# A dynamic model for assessing universal Hepatitis A vaccination in Canada

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# Abstract

Vaccination against Hepatitis A virus (HAV) in Canada is currently targeted toward high-risk groups. However, universal vaccination has been adopted in several other countries with a similar disease burden. Here we develop an age-structured compartmental model of HAV transmission and vaccination in Canada to assess potential universal vaccination strategies. The model predicts that universal vaccination at age 1 (respectively 4, 9, 15), with phasing out of targeted vaccination, would reduce reported incidence by 60% (respectively 52%, 36%, 31%) and mortality attributable to HAV by 56% (respectively 45%, 26%, 25%), relative to continued targeted vaccination, over eighty years.



Running Headline: Universal vaccination against Hepatitis A in Canada

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# 1. Introduction

Hepatitis A virus (HAV) is endemic in many regions of the world [1,2]. Although infection is largely subclincal in children, over 70% of infected adults develop clinical symptoms, many of whom do not seek medical attention [3,4]. Symptoms include nausea, loss of appetite, fatigue, fever, abdominal pain and jaundice [3]. Clinical illness usually lasts four weeks, chronic infection does not occur [5], and immunity appears to be lifelong. HAV infection is more severe when experienced by older individuals or those with underlying chronic liver disease [6,7]. The most serious complication of hepatitis A is fulminant hepatic failure. The rate of mortality attributable to HAV increases from 0.2% in symptomatic young adults to 1.7% in symptomatic individuals 60 years and older [8].

HAV is transmitted by the fecal-oral route. Unlike in many countries, transmission in Canada is primarily person-to-person [4] and foodborne outbreaks are infrequent [9]. Children play a prominent role in transmission due to poor hygienic habits and subclinical infection [10]. HAV is not endemic in Canada, but travellers to endemic countries often return with HAV, making travel a particularly significant contributor to disease incidence [11,12].

In Canada, reported HAV incidence in the pre-vaccine era (1980-1994) was 6.3 cases per 100,000 per year [13], with an upward trend. Because of subclinical infection and under-reporting (by a factor of 10 in the United States and 7.6 in Canada) the actual

incidence of HAV is higher than the reported incidence [4,14] (Appendix B.1). The reported incidence of HAV in Canada is roughly constant across age classes [13], but because of a higher frequency of subclinical infections in children [3,15,16], true infection rates are higher in children than other age classes (Table 1).

Hepatitis A vaccine, which became available in the early 1990s, is safe and effective and has reduced incidence in countries such as the United States, Israel, Spain and Canada [17-20]. In Canada, a policy of targeted vaccination for high-risk groups (such as travellers to endemic countries, men who have sex with men, intravenous drug users, and residents of communities with higher prevalence) has been in place since 1994. The average incidence from 1995 to 2003 was 3.8 per 100,000 per year. The average incidence from 2000 to 2003 was even lower at 1.4 per 100000 per year. However, it is difficult to determine to what extent this decline is due to vaccination and to what extent it represents a trough in naturally recurrent cycles of epidemic activity [20]. Incidence may also rise in coming years if travel by Canadian residents to endemic countries continues to climb [21].

Dynamic models explicitly represent known or hypothesized epidemiologic mechanisms, and can map out the time evolution of a system under various scenarios [22]. They provide insight into infectious disease epidemiology and can help assess the efficacy of control strategies. They are particularly valuable for assessing vaccination policies because they can capture the indirect effects of herd immunity [23]. Despite the licensure and widespread use of HAV vaccine, there are few dynamic models to help

assess current or potential HAV vaccination strategies [20,24,25]. In this study we develop and analyze an age-structured compartmental (dynamic) model for HAV transmission and vaccination in Canada. Our goal is to predict the impact of several plausible universal vaccination strategies in children and adolescents, in order to identify the most promising approach for reducing morbidity and mortality from HAV in Canada.

# 2. Methods

## *2.1. Model structure*

Our model stratifies individuals according to age *a* and epidemiologic status (susceptible, exposed, infectious, recovered, or vaccinated). Individuals flow between compartments at specified rates. Susceptible individuals of age *a* may become infected through contact with an infectious individual of age *j* also living in Canada. This results in a "Who Acquires Infection From Whom" (WAIFW) matrix describing domestic transmission rates between individuals of specified age classes [22]. Nearly 40% of cases in Canada are attributable to travel in HAV-endemic countries (B. Duval, unpublished data, 2006). We therefore suppose that a susceptible individuals of age *a* may also be infected by travel to an endemic country, defining age-specific travel transmission rates. Vaccine-derived immunity wanes at some constant rate, while immunity from natural

infection is lifelong. Individuals are born susceptible, age, and die at an age-specific death rate from non-HAV causes. There is also a death rate due to HAV. Vaccine compliance rates can be specified for any age. The differential equations are in Appendix A, and the parameterization is described in Section 2.3, Table 1, and Appendix B.

## *2.2. Model assumptions*

Population sizes, birth rates, and death rates are assumed to be constant and correspond to those for Canada from 1980-1994, the years used to parameterize the model. Although population size has actually increased since 1994, assuming a constant population size will not influence predictions—beyond a rescaling to future population sizes—because we use "standard incidence" to model transmission [26]. However, changes in the relative sizes of age classes, such as due to aging "baby boomers", could potentially influence predictions. Also, the model assumes a constant force of infection after 2006, whereas travel transmission rates may increase or decrease depending on the net effect of increasing international travel and decreasing incidence in endemic countries. Domestic transmission rates are taken to be constant but may decrease further in future. It is also assumed that the effects of targeted vaccination to date reflect future effects of targeted vaccination. Maternal immunity for Hepatitis A is short-lived [4] and conferred upon relatively few children in low-incidence countries such as Canada. Hence maternal immunity is not represented in our model.

## *2.3. Parameterization*

Parameter values are summarized in Table 1 and technical details appear in Appendix B. Parameter values were estimated by grouping individuals into one of seven age classes to reflect age groupings in available data sources: 0-4, 5-9, 10-19, 20-29, 30-39, 40-59, 60+ . In all equations, parameter values for age classes are distinguished by the index *c*, and for age are distinguished by the index *a* as above. The model was parameterized using data from 1980 to 1994, the year of vaccine licensure. To estimate the true force of infection we combined incidence data [13] and seroprevalence data [12,27-30] using catalytic modeling [14]. Catalytic modeling uses integral equations to reconcile case reporting data (which are available for each year but are significantly under-reported) and seroprevalence data (which are a reliable indicator of past infection but do not indicate in which year the infection occurred). The reported number of cases in year *y* in age class *c* are adjusted for (a) the probability of jaundice and (b) under-reporting rates until the discrepancy with the expected seroprevalence in that year and age class is minimized. A model is assumed for the declining force of infection in age class *c* over time and the age-specific probabilities of developing jaundice must be estimated (details in Appendix B.1).

With these estimates of the force of infection, with data on the proportion of cases attributable to travel [11,31,32] (B. Duval, unpublished data, 2006), and with an assumed

form for the WAIFW matrix, we computed the domestic and travel transmission rates. To account for a cohort effect [4], travel transmission was assumed to rise in the past 50 years according the same trend as rising per capita travel volume to endemic countries [21], and domestic transmission was assumed to follow a declining mathematical function which was fitted by minimizing the least-squares error between modelled seroprevalence and observed seroprevalence data (Appendix B.2). The effects of targeted vaccination between 1995 and 2005 were modelled as a reduction in the travel transmission rate (Appendix B.3). Other parameters were taken from the clinical, epidemiological, and demographic literature (Table 1).

### *2.4. Model validation*

The goodness-of-fit statistic between age-specific values of predicted and reported incidence for 1980-1994 was $R^2$=0.96, indicating excellent agreement between model and data. The reported incidence (per 100,000 per year) for 1980-1994 by age class was 6.8, 17.0, 7.8, 9.4, 7.2, 3.7, 1.8. The predicted incidence for 1980-1994 by age class was 8.1 (6.4,12.1), 17.4 (13.6,25.6), 8.3 (6.1,11.8), 10.0 (7.5,14.0), 9.9 (7.5,13.9), 3.7 (2.8,5.0), 2.1 (1.5,3.1). Parenthetical values denote 96% confidence intervals. Additionally, the fitted model reproduced the observed rising trend in reported incidence during the years 1980-1994 (y=0.21x+4.61, $R^2$=0.24; the $R^2$ value is low because of recurrent epidemic activity). Interestingly, the dynamic model predicts a concurrent

decline in the true incidence (ie, reported incidence adjusted for subclinical infection and under-reporting) during these years. This seems paradoxical. However, a decline in true incidence brings about an increased mean age at infection. Since symptoms are more likely to develop in older individuals, this results in a net increase in reported HAV infections, even as the true number of HAV infections declines.

### *2.5. Vaccination strategies considered*

We assess universal vaccination at ages 1, 4, 9, or 15 years, for the years 2006-2085. Vaccination at 4, 9, and 15 years fits conveniently with currently scheduled Canadian immunizations, and vaccination at 1 year facilitates comparison with the recent ACIP recommendation on routine hepatitis A vaccination of children in the US [33]. We assume two doses of vaccine separated by six months with 95% compliance. We assume that both travel and domestic transmission rates remain constant after 2006. Targeted vaccination after 2006 is still applied to non-vaccinated cohorts and individuals whose last vaccine dose was 25 years ago, as a booster to counteract the effects of waning vaccine-derived immunity.

### *2.6. Sensitivity Analysis*

Once estimates of incidence and mortality under a universal vaccination policy were determined by simulations of the dynamic model, a univariate sensitivity analysis was carried out to determine the sensitivity of model predictions to parameter values. The analysis was carried out with respect to the rate of waning of vaccine-derived immunity (range: 0 to 0.05/yr), vaccination compliance rates (range: 50% to 100% compliance), travel transmission rates (range: 50% linear decrease/increase over 80 years on 2006 values), and domestic transmission rates for the years 2006-2085 (range: 0% to 50% linear decrease over 80 years on 2006 values).

## 3. Results

Under the four scenarios of vaccination at ages 1, 4, 9, or 15 with phasing out of targeted vaccination, we determine the predicted annual incidence of reported cases (Table 2) and cumulative number of deaths attributable to HAV (Table 3) for 2006-2085. For comparison we also present the predicted incidence and mortality that would occur under continuation of the targeted strategy and under no vaccination. In all cases, the introduction of universal vaccination results in significant further reductions in morbidity and mortality. Universal vaccination at age 1 (respectively 4, 9, 15, targeted alone) results in an average incidence of 1.7 (respectively 2.0, 2.7, 2.9, 4.2) per 100,000 per year from 2006-2085, and a cumulative mortality attributable to HAV of 215 (respectively 270, 366, 368, 493) for the same time period. Figure 1 depicts the time evolution of the

proportion of susceptible, exposed, infectious, recovered and vaccinated individuals under universal vaccination at age 4. The proportion of individuals with natural immunity (ie, recovered) and the proportion susceptible decline over time as the proportion of vaccinated individuals increases.

The impact of universal vaccination is larger for strategies that vaccinate younger. Moreover, there is a pronounced difference between vaccinating at ages 1 or 4 versus vaccinating at ages 9 or 15. This is because the 0-4 age class experiences a disproportionately large force of infection (Table 1). Relative efficacies of the strategies are similar if subclinical HAV infection and under-reporting are included. The effects of herd immunity are apparent in these results. It is observed in plots of incidence versus time that the average incidence declines almost exponentially as herd immunity builds over the course of a generation.

According to the univariate sensitivity analysis, predictions of the average reported incidence do not vary much with changes in the domestic transmission rate (Figure 2). Predictions are more sensitive to changes in other parameters. However, the relative efficacies of the four strategies are relatively unchanged, with vaccination at 1 or 4 years always significantly outperforming vaccination at 9 or 15 years.

# 4. Discussion

We developed an age-structured compartmental model of Hepatitis A

transmission and vaccination in Canada in order to assess the efficacy of several potential universal vaccination strategies. The principal findings were that (a) all strategies would result in significant additional reductions in morbidity and mortality, relative to continuation of the targeted policy alone, and (b) reductions would be especially large for vaccination at ages 1 or 4, compared to vaccination at ages 9 or 15.

Reductions are largest for vaccinating in the 0-4 age class because the probability of eventually becoming infected increases as vaccination is delayed until later in life, and also because this age class experiences the highest force of infection by a significant margin (Table 1) [10]. In reality, the absolute reductions in symptomatic incidence would be larger, since here we presented results only for known (reported) cases. For diseases that are more serious in older individuals, vaccination programmes can sometimes increase morbidity and mortality by increasing the mean age at infection [22]. Our model predicts that this should not be a risk in the case of HAV vaccination, under any likely universal vaccination strategy.

In the United States after the introduction of HAV vaccination for toddlers, reported HAV incidence fell from 11.8 to 3.7 per 100,000 per year [17], in line with the predictions of our model as well as a dynamic model developed for the United States [20]. In Israel, reported incidence of HAV fell more dramatically, from 50.4 to 2.5 per 100,000 per year [19]. The discrepancy with Canadian predictions reflects the fact that Israel was a HAV-endemic country before vaccination, and had a lower mean age at infection before universal vaccination, so immunization of toddlers had a greater impact.

Additionally, travel makes up a very large component of HAV incidence in Canada [11], hence herd immunity effects are weaker.

Here, we have assumed that the average incidence between 1995 and the present will continue to reflect long-term incidence under a targeted policy. However, incidence in Canada may remain indefinitely at low levels experienced in the past few years. Alternatively, incidence may increase due to the inherently cyclical nature of epidemic activity and particularly the end of the "honeymoon period" [34], and due to possible increases in mean age at infection, and a probable increase in travel to endemic countries. Few individuals visit travel clinics before traveling to endemic countries [11]. Hence, as large numbers of retiring baby-boomers begin travelling overseas, there may be an increase in the number of symptomatic and hospitalized HAV cases. According to our sensitivity analysis on travel transmission rates, the relative efficacies of the universal vaccination strategies should remain the same even as the absolute efficacies vary according to assumptions about future trends in travel-related incidence.

A better understanding of the effects of targeted vaccination versus universal vaccination would require developing a model in which individuals are also stratified by social group (eg, travellers, men who have sex with men, First Nations communities). This complex undertaking would require demographic and seroprevalence data on the various social groups as well as an understanding of their epidemiologic interactions. Such a socially structured model would be necessary to better predict future incidence

under a targeted policy, and the impact of universal vaccination in a population previously subject to targeted vaccination.

This study indicates that vaccinating at age 1 would be the best universal strategy from the viewpoint of reducing morbidity and mortality. However, logistic and economic issues must also be weighed in considering alternative vaccination strategies. Targeted strategies tend to require fewer doses of vaccine than universal policies and attain full efficacy more quickly, since they do not rely upon herd immunity to the same extent. However, it is often difficult to attain high coverage in at-risk groups [11, 35], there is generally a greater cost per vaccine administered, and costly post-exposure interventions will need to be in place as long as only targeted vaccination is used. Additionally, targeted vaccination usually targets groups where individuals develop clinically apparent disease, rather than those individuals (such as children) who exhibit subclinical infection and are therefore responsible for significant, though under-reported, transmission [10].

Likewise, cost-effectiveness may vary significantly between alternative vaccination strategies. Cost-effectiveness analyses (CEAs) are typically based upon cohort models, which do not account for herd immunity. Herd immunity effects can be significant [20], therefore CEAs based upon dynamic models are generally more accurate than CEAs based upon cohort models [23,34]. An important direction for future research is the integration of a dynamic model into a cost-effectiveness analysis (CEA) of universal Hepatitis A vaccination in Canada. In an age of increasing medical costs and

scarcity of medical resources, CEAs based upon the most accurate models available become ever more important for evidence-based evaluations of vaccination policies.

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# Appendix A

The differential equations for the age-structured SEIRV model are

$$\begin{aligned}
\frac{dS_a}{dt} &= -S_a \sum_{j=1}^{80} \beta_{aj} I_j / N_j - \tau_a S_a + fV_a \\
\frac{dE_a}{dt} &= S_a \sum_{j=1}^{80} \beta_{aj} I_j / N_j + \tau_a S_a - \delta E_a \\
\frac{dI_a}{dt} &= -\gamma_a I_a + \delta E_a \\
\frac{dR_a}{dt} &= \gamma_a I_a \\
\frac{dV_a}{dt} &= -fV_a
\end{aligned} \tag{1}$$

where $a$ is the age in years ($1 \le a \le 80$), $S_a$ (resp. $E_a$, $I_a$, $R_a$, $V_a$) is the number of Susceptible (resp. Exposed, Infectious, Recovered, Vaccinated) individuals of age $a$, $f$ is the mean rate at which vaccine-derived immunity wanes, $1/\delta$ is the mean latent period, $1/\gamma_a$ is the mean duration of infectiousness, $\beta_{aj}$ is the rate at which a susceptible of age $a$ becomes infected by contact with infectious individuals in age class $j$ in Canada, and $\tau_a$ is the rate at which a susceptible of age $a$ becomes infected from travel in an endemic country. Death and aging processes were included by applying the conditions

$$S_{a+1} = (1-d_a)S_a \text{ , } E_{a+1} = (1-d_a)E_a \text{ , } I_{a+1} = (1-d_a)I_a \text{ , } R_{a+1} = (1-d_a)R_a \text{ , } V_{a+1} = (1-d_a)V_a \tag{2}$$

at the start of each year for $1 < a < 80$, where $d_a$ is the per capita death rate in age $a$, and birth was included by applying the condition

$$S_1 = b \text{ , } E_1 = 0 \text{ , } I_1 = 0 \text{ , } R_1 = 0 \text{ , } V_1 = 0 \tag{3}$$

at the start of year year, where b=400000 is the annual number of births. For a vaccination programme being applied to a cohort of age *a* at time *t*, we applied the condition

$$S_a = (1 - \varepsilon_a g_a) S_a \ , \ V_a = \varepsilon_a g_a S_a \tag{4}$$

where $\varepsilon$ is the vaccine efficacy and $g_a$ is the vaccine coverage at age *a*.

For the purposes of parameter estimation, individuals were grouped into one of seven age classes: 0-4, 5-9, 10-19, 20-29, 30-39, 40-59, 60+ (see Table 1). Parameters for each age class *c* were determined and then each parameter for age *a* was set equal to the corresponding parameter estimated for the age class *c* of which age *a* is a member, with linear interpolation.

# Appendix B

## *B.1. Catalytic modelling*

Catalytic modelling [14] fits the following integral equation to case reporting and seroprevalence data:

$$P_C(C,Y) = 1 - \exp\left[-\int_0^C F(c) \cdot G(y) dc\right] \tag{6}$$

where $P_C(C,Y)$ is the seroprevalence in Canadian-born individuals of age class $C$ in year $Y$, where $y=Y-C+c$, where $G(y) = \chi \exp[-\delta \cdot (1990 - y)]$ is the component of force of infection which depends on the year $y$ (and declines at rate $\delta$ and with under-reporting factor $\chi$), where $F(c) = I(c)/\left(J(c) \cdot (1 - P_T(c))\right)$ is the component of force of infection which depends upon age class $c$, where $I(c)$ is the reported incidence in age class $c$, $J(c)$ is the age-specific probability of developing jaundice in age class $c$, and $P_T(c)$ is the seroprevalence in the whole population in age class $c$.

Our catalytic model is similar to that described elsewhere [14] except we use a piecewise linear jaundice model: $J(c) = \beta a$ (for $c<\alpha$) and $J(c) = \beta\alpha$ (for $c\geq\alpha$). This model was found to give better agreement between incidence and seroprevalence data for Canadian data. The two free parameters $\beta$, $\alpha$ of the jaundice model were fitted from age-specific data on the frequency of jaundice from seven studies [3,14-16,36-38], weighted according to the sample size of the study. The probabilities of jaundice thus computed were, for the seven age classes in order: 0.11, 0.34, 0.70, 0.81, 0.81, 0.81, 0.81. The under-reporting factor was determined to be 7.6. By adjusting reported incidence for subclinical infection and underreporting using the jaundice model and the under-reporting factor and estimating the proportion seropositive by age from seroprevalence surveys [12,27-30], we obtained estimates of the true force of infection $\lambda_c$, the probability per year that a susceptible individual in age class $c$ becomes infected.

## *B.2. Estimation of domestic and travel transmission rates*

The travel transmission rate, $\tau_c$, can be computed from $\tau_c = \kappa_c \lambda_c$, where $\lambda_c$ is the true force of infection estimated from catalytic modelling and $\kappa_c$ is the proportion of infections obtained through travel in an endemic country in age class *c*. In Canada, per capita travel volume to endemic countries has risen quadratically from 1950 and 1994 [21] according to the fitted model $y = 2.38 \times 10^{-5} t^2 + 1.52 \times 10^{-3} t + 2.98 \times 10^{-3}$ ($r^2$=0.98, *y*=per capita travel volume per year, *t*=number of years since 1950). We assumed that $\tau_c$ rose according to the same regression, scaled for agreement with known recent time points [11,31,32] (B. Duval, unpublished data, 2006).

Since $\tau_c = \kappa_c \lambda_c$ and $\lambda_c = \tau_c + \sum \beta_{cj} I_j / N_j$ we have $\sum \beta_{cj} I_j / N_j = (1 - \kappa_c) \lambda_c$.

The 7x7 values for $\beta_{cj}$ form a 'Who Acquires Infection From Whom' (WAIFW) matrix. We assumed $\beta_{11}=\overline{\omega}_1$, $\beta_{12}=\beta_{22}=\beta_{21}=\overline{\omega}_2$, $\beta_{13}=\beta_{23}=\beta_{33}=\beta_{32}=\beta_{31}=\overline{\omega}_3$, *etc.* to obtain seven distinct matrix entries ($\overline{\omega}_1 \ldots \overline{\omega}_7$) corresponding to the seven age-specific force of infection values ($\lambda_1 \ldots \lambda_7$), allowing us to solve the equations for $\beta_{aj}$. After experimenting with various forms for the WAIFW matrix [22], we found that the form used here provided good agreement with seroprevalence data, while also being the most robust to variation in parameter values. Other matrix forms, such as those incorporating special entries for parent-child transmission, asymmetric transmission between parents and children, or elements of assortative mixing, yielded negative values for the transmission rates either for the base case parameter values or for parameter values sampled in the uncertainty analysis. This occurs, for instance, for the assortative matrix $\beta_{11}=\overline{\omega}_1$, $\beta_{22}=\overline{\omega}_2$,

$\beta_{33}=\overline{\omega}_3$, $\beta_{44}=\overline{\omega}_4$, $\beta_{55}=\overline{\omega}_5$, $\beta_{66}=\overline{\omega}_6$, $\beta_{ij}=\overline{\omega}_7$ otherwise, and for the matrix with distinct entries for transmission between children: $\beta_{11}=\overline{\omega}_1$, $\beta_{22}=\overline{\omega}_2$, $\beta_{33}=\beta_{44}=\beta_{55}=\overline{\omega}_3$, $\beta_{12}=\beta_{13}=\beta_{21}=\beta_{23}=\beta_{31}=\beta_{33}=\overline{\omega}_4$, $\beta_{14}=\beta_{24}=\beta_{34}=\beta_{43}=\beta_{42}=\beta_{41}=\beta_{15}=\beta_{25}=\beta_{35}=\beta_{45}=\beta_{54}=\beta_{53}=\beta_{52}=\beta_{51}=\overline{\omega}_5$, $\beta_{16}=\beta_{26}=\beta_{36}=\beta_{46}=\beta_{56}=\beta_{66}=\beta_{65}=\beta_{64}=\beta_{63}=\beta_{62}=\beta_{61}=\overline{\omega}_6$, $\beta_{ij}=\overline{\omega}_7$ otherwise.

Hence, we estimated $\overline{\omega}_1 \ldots \overline{\omega}_7$ = 7.33, 4.30, 0.81, 1.06, 1.39, 0.87, 1.11 $yr^{-1}$, the average domestic transmission rates for the years 1980-1994. Transmission rates are largest in the youngest age classes, and generally decrease along the diagonal of the WAIFW matrix as one moves in the direction of older age classes, except for a small increase in the 20-29 and 30-39 age class, presumably due to higher risk activities in these groups. The transmission rates also decrease in the direction of the cross-diagonal, ie, in the direction of greater disassortative mixing. This pattern is observed in WAIFW matrices for many infectious diseases [39]. Similar assumptions have been made for other diseases transmitted person-to-person, and in which transmission by children plays a significant role [22].

To account for the cohort effect [4], we furthermore assumed that the domestic transmission rates decreased over time according to the function $\omega_c(t) = \overline{\omega}_c\left\{A + B\left[1 - \tanh\left(C\left(t - D\right)\right)\right]\right\}$. By fitting modelled seroprevalence to 11 data points from seroprevalence surveys for Canadian-born individuals of distinct age classes and times between 1980-1994 [12,27-30], we obtained least-squares error at $A$=0.73,

$B$=0.84, $C$=0.038, $D$=1960, with goodness-of-fit statistic $R^2$=0.97. A piecewise linear-exponential function yielded similar agreement.

### *B.3. Effects of targeted vaccination, 1995-2005*

The effects of targeted vaccination from 1995-2005 were modelled as a reduction in the travel transmission rates. For each age class $c$, the parameter $\tau_c$ was reduced during the years of targeted vaccination such that the average predicted incidence for 1995-2003 in age class $c$ matched the average observed incidence for 1995-2003 in age class $c$. The average observed (reported) incidence for 1995-2003 across all age classes in Canada was 3.8 per 100,000 per year.

Table 1

Parameter values by age class, and corresponding references.

| Parameter | Meaning | Value | Relevant References |
|---|---|---|---|
| $b$ | Birth rate | 400000 | [40] |
| $d_1 \ldots d_7$ | Age-specific non-HAV death rate | 0, 0, 0, 0, 0.75, 0.67, 1 | [40] |
| $1/\delta$ | Mean duration of latent period | 2 weeks | [41,42] |
| $1/\gamma_1 \ldots 1/\gamma_7$ | Age-specific mean duration of infectious period | 3.5, 3.0, 2.5, 2.5, 2.5, 2.5, 2.5 weeks | [42,43] |
| $\theta_1 \ldots \theta_7$ | Age-specific death rate (attributable to HAV infection) in symptomatic cases | 30, 18, 18, 18, 21, 58.5, 272 per 10,000 | [44,45] |
| $\rho$ | Under-reporting factor | 7.6 | [12,13,27-30] Appendix B.1 |
| $J_1 \ldots J_7$ | Age-specific probability of developing jaundice | 0.11, 0.34, 0.70, 0.81, 0.81, 0.81, 0.81 | [3,14-16,36-38] Appendix B.1 |
| $\lambda_1 \ldots \lambda_7$ | Age-specific true force of infection | 689.7, 488.7,115.9, 129.0, 156.4, 97.7, 117.9 per 100000 per year | [12,13,27-30], Appendix B.1 |
| $\kappa_1 \ldots \kappa_7$ | Age-specific proportion of cases attributable to travel | 0.37, 0.37, 0.37, 0.27, 0.22, 0.20, 0.15 | [11,21,31,32] |
| $\varepsilon$ | Vaccine efficacy | 0.97 | [46,47] |
| $f$ | Rate of loss of vaccine-derived immunity | 0.0165 $year^{-1}$ | [44] |
| $N_1 \ldots N_7$ | Population sizes of age classes | 2, 2, 4, 4, 4, 6, 4 million | [40] |

Table 2

Predicted average annual incidence of reported cases (per 100,000 per year) for 2006-2085 under various vaccination scenarios.

| Age Class | Vaccination | | | | | No vaccination |
|---|---|---|---|---|---|---|
| | 1 year | 4 years | 9 years | 15 years | Targeted | |
| 0-4 | 1.2 | 2.6 | 3.3 | 3.3 | 3.3 | 10.0 |
| 5-9 | 1.9 | 1.4 | 7.2 | 7.8 | 7.7 | 21.2 |
| 10-19 | 1.7 | 1.6 | 1.2 | 3.3 | 4.1 | 13.0 |
| 20-29 | 2.2 | 2.4 | 2.4 | 1.8 | 5.0 | 13.1 |
| 30-39 | 1.9 | 2.2 | 2.8 | 2.7 | 4.7 | 14.0 |
| 40-59 | 1.4 | 1.7 | 2.2 | 2.1 | 3.2 | 9.5 |
| 60+ | 1.5 | 1.9 | 2.6 | 2.6 | 3.2 | 9.4 |
| All ages | 1.7 | 2.0 | 2.7 | 2.9 | 4.2 | 12.2 |

Table 3

Predicted cumulative number of deaths attributable to HAV for 2006-2085 under various vaccination scenarios[a].

| Age Class | Vaccination | | | | | No vaccination |
|---|---|---|---|---|---|---|
| | 1 year | 4 years | 9 years | 15 years | Targeted | |
| 0-4 | 5.6 | 12.6 | 15.7 | 15.6 | 15.9 | 48.0 |
| 5-9 | 5.5 | 4.1 | 20.8 | 22.4 | 22.1 | 61.1 |
| 10-19 | 9.8 | 9.3 | 7.1 | 18.8 | 23.4 | 75.0 |
| 20-29 | 12.5 | 13.6 | 14.0 | 10.4 | 29.0 | 75.7 |
| 30-39 | 12.5 | 14.8 | 19.0 | 18.3 | 31.8 | 93.8 |
| 40-59 | 38.9 | 48.1 | 62.2 | 59.1 | 89.6 | 267.6 |
| 60+ | 129.9 | 167.8 | 227.0 | 223.6 | 281.2 | 814.1 |
| All ages | 214.6 | 270.2 | 365.7 | 368.2 | 492.9 | 1435.2 |

[a] for 1980-1994 population sizes.

# Figure Captions

Figure 1: Time evolution of model variables (see Appendix A) upon start of universal vaccination at age 4 in 2006: the proportion susceptible at time *t* across all age classes (*S*), the proportion exposed at time *t* across all age classes (*E*), the proportion infectious at time *t* across all age classes (*I*), the proportion recovered at time *t* across all age classes (*R*), and the proportion vaccinated at time *t* across all age classes (*V*).

Figure 2: Sensitivity analysis with respect to variation in: (A) rate of waning of vaccine-derived immunity, (B) vaccination compliance rates, (C) travel transmission rates, and (D) domestic transmission rates. Vertical axis shows average annual reported incidence for 2006-2085.

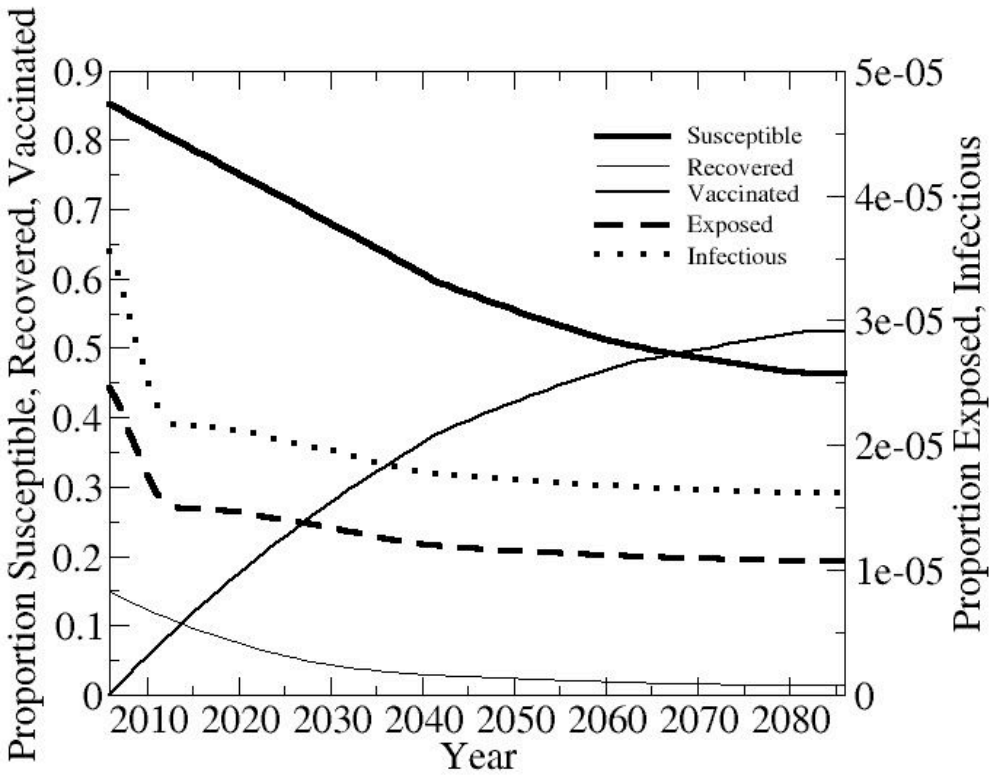


Figure 1

*Vaccine*, CT Bauch *et al*

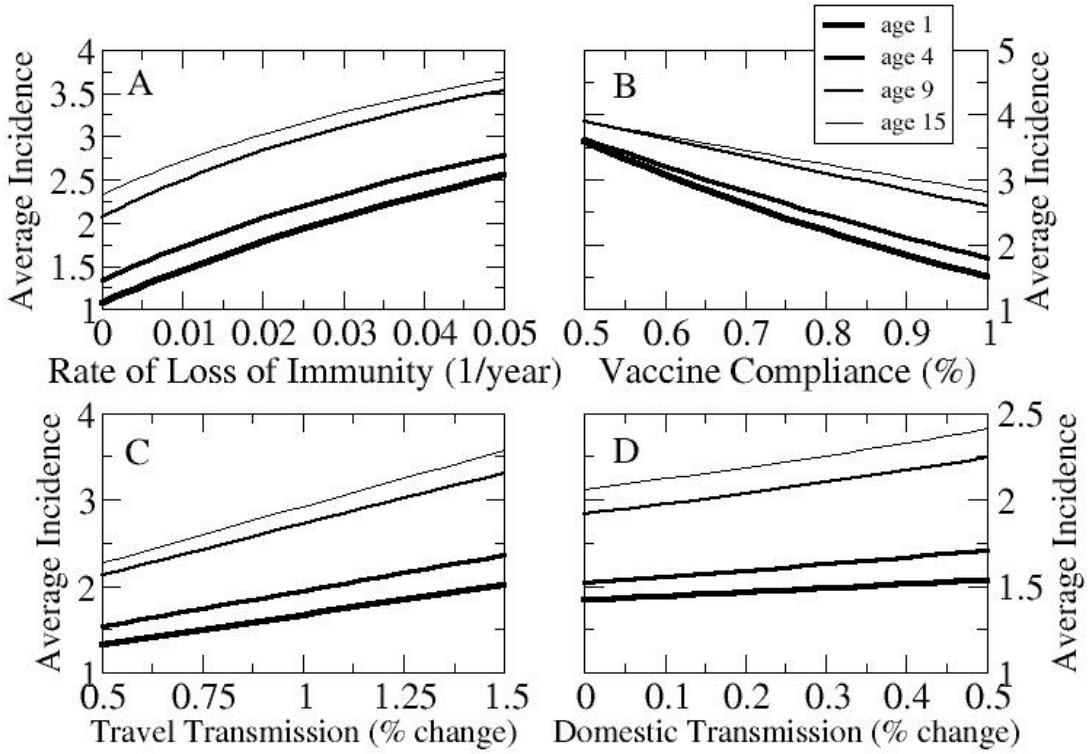


Figure 2

*Vaccine*, CT Bauch *et al*