Cost-effectiveness analysis of hepatitis A vaccination in Canada using a dynamic model

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HAV epidemiology in Canada

- Hepatitis A virus (HAV) incidence is relatively low.
- Spread is primarily person-to-person (fecal-oral route) with very rare foodborne outbreaks.
  - Average incidence 1980-1994: 6.3/100,000/yr
  - Average incidence 1995-2003: 3.8/100,000/yr
- Risk factors include MSM, IDUs, travelers.
- Vaccination in Canada is targeted toward high-risk groups.
Hepatitis A epidemiology

- Average Canadian incidence 1980-94: 6.3/100,000/yr
- Average Canadian incidence 1995-03: 3.8/100,000/yr

Source: Health Canada, CDC
Hepatitis A epidemiology

Source: Pham et al 2005
Research Rationale and Approach

- The cost-effectiveness and health outcomes of universal vaccination relative to targeted vaccination, in a low incidence country, are not currently known.

- Research Questions:
  - What are the expected health outcomes under universal hepatitis A vaccination in Canada?
  - Which universal vaccination schedules are the most cost-effective?

- We carried out a cost-utility analysis comparing universal vaccination to continuing the targeted policy.
Cost-utility methodology

- Assesses value for money.
- **Cost-effectiveness ratio:**
  increase in costs / gain in health units
- **Net Health Benefits, in health units:**
  \[(\text{gain in health}) - \frac{\text{(increase in costs)}}{\lambda}\]
- **Net Health Benefits, in monetary units:**
  \[\lambda(\text{gain in health}) - \text{(increase in costs)}\]

\[\lambda = $50,000/QALY\]
Cost-utility methodology

- Costs measured in 2005 Canadian dollars.
- Both **payer** and **societal** perspectives used
  - Payer = costs to Ministry of Health
  - Societal = MOH costs + time costs + private sector costs.
- Health measured in QALYs = Quality Adjusted Life Years.
QALY and Utilities

- Health has dimensions of **quality** and **quantity**
- Utility is
  - Used to weight length of life;
  - A measure of patient preference for standardized health states;
  - Measured on a 0 to 1 scale.
- Example:
  - Life expectancy of 5 years, utility of 0.5 means 2.5 QALYs are accumulated.
Methods for collecting costing data

- A systematic review of data on Hepatitis A outcomes and costs was performed.
- Canadian data were used whenever possible.
- Expert opinion and consensus used if no data available.
Vaccination Costs

- Costs of vaccination from the ministry perspective included:
  - Cost of vaccine (varied depending on strategy)
  - Cost of administration (ditto)
  - Cost of adverse events
- Societal costs included
  - Time costs due to getting vaccinated
  - Private sector vaccination
- Both proposed and current strategies were costed in this way.
Infection Costs

- Costs of infection from the ministry perspective included:
  - Physician visit
  - Outpatient clinic visits
  - Hospitalization
  - Diagnostic testing
  - Liver transplants
  - Public health interventions

- Additional infection costs from the societal perspective included:
  - Time costs (lost time at work due to acute infection and convalescence)

- Did not include home care or long-term care costs.
## Summary of strategies considered, and their costs

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
<th>Cost per person vaccinated</th>
</tr>
</thead>
</table>
| Current policy | High-risk groups only                                                                                                                                                                                      | Ministry: $81  
 |                |                                                                                                                                                                                                          | Society: $212                                  |
| 4+9            | One dose at age 4 in a clinic with other scheduled vaccines. One dose at age 9 in a school setting by replacing a single HB vaccine dose with a combined HA/HB vaccine dose. Current policy is phased out in unvaccinated cohorts. | Ministry: $42.57  
 |                |                                                                                                                                                                                                          | Society: $43.17                                |
| 9+9            | Two doses at age 9 in a school setting by replacing HB vaccine with combined HA/HB vaccine. Current policy is phased out in unvaccinated cohorts.                                                                   | Ministry: $18.12  
 |                |                                                                                                                                                                                                          | Society: $18.72                                |
## Summary of infection costs

<table>
<thead>
<tr>
<th>Age Class</th>
<th>Direct Costs (ministry)</th>
<th>Time Costs</th>
<th>Direct + time costs (society)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>$ 1,235</td>
<td>$ 598</td>
<td>$ 1,833</td>
</tr>
<tr>
<td>5-9</td>
<td>$ 1,235</td>
<td>$ 665</td>
<td>$ 1,900</td>
</tr>
<tr>
<td>10-19</td>
<td>$ 1,140</td>
<td>$ 729</td>
<td>$ 1,869</td>
</tr>
<tr>
<td>20-29</td>
<td>$ 1,163</td>
<td>$ 569</td>
<td>$ 1,732</td>
</tr>
<tr>
<td>30-39</td>
<td>$ 1,537</td>
<td>$ 1,446</td>
<td>$ 2,983</td>
</tr>
<tr>
<td>40-59</td>
<td>$ 1,923</td>
<td>$ 4,341</td>
<td>$ 6,264</td>
</tr>
<tr>
<td>60+</td>
<td>$ 1,556</td>
<td>$ 2,080</td>
<td>$ 3,636</td>
</tr>
</tbody>
</table>
Need for dynamic model

- We also need to estimate how many cases and deaths would be averted by universal vaccination.

- Conventional analyses use **cohort models** which cannot capture herd immunity effects of vaccination.

- Instead we use **dynamic models** which capture herd immunity by modelling transmission mechanisms via computer simulation.
Dynamic model description

- Classify individuals according to:
  - Epidemiological status: susceptible (S), latent (E), infectious (I), recovered (R), vaccinated (V).
  - Age: 0-4, 5-9, 10-19, 20-29, 30-39, 40-59, 60+
- Age-dependence: probability of becoming infected, transmitting infection, developing jaundice, being vaccinated, etc.
- Calibrated using data on case reports, seroprevalence, clinical literature, demographics, vaccine coverage.
Dynamic model description

V = Vaccinated
S = Susceptible
E = Infected but not yet infectious
I = Infectious
R = Recovered

Aging
Vaccination
Waning immunity
Death
Infection (travel)
Infection (domestic)
Becomes infectious
Recovery/Death
Dynamic Model Output

![Graph showing the proportion of susceptible, recovered, vaccinated, exposed, and infectious individuals over time. The x-axis represents years from 2010 to 2080, and the y-axis represents the proportion from 0 to 0.8. Different line styles and colors represent different statuses: black for susceptible, red for recovered, green for vaccinated, purple for exposed, and blue for infectious.](image-url)
Summary of Methodology

- Dynamic model
- Costing data, Utilities estimates
- Cases & deaths

Cases & Deaths, infection costs, vaccination costs, net benefits, costs per QALY gained

Probabilistic uncertainty analysis applied
Univariate sensitivity analysis applied
Summary of Other Assumptions

- Discounting: 5% on costs and QALYs
- Waning immunity: 3.2/1.7/0.6% per year (Jacobs et al Inf. Control & Hosp. Epi. 2004;25:563)
- 80 years of vaccination: 2006-2085
- Compliance: 94% (child, school-based), 80% (child, clinic-based), 25% (adult, clinic-based)
- Targeted vaccination is phased out.
- Utility during acute HAV infection is taken to be 0.6 (Chodick et al. 2002, Arguedas et al. 2002).
- Transmission rates, current policy costs and coverage are constant after 2006.
## Costs, cases, deaths (average discounted values)

Red = ministry, black = society

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Targeted Vaccine Costs, millions $</th>
<th>Universal Vaccine Costs, millions $</th>
<th>Infection Costs, millions $</th>
<th>Total Costs, millions $</th>
<th>Marginal Costs, millions $</th>
<th>Marginal QALYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>7.44 ± 0.65</td>
<td>0</td>
<td>0.45 ± 0.02</td>
<td>7.89 ± 0.65</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>19.48 ± 1.77</td>
<td>0</td>
<td>0.93 ± 0.05</td>
<td>20.41 ± 1.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+9</td>
<td>5.94 ± 0.54</td>
<td>3.41 ± 0.34</td>
<td>0.24 ± 0.02</td>
<td>9.59 ± 0.64</td>
<td>1.69 ± 0.36</td>
<td>9.70 ± 0.59</td>
</tr>
<tr>
<td></td>
<td>15.71 ± 1.47</td>
<td>3.44 ± 0.34</td>
<td>0.52 ± 0.04</td>
<td>19.67 ± 1.51</td>
<td>-0.74 ± 0.45</td>
<td></td>
</tr>
<tr>
<td>9+9</td>
<td>5.94 ± 0.54</td>
<td>1.59 ± 0.16</td>
<td>0.36 ± 0.03</td>
<td>7.88 ± 0.56</td>
<td>-0.01 ± 0.18</td>
<td>3.69 ± 0.93</td>
</tr>
<tr>
<td></td>
<td>15.70 ± 1.46</td>
<td>1.64 ± 0.17</td>
<td>0.77 ± 0.06</td>
<td>18.11 ± 1.48</td>
<td>-2.28 ± 0.33</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Reported Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>846</td>
<td>4.2</td>
</tr>
<tr>
<td>4+9</td>
<td>379</td>
<td>2.5</td>
</tr>
<tr>
<td>9+9</td>
<td>606</td>
<td>3.7</td>
</tr>
</tbody>
</table>

For 1980-1994 population values
## Cost-utility results

### Ministry perspective

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs per QALY Gained, $</th>
<th>Net Benefits, health units</th>
<th>Net Benefits, millions $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>9+9</td>
<td>- $46,000 ± $790,000</td>
<td>3.8 ± 3.0</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>4+9</td>
<td>$175,000 ± $36,000</td>
<td>-24.2 ± 7.1</td>
<td>-1.2 ± 0.4</td>
</tr>
</tbody>
</table>

### Society perspective

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs per QALY Gained, $</th>
<th>Net Benefits, health units</th>
<th>Net Benefits, millions $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>9+9</td>
<td>- $835,000 ± $4,333,000</td>
<td>49.4 ± 6.3</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>4+9</td>
<td>- $77,000 ± $48,000</td>
<td>24.5 ± 9.0</td>
<td>1.2 ± 0.5</td>
</tr>
</tbody>
</table>

Threshold for net benefits = $50,000
### Special Case: ceasing targeted vaccination altogether in 2006

#### Ministry perspective

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs per QALY Gained, $</th>
<th>Net Benefits, health units</th>
<th>Net Benefits, millions $</th>
</tr>
</thead>
<tbody>
<tr>
<td>9+9</td>
<td>53,600 ± 3,500</td>
<td>-1.5 ± 1.5</td>
<td>-0.1 ± 0.1</td>
</tr>
<tr>
<td>4+9</td>
<td>65,500 ± 8,600</td>
<td>-12.4 ± 6.8</td>
<td>-0.6 ± 0.3</td>
</tr>
</tbody>
</table>

#### Society perspective

<table>
<thead>
<tr>
<th>Strategy</th>
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<th>Net Benefits, health units</th>
<th>Net Benefits, millions $</th>
</tr>
</thead>
<tbody>
<tr>
<td>9+9</td>
<td>34,700 ± 3,500</td>
<td>6.6 ±1.8</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>4+9</td>
<td>44,600 ± 8,700</td>
<td>4.4 ± 7.0</td>
<td>0.2 ± 0.4</td>
</tr>
</tbody>
</table>
### Special Case: comparison with cohort model predictions

#### Ministry perspective, dynamic model

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs per QALY Gained, $</th>
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</tr>
</thead>
<tbody>
<tr>
<td>9+9</td>
<td>-46,000 ± 790,000</td>
<td>3.8 ± 3.0</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>4+9</td>
<td>175,000 ± 36,000</td>
<td>-24.2 ± 7.1</td>
<td>-1.2 ± 0.4</td>
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</table>

#### Ministry perspective, cohort model

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs per QALY Gained, $</th>
<th>Net Benefits, health units</th>
<th>Net Benefits, millions $</th>
</tr>
</thead>
<tbody>
<tr>
<td>9+9</td>
<td>-67,000 ± 2,673,000</td>
<td>1.8 ± 3.3</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>4+9</td>
<td>467,000 ± 99,000</td>
<td>-32.1 ± 7.1</td>
<td>-1.6 ± 0.4</td>
</tr>
</tbody>
</table>
We studied the sensitivity of model predictions to variations in parameters, for 9+9 strategy:

- rate of waning immunity (0% to 2% annual)
- change in travel transmission rate over time (decline to 50%, climb to 150%)
- under-reporting of symptomatic cases (1:1 to 1:3)
- HAV mortality rate (± 50%)
- Utility during acute HAV (± 50%)
- universal vaccination costs (± 50%)
- infection costs (± 50%)
- costs of current policy (-20%, +40%)
- efficacy of current policy in reducing incidence (1.7 to 3.3 per 100,000 per year with targeted alone)
Sensitivity Analysis

The “9+9” strategy is cost-effective from ministry perspective as long as:

- incremental cost of two doses of bivalent HA/HB vaccine versus two doses of monovalent HB vaccine is less than $21 (base case is $18).
- long-term reported incidence under the current strategy remains above 2.2/100,000/year (base case is 3.3/100,000/year).

Applies at a threshold of $50,000/QALY.
Conclusions

- Absolute QALY gains of implementing universal HA vaccination in Canada are small
  - 10-30 QALYs gained per year before discounting.
- However, a “9+9” strategy that replaces two doses of HB vaccine at age 9 with two doses of combined HA/HB vaccine appears to be economically attractive:
  - Cost-effective from ministry perspective, at $50,000/QALY threshold (positive net benefits).
  - Cost-saving from societal perspective.
- Using dynamic models instead of cohort models can make cost-effectiveness analyses of vaccination programmes more accurate.
Relevant publications


