analysis for key variables. The x-axis represents the range of the ICER when the base-case values are varied. The vertical line represents the base-case ICER (\$3,391,504 per QALY gained). Not all variables that were tested in one-way sensitivity analysis are shown in this graph due to the small changes around the x-axis found across the range of parameters tested.

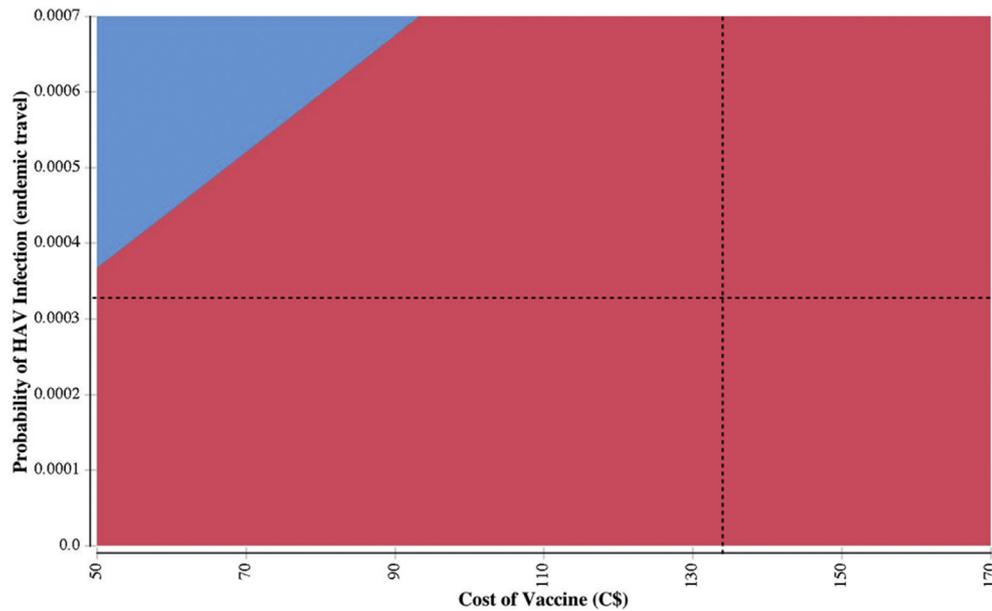


Fig. 4. Two-way sensitivity analysis on travel vaccine cost and probability of HAV infection when traveling in endemic regions for the base-case comparing the expanded program to the status quo (discounted at 1.5%). This graph shows the impact on the decision of simultaneous changes in the values of two variables (vaccine program cost, probability of HAV infection when traveling to endemic region) in a region graph. The region graph identifies changes in the preferred strategy using a cost-effectiveness threshold of C\$50,000 per QALY gained. The blue region denotes variable combinations for which the expanded hepatitis A travel vaccine program is the preferred strategy. The red region denotes variable combinations for which status quo (privately purchased hepatitis A vaccine for travel) is the preferred strategy. Dotted lines indicate base-case values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

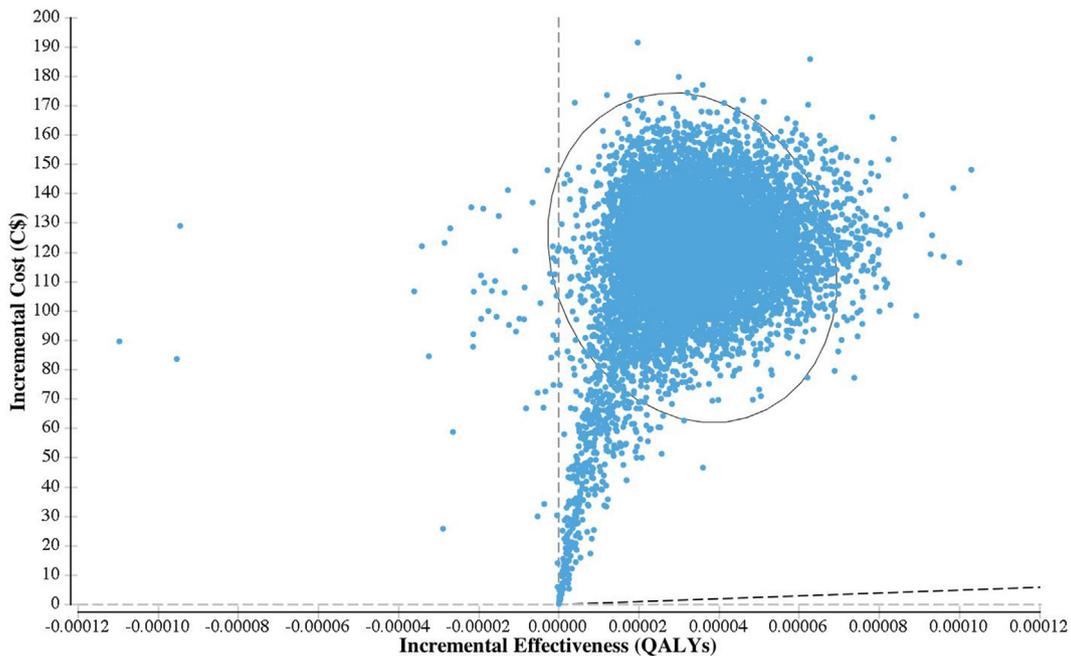


Fig. 5. Scatterplot of Probabilistic Sensitivity Analysis results. The scatterplot depicts 10,000 iterations of the 100,000 total iterations that were analyzed in probabilistic sensitivity analysis for the comparison of the expanded high risk travel vaccination program compared to the status quo (privately purchased hepatitis A vaccine for travel). The black dotted line indicates a cost-effectiveness threshold of \$50,000, iterations falling below this line would indicate that the expanded high risk hepatitis A travel vaccine program is cost-effective at a \$50,000 threshold. Each dot in the scatterplot represents one iteration of the model using distributions around key data parameters. The ellipses around the dots indicates the 95% confidence interval.

expansion of relevant target populations, and the voluntary nature of vaccination given a behaviour-associated risk; however, uptake may be overestimated given that the HPV vaccine prevents cancer (a severe outcome), which may result in a higher proportion of people choosing to be vaccinated for HPV than hepatitis A. Conversely, hepatitis A vaccine uptake may be underestimated given

that hepatitis A may be perceived primarily as a foodborne and waterborne illness rather than a sexually transmitted virus that potentially makes self-identification for vaccination more likely. An additional limitation due to lack of context-specific data is that the seroprevalence estimate used to inform the proportion of the cohort that began in the well (susceptible to HAV) health state

was conservative and based only broadly on Canadian data. A study conducted in children in Quebec found that 97% of teenagers would be susceptible to HAV based on low seroprevalence [46]. Further, it is not clear how many travellers would be susceptible, how many may already be eligible for hepatitis A vaccination under the current high-risk program, nor how many of these would have actually received vaccination under the existing program.

Third, our Markov cohort model does not incorporate dynamic transmission typical of infectious diseases. In this case, our analysis likely underestimates infection risk, leading to a resulting underestimate of status quo infection costs. If secondary transmission were incorporated, the incremental cost of the expanded program would likely be less – and the incremental gain in QALYs could possibly be greater – than our results indicate (i.e., our results potentially underestimating the cost-effectiveness). This is an important consideration due to possible local transmission of hepatitis A in Ontario following a travel-related importation. While we accounted for costs associated with public health follow up to prevent secondary transmission, the assumptions we made regarding how much follow up would occur may vary significantly. For example, a review of the response to hepatitis A infected food handlers in Canada found that six of 16 food-handler post-exposure prophylaxis interventions resulted in on average 5000 doses of hepatitis A vaccine being offered [47]. The model did not account for the possibility of preventing a large post-exposure prophylaxis intervention, which may have underestimated the cost-effectiveness of expanding hepatitis A vaccination for travellers.

Finally, estimates regarding travel to endemic regions were based on general trends of trips taken by Canadians [21], and did not include more comprehensive data concerning travel purpose, length of stay, movements and behaviours during the trip, or nature of accommodations. Crowcroft discusses how travel to an endemic region is merely a broad, macro-level factor associated with HAV risk; however, it is the behaviours undertaken during travel that fully inform likelihood of HAV infection [9]. For example, local industrialization and hygiene influence HAV transmission [7]; a businessperson staying at a hotel, and a backpacker living in rural lodgings would have varying risks of infection with HAV, even given travel to the same endemic location. More comprehensive data regarding travel intent, trip behaviours, and specific destinations would facilitate characterization of infection risk. Further, the population that was considered in our analysis was restricted to only those not currently eligible for publicly-funded vaccination and it is possible that a travel vaccine program could increase vaccination coverage in groups already eligible for the existing high risk program (e.g., due to the less stigmatized nature of requesting the vaccine for travel rather than in relation to injection drug use).

Sensitivity analyses reveal that the model is particularly sensitive to the probability of HAV infection when travelling to an endemic location. If it is possible to identify travellers at increased risk, then targeting travellers at high risk may provide better value for money.

Strengths of this analysis include that data was selected through targeted literature searches to be representative of the Ontario population, parameters were tested extensively in sensitivity analyses (one-way, two-way and probabilistic), and the model accounted for both short-term and long-term health outcomes. Further, this study was strengthened by the inclusion of public health contact tracing costs, which can represent significant costs and opportunity costs to public health units.

Results of this analysis – where vaccination is not cost-effective – align with studies investigating potential adult-focused HAV vaccination where endemicity is low [33]. Conversely, increased eligibility for publicly-funded HAV vaccination has been found to be cost-effective where endemicity is intermediate or high in the study country [48,49]. The current analysis raises questions of

what conditions would increase the likelihood of expanded publicly-funded pre-exposure HAV vaccination being found to be cost-effective. First, one possibility stems from the usefulness of more comprehensive travel data. Targeted publicly-funded vaccination of a subset of travellers to endemic regions who experience elevated infection risks relative to other travellers and/or those at risk for severe hepatitis A may provide more substantial health gains while only vaccinating a subset of the population.

Second, Bauch (2007) discusses how monovalent HAV vaccination is likely not cost-effective in non-endemic countries when compared to usual thresholds; however, combining HAV with hepatitis B (HBV) vaccine in a single administration of both antigens could be economically feasible [5]. Indeed, researchers have identified universal HAV vaccination targeting school-aged children – along with use of a bivalent HAV/HBV vaccine – as a potentially cost-effective public health intervention [11,50,51].

Consequently, in a non-endemic country, such as Canada, administering a bivalent HAV/HBV vaccine as part of an existing HBV vaccination program could potentially prevent HAV transmission in a cost-effective manner, and this question can be assessed in the future. Health gains could be made through preventing local transmission of hepatitis A, and protecting individuals from travel-associated acquisition later in life, and costs of administration could be minimized by taking advantage of an existing vaccination infrastructure.

5. Conclusions

The expanded vaccination program may substantially exceed commonly accepted cost-effectiveness thresholds. Further research concerning possible cost-effectiveness of expansion of a publicly-funded high-risk hepatitis A vaccination program to travellers to endemic areas should focus on a more comprehensive understanding of specific travel-related risks (e.g., purpose of travel, length of stay) during travel to endemic regions, as well as behavioural risk factors for infection (e.g., sexual behaviours, drug use), and risk factors for severe hepatitis A (e.g., chronic liver disease, immunocompromising conditions, and older age).

Declarations

Conflict of interest statement: The authors have no conflicts of interest to declare.

Funding: This project had no funding.

Author contributions: All authors attest they meet the ICMJE criteria for authorship. LCR and BS conceptualized the project. KA, ML and LCR conducted data collection. LCR built the economic model and conducted all analyses. KA wrote the first draft of the manuscript. LM provided public health expertise, and BS and PC provided guidance in economic evaluation methods. All authors critically reviewed and approved the manuscript for submission.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.01.070>.

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