

Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada

Murray D. Krahn^{a,*}, Ava John-Baptiste^b, Qilong Yi^c, Andrea Doria^d,
Robert S. Remis^e, Paul Ritvo^f, Samuel Friedman^g

^a Department of Medicine, University Health Network, Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

^b Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

^c Department of Public Health Sciences, University of Toronto, Toronto, ON, Canada

^d Department of Medical Imaging, Hospital for Sick Children, Toronto, ON, Canada

^e Department of Public Health Sciences, University of Toronto, Toronto, ON, Canada

^f School of Kinesiology and Health Sciences and Department of Psychology, York University, Division of Preventive Oncology, Cancer Care Ontario, Department of Public Health Sciences, University of Toronto, Division of Epidemiology, Biostatistics and Behavioural Science, Ontario Cancer Institute, Toronto, ON, Canada

^g National Development and Research Institutes, New York, USA, Center for Urban Epidemiologic Studies, New York Academy of Medicine, New York, USA, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA

Received 15 May 2004; received in revised form 24 September 2004; accepted 27 September 2004

Available online 31 October 2004

Abstract

Hepatitis C virus (HCV) vaccine development remains at an early stage. We explored the economic and health consequences of potential HCV vaccines by comparing universal vaccination with a hepatitis C vaccine to no vaccination in two groups: (1) injecting drug users (IDU); (2) all 12 year olds, using a Markov cohort simulation. Among IDUs, vaccination would avert 248 cases of HCV infection and 89 HCV-related deaths per 1000 individuals, and reduce costs. In average risk cohorts, vaccination did not reduce costs but was reasonably cost effective. These results provide encouragement to vaccine developers that a vaccine that is moderately effective and reasonably priced should not face economic barriers to implementation and will be attractive to third party payers.

© 2004 Elsevier Ltd. All rights reserved.

Keywords: HCV; Cost; Cost effectiveness; Vaccine; Vaccination; IDU

1. Background

Hepatitis C virus (HCV) is a leading cause of chronic liver disease in North America and across the globe. The prevalence of HCV infection in Canada is about 0.8%

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; QOL, quality of life; QALY, quality-adjusted life year; IDU, injection drug user; HUI 3, Health Utilities Index Mark 3; ICER, Incremental cost-effectiveness ratio

* Corresponding author. Present address: University Health Network, Toronto General Hospital, 200 Elizabeth Street, ES-9-407, Toronto, Ont., Canada M5G 2C4. Tel.: +1 416 416 340 4155; fax: +1 416 416 595 5826.

E-mail address: murray.krahn@uhn.on.ca (M.D. Krahn).

($n = \sim 240,000$) [1]. Approximately 170 million people are infected worldwide, with a global seroprevalence rate of about 3% [2].

Although the incidence of new infection is falling in developed countries as a result of blood screening, HCV infection remains a major public health problem. The number of infected individuals in North America will not fall significantly until approximately 2015 [3]. HCV-related costs continue to rise, and HCV-related mortality will double or triple during the next 10–20 years [4]. New infections continue to occur, primarily among high-risk groups such as injection drug users (IDUs). Over 30,000 new HCV infections still occur each year in the US and Canada. Thus, interest remains

strong in the development of preventive and therapeutic HCV vaccines.

Despite substantial progress, however, HCV vaccine development remains at an early stage. Vaccine developers face formidable scientific and technological challenges, including the high level of heterogeneity of the HCV genome, poorly understood immunologic mechanisms underlying persistent infection, lack of reproducible cell culture systems and (until recently) small animal models [5,6]. Researchers and pharmaceutical manufacturers are actively exploring approaches based on the use of HCV-related proteins and peptides, DNA, use of live viral and bacterial vectors, and combination approaches. Several promising small mammal and primate studies have been completed and phase I human trials have been carried out by Chiron and Immunogenetics corporations [5,6].

In 2002, the Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Diseases (CANVAC), a network of 74 Canadian scientists in collaboration with biopharmaceutical companies, funded this study as part of a program of behavioral, social science, and economic studies to lay the groundwork for the introduction of new antiviral vaccines. The objective of this study was to explore the economic and health consequences of the introduction of innovative HCV vaccines, under a variety of scenarios regarding vaccine efficacy, durability, and cost.

1.1. Strategies

We compared a policy of universal vaccination with a hepatitis C vaccine to a policy of no vaccination in two groups. First, we considered vaccination of a high-risk group, injection drug using (IDU) individuals who were HIV and HCV negative at the time of vaccination. Because targeted high-risk vaccination has shown limited success in preventing other viral illnesses such as hepatitis B virus infection, we also evaluated the effect of vaccinating general population cohorts who are HCV and HIV negative. Our baseline strategy involved vaccinating 12-year old school children. This strategy would allow HCV vaccine to be administered in the school, as an addition to provincially administered universal hepatitis B vaccination programs in Canada. School-based vaccination programs for HBV achieve high coverage rates and have low vaccine administration costs (14). We also considered strategies that involved vaccination of older cohorts.

1.2. Decision analytic model

We used a Markov-based decision analytic model programmed in DATA Professional (Tree Age Software, Williamstown, Massachusetts) to evaluate the potential health and economic effects of alternate vaccination strategies. In a Markov simulation, cohort members move between predefined states of health over time periods or cycles (annual cycles in our study) until all members have died. By tracking the proportion of the cohort who experience adverse

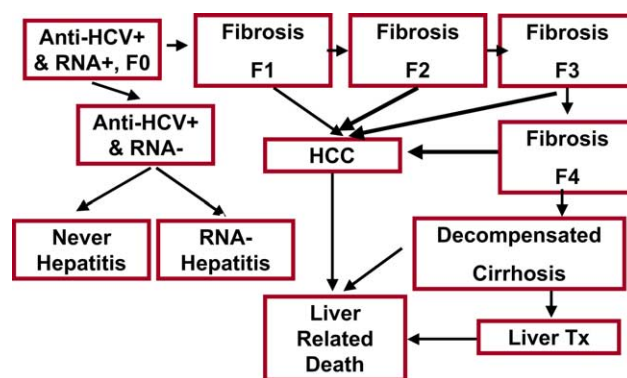


Fig. 1. Schematic of the Markov model of the natural history of HCV infection. This schematic depicts health states and potential health state transitions in the natural history of HCV infection. Abbreviations: F0–F4, liver fibrosis stages in the METAVIR staging system, in which F0 represents no fibrosis, and F4 indicates the presence of liver cirrhosis [72]; HCV±, individuals with a positive/negative test for antibodies to the HCV virus; RNA±, individuals with/without detectable circulating HCV virus; HCC, hepatocellular carcinoma; Tx, transplant.

health events and their associated costs, the computer simulation captures the number of adverse events, quality-adjusted life years (QALYS) and costs associated with each strategy [7,8].

Persons who are offered vaccination may or may not accept it. We expect that most, though not all, of those receiving vaccination will develop a protective immunological response (antibody mediated, cell mediated or both), which will attenuate over time. Protected and unprotected persons will be exposed to an annual risk of developing HCV and, for IDUs, an annual risk of developing HIV infection. IDUs experience a high risk of mortality from HCV, from HIV and from other lifestyle-related events. Some injection drug users within each year will stop injecting and, if HIV and HCV negative, will assume the same mortality and infection risk profile as the general population.

Health states and allowed transitions between health states for HCV-infected individuals are depicted in Fig. 1. Our HCV model represents a further development of a model used to estimate the prognosis of individuals infected with HCV through the blood supply [9,10]. In this model, HCV prognosis is a function of liver fibrosis stage, and to a lesser extent, HCV serologic status. HCV-infected individuals are initially assumed to have no fibrosis but progress over time to more severe fibrosis stages. This process is halted if a patient responds to antiviral therapy. Those developing liver cirrhosis (stage F4) may develop decompensated liver disease or hepatocellular carcinoma and may die from these complications of liver disease or require a liver transplant.

1.3. Model assumptions

The following assumptions were incorporated into our model: (1) progression is unidirectional, (2) regression from a

later liver fibrosis stage to an early stage (e.g. F1–F0, F2–F1, F3–F2) does not occur. (3) The duration of a cycle in our model is one year, during which only one stage transition per individual can occur. (4) Patients become aware of HCV status at a constant rate after infection, though many remain undetected for long periods of time. (5) Patients are offered combined antiviral therapy (ribavirin plus interferon) only once, in the F0 health state, in both the vaccine and non-vaccine strategy arms if they have not cleared the virus. (6) A sustained response to antiviral treatment is considered a cure and no further liver disease progression can occur. (7) Liver transplantation is performed only in patients with decompensated cirrhosis.

1.4. Outcome measure

We expressed outcomes of the analysis using the concept of quality-adjusted life years (QALYS). QALYS are measured by adjusting each year of life lived by a 0–1 scaled quality of life measure called utilities [11]. QALYS are a standardized way of expressing the gains in health produced by any health intervention, and are frequently used to estimate the cost effectiveness of preventive health programs including vaccination [12–14].

1.5. Model probabilities

Probabilities representing the likelihood of HCV-related events were identified through a systematic MEDLINE review, manual searches of bibliographies of identified articles, reviews of conference proceedings, previous studies by the investigators, and the investigators' files. Probabilities used in our model are displayed in Table 1.

When several studies were available, probabilities were estimated by pooling event rates using the following equation: Summary transition rate = $\sum P_i \times W_i / \sum W_i$ where P_i and W_i are the individual transition probability and weight, respectively [15]. The weight for each study is the inverse of the variance for the transition probability or number of patients in the study. Since most studies reported a rate of developing an event rather than a probability, transformation between rates and probabilities was made using the following formula: Probability = $1 - \exp(-\text{rate})$ [8,16].

1.6. Vaccination

Estimates of vaccine efficacy and compliance are, of course, speculative as an approved vaccine does not yet exist. However, some insight into behavioral and immunologic issues may be provided by considering experience with other viral hepatitis vaccines.

We estimated vaccine compliance rates from hepatitis B vaccination programs in school-based vaccination programs [17,18] and among IDUs [19–23]. Most vaccines have efficacy (ability to prevent infection among those who respond

to vaccine) rates of greater than 90%. We conservatively set this rate at 80% for a new HCV vaccine. The annual rate of loss of protective immunity (2.5% per year) was also based on experience with HBV vaccine [18,24]. Wide confidence limits around these speculative estimates allow incorporation of their considerable uncertainty into the final estimates of vaccine-related costs and effectiveness.

1.7. Incidence of HCV infection

Yearly age specific incidence rates for HCV infection in Canada were estimated using two methods. We first obtained a published estimate of the ratio of true incidence (18/100,000/year) to reported incidence (7.1/100,000/year) in the US [3,25]. We applied this ratio to reported age-specific incidence data from the enhanced surveillance program in Canada, which reported an overall incidence rate of 2.9/100,000/year. The true overall incidence rate was estimated to be 7.4/100,000 ($2.9 \times 18/7.1/100,000$).

We also used a second method to estimate incidence. Remis et al. developed an age-specific HCV incidence model for Canada, fitting age-specific incidence parameters to reported point prevalence estimates in a variety of general and high-risk populations (unpublished data). Remis estimated an overall HCV incidence rate of 16.3/100,000 in Canada, more than double that of our initial estimate. We adopted the first method in order to use a conservative incidence estimate in our baseline model and explored alternate incidence scenarios in a sensitivity analysis.

1.8. HCV incidence in injection drug users

The incidence rate of HCV in injection drug users IDUs is much higher than in the general population. Based on four studies recently reported in the US and Canada, the weighted average incidence rate is 14.5% per year, varying from 6.4 to 37.3% [26–29]. When injection drug use ceases, we assumed that the risk of HCV infection reverts to that of the general population.

1.9. Excess mortality ratio in injection drug users

Injection drug users have a much higher mortality rate than the general population. Injecting drug users are at risk of drug overdose, bacterial infection and have a high burden of co-morbidity that may lead to unexpected death. Reported excess mortality ratios vary by geographic region [30–39]. We estimated excess mortality rates for Canada by pooling rates from all studies that report a ratio of IDU to general population mortality. The pooled weighted mortality ratio is 14.28 [30–37]. Because age ranges in published studies are wide, we applied this excess mortality rate to all IDUs currently using drugs.

We pooled data from six reports in order to estimate the relative excess mortality rate among HIV positive IDUs in comparison to HIV negative IDUs [31,37,40–42].

Table 1
Model probabilities, utilities, and costs

Variable	Baseline value	Range	Reference
Vaccine variables			
Probability of vaccine compliance, general population	0.90		[17,24]
Probability of vaccine compliance, IDUs	0.51	0.51–0.88	[19–23,69]
Vaccine response rate	0.90		Assumption
Vaccine efficacy	0.80		Assumption
Annual loss of immunity	0.025		Assumption
HCV and HIV incidence and mortality			
HCV incidence rate, general population (per 100,000/year)	7.4	7.4–16.3	See text p. 8
Age 10–19 (per 100,000/year)	1.0	1.0–2.2	
Age 20–39	23.2	23.2–51.2	
Age 40–69	8.8	8.8–19.3	
Age >70	0.9	0.9–2.0	
HCV incidence rate, IDU (per person/year)	0.145		[26–29]
HIV incidence rate, IDU (per person/year)	0.01		[43]
IDU mortality/general population mortality ratio	14.3		[30–37]
IDU HIV+ mortality/all IDU mortality ratio	2.5		[31,37,40–42]
Cessation of injecting drug use (prevalence)			
Age 20–29	1.00		Expert opinion
Age 30–39	0.74		
Age 40–49	0.40		
Age 50–69	0.09		
Age >70	0.00		
HCV prognostic model			
Annual rate of identification as being HCV+	0.0297		[9]
Probability of spontaneous clearance	0.150	0.050–0.250	[9]
Probability of progression F0 to F1	0.109	0.095–0.123	[9]
Probability of progression F1 to F2	0.111	0.091–0.131	[9]
Probability of progression F2 to F3	0.119	0.099–0.139	[9]
Probability of progression F3 to F4	0.124	0.099–0.146	[9]
Probability of progression F1 to HCC	0.0001	0.00001–0.001	[9]
Probability of progression F2 to HCC	0.0001	0.00001–0.001	[9]
Probability of progression F3 to HCC	0.001	0.001–0.010	[9]
Probability of progression F4 to HCC	0.021	0.018–0.024	[9]
Probability of progression F4 to decompensation	0.046	0.038–0.054	[9]
Probability of death from decompensated cirrhosis	0.138	0.074–0.202	[9]
Probability of dying from HCC	0.860	0.570–0.900	[9]
Probability of liver transplant	0.033	0.017–0.049	[9]
Probability of transplant death, (year 1)	0.169	0.127–0.210	[9]
Probability of transplant death, successive years	0.034	0.024–0.043	[9]
Probability of treatment with combination therapy			
F0	0.315	0.192–0.382	[9]
F1	0.800	0.750–0.950	
F2	0.800	0.750–0.950	
F3	0.800	0.750–0.950	
F4	0.754	0.500–0.900	
Decompensated cirrhosis	0.052	0.004–0.072	
Probability of sustained response to CMB treatment			
F0	0.361	0.7–1.3	[9]
F1	0.361		
F2	0.432		
F3	0.432		
F4	0.208		
Decompensated cirrhosis	0.208		
Costs			
Vaccine cost (per dose, 3 doses)	\$51	30–100	[49] ^c
Vaccine administration	\$31	30–100	[50]
Vaccine administration	\$16	10–100	[24]

Table 1 (Continued)

Variable	Baseline value	Range	Reference
Annual cost of care			
Mild/moderate chronic hepatitis (F0 to F3)	\$158	\$89–300	[70] ^{a,b}
Compensated cirrhosis (F4)	\$210		[70] ^{a,b}
Decompensated cirrhosis	\$10,925	\$9000–15,000	[70] ^{a,b}
HCC	\$7122	\$5000–26825	[70] ^{a,b}
Liver transplantation, 1st year	\$102,920	\$70,000–135,035	[71] ^b
Liver transplantation, successive years	\$12,809	\$11,000–15,427	[70] ^{a,b}
Costs of treatment ^d			
CMB, 24 weeks	\$4548	\$1200–8000	[70] ^{a,b}
CMB, 48 weeks	\$8707	\$2400–15,000	[70] ^{a,b}
HIV infection	14,930		
Utilities			
Canadian population norms (sustained virological response, spontaneous resolution, never infected)	0.930	0.928–0.932	[52]
Mild/moderate chronic hepatitis (F0 to F3)	0.73	0.64–0.83	[51]
Compensated cirrhosis (F4)	0.74	0.66–0.83	[51]
Decompensated cirrhosis	0.69	0.52–0.85	[51]
Liver transplantation	0.70	0.63–0.77	[51]
Hepatocellular carcinoma (HCC)	0.51	0.26–0.76	[51]
Sustained virological responder	0.77	0.63–0.77	[51]
Disutility of interferon therapy	0.14	0.05–0.30	[51]
Utility, HIV infection	0.80	–	[56]
Utility, ongoing injecting drug use	0.65	–	[56]

Abbreviations: HCC, hepatocellular carcinoma; F0, no fibrosis; F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; and F4, fibrosis stage 4.

^a US Medicare charges were converted to costs using a ratio of 1.62.

^b Canadian costs were obtained using 1998 Medical and Health Care Purchasing Power Parities (<http://www.statcan.ca/english/IPS/Data/62-001-XPB.htm>) to convert US dollars to Canadian currency, and then inflated to 2003 dollars, using the consumer price index for health and personal care.

^c HCV vaccine cost estimated from the cost per vaccine for hepatitis A.

^d Treatment costs include the costs of drugs, and monitoring (including follow-up).

1.10. HIV incidence rate among IDUs

HIV incidence rates among IDUs were derived from a study by Remis et al. which modeled HIV incidence rates from 1980 to 2015 [43]. We used a rate of 1.0% in our model. At this rate, a cohort with mean age of 30 and an average of 10 years of drug use will have a 10% HIV prevalence rate.

1.11. Annual drug stopping rate

The prevalence of successful withdrawal from injecting drug use by age among IDUs was based on expert judgment of the investigators (RR).

1.12. HCV-related costs

The analysis was performed from a societal perspective. Future costs and health effects were discounted at 3% annually [44]. Costs were obtained from published sources, and were estimated from charge data using cost to charge conversion ratio of 1.62 [45–48]. Cost data were converted to Canadian dollars at the purchasing power parity conversion rate and inflated to 2003 levels using the consumer price index for health care and personal items (<http://www.statcan.ca/english/IPS/Data/62-001-XPB.htm>).

Estimates for the potential cost of a future HCV vaccine were based on the approximate costs of hepatitis A vaccine in the Canadian context [49]. Administration costs for general

population cohorts were based on published costs of school-based hepatitis B vaccination [24]. Vaccine administration for IDUs was expected to occur within the context of an existing clinical or public health program (e.g. needle exchange site, harm reduction project). Therefore, administration costs for IDUs were assumed to require only a separate visit for each injection to a primary care physician or site at which primary care is delivered (Ontario Health Insurance Plan fee codes A008, G537 [50]) Costs of ongoing HCV and HIV care, including decompensated liver disease and transplantation, were derived from studies in which HCV-related health states were commensurate with those represented in our model. Cost estimates were based on best quality single studies rather than from pooled data.

1.13. Utilities for health outcomes

Utilities for HCV-related health states were derived using published Health Utilities Index Mark 3 (HUI Mark 3) data derived from a sample of 200 hepatitis C patients with all levels of disease severity, from early disease to hepatocellular carcinoma to post-transplantation [51]. Utilities derived from instruments that incorporate community weights are the reference standard for cost-utility analyses performed from the societal perspective [11].

Several assumptions were made about HCV-related utilities to simplify the analysis. All patients who were not currently infected with HCV (i.e. those with a sustained

virologic response to treatment, those who spontaneously clear HCV infection and those who have never been infected) were assigned the utility value for the general Canadian adult population that reports no co-morbidities [52]. This assumption may lead to a slight overestimate of the benefits of vaccination, as HCV utilities and quality of life in sustained virologic responders are lower than general population values [51,53]. In assigning utilities for the different fibrosis stages, we assumed that F0, F1, F2, and F3 all shared the same utility. Evidence suggests that, in the absence of cirrhosis, there is no difference in the health-related quality of life of HCV infected individuals between those with mild and moderate chronic hepatitis [54]. The adverse effects of antiviral HCV treatment [55], as well as HIV infection and ongoing injecting drug use, were estimated from published sources [56].

The short-term impairment in quality of life (disutility) associated with combination antiviral therapy (interferon and ribavirin) was elicited using the EQ-5D, an instrument similar to the HUI Mark 3 [57,58].

1.14. Analysis

We performed an expected value analysis, in which the expected future costs and consequences were calculated using the baseline parameter values. This analysis was supplemented with one-way sensitivity analyses, in which the sensitivity of the analytic result to changes in an individual parameter value was estimated. In addition, we performed a Monte-Carlo simulation in which values for model parameters were drawn from pre-specified probability distributions. This method facilitated simulation of 95% confidence intervals for expected costs, quality-adjusted life years, and incremental cost per quality-adjusted life year gained.

2. Results

2.1. IDU population (Table 2)

At our baseline estimate of vaccine efficacy and uptake, vaccinating an IDU population would result in the prevention of 248 HCV infections per 1000 persons offered vacci-

nation over the lifetime of the cohort. It would also result in the prevention of 89 HCV-related deaths. The health benefit expressed in quality-adjusted life years gained per person vaccinated was very substantial, at an estimated 1.6 QALYs. Vaccination also resulted in net cost saving, with an estimated reduction in costs of approximately \$400 per person (in HCV-related costs) offered vaccination. Thus, a universal vaccination strategy in this group can be said to be dominant over the alternative strategy of not vaccinating, as such a policy would both improve health overall as well as reduce costs (Table 2).

2.2. Average risk-school age population (Table 2)

Because of the lower HCV infection risk, vaccinating a general population would result in a smaller health gain per person vaccinated, preventing 180 cases of HCV and 73 HCV-related deaths per 100,000 offered vaccination. For the annual birth cohort in Canada of 400,000, we project that universal HCV vaccination would prevent approximately 300 HCV-related deaths. As expected, health gains per person vaccinated expressed in QALYs were much smaller than for the IDU population, at 0.008 QALYs, or approximately 3 quality-adjusted days. In this population, a universal vaccination program is no longer cost saving, but results in improved health at an increased cost, yielding an incremental cost effectiveness ratio of \$18 045/QALY.

2.3. Sensitivity analysis (Table 3)

We explored the effects of uncertainty with respect to key model variables on the attractiveness of vaccination policies in both groups using one- and two-way sensitivity analyses and Monte-Carlo simulations involving probability distributions for all variables. One-way sensitivity analyses (Table 3) demonstrated that the analytic result was insensitive to all variables in the high-risk scenario. That is, the incremental cost effectiveness ratio did not exceed standard thresholds of \$50,000 per QALY for any change in any parameter value. In the average-risk scenario, the analytic result was most sensitive to the HCV incidence rate, vaccine cost, and the age of vaccination. At our higher estimate of vaccine incidence

Table 2

Results of baseline cost-effectiveness analysis (overall HCV incidence rate in Canadian population = 7.4/100,000, and in the IDU population = 14.46%)

	Strategy	Lifetime cases of HCV (/1000)	Lifetime HCV-related deaths (/1000)	Cost	QALYs (95% CI)	ICER (95% CI)
Injecting drug user	Vaccine	460	139	\$33,490	18.786	–
	No vaccine	708	227	\$33,889	17.202	–
	Marginal	248	88	\$ –399	1.584 (0.431, 3.100)	Dominated (\$ –740, \$340)
		(/100000)	(/100000)			
Average risk 12 year old	Vaccine	380	88	\$176	26.558	
	No vaccine	560	161	\$32	26.550	
	Marginal	180	73	\$144 (\$76–211)	0.008 (0.002, 0.017)	\$18,000 (\$7000, \$66,700)

Abbreviations: IDU, injecting drug user; CI, confidence interval; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio, expressed as discounted incremental cost per discounted incremental quality-adjusted life year, in 2003 Canadian dollars (US\$ 1 ≅ CAN\$ 1.31).

Table 3
Univariate sensitivity analyses

	Value	Incremental cost effectiveness ratio ^a	
		IDU	Average risk 12 year old
Vaccine response rate	1.0	-270	16,700
	Baseline (0.90)	-250	18,000
	0.5	-150	35,400
Vaccine efficacy	1.0	-270	14,700
	Baseline (0.80)	-250	18,100
	0.5	-190	31,300
Vaccine compliance	1.0	-250	18,000
	Baseline (0.51, 0.90)	-250	18,000
	0.5 × Baseline	-250	18,000
Annual loss of immunity	0.05	-240	26,300
	Baseline (0.025)	-250	18,000
	0	-270	13,000
HCV incidence	2 × Baseline	-300	3300
	Baseline (0.000074/year, 0.145/year)	-250	18,000
	0.5 × Baseline	-190	81,000
Vaccine cost (3 doses)	\$1000	220	118,000
	\$ Baseline (\$153)	-250	18,000
	\$20	-330	3200
Age at vaccination	10	370	21,000
	Baseline (12)	-250	18,000
	30	-600	43,400

^a Incremental discounted cost (2003 \$C) per incremental discounted quality-adjusted life year.

(16.3/100,000/year), universal vaccination resulted in greater clinical benefit, greater cost saving (IDU population) and a more attractive cost effectiveness ratio (average risk 12 year old population: \$13,900/QALY (\$8400–17600/QALY))

For a vaccine that does not yet exist, the variables with the greatest degree of uncertainty are vaccine cost and vaccine efficacy. Table 4 shows incremental cost-effectiveness ratios (ICERs) for combinations of these val-

ues. Vaccinating IDUs was an economically attractive strategy (ICER < \$50,000/QALY gained) for all combinations of vaccine cost and efficacy considered. A 50% effective vaccine remained highly attractive even at a vaccine cost of \$300. Thus, vaccination programs for IDUs, even with much higher costs associated with recruitment, advertising, screening, or the vaccine itself, would be highly economically attractive, given at least moderate efficacy. For the general population,

Table 4
Two-way sensitivity analysis on efficacy and cost of vaccination

Vaccine cost (\$) (3 doses)	Vaccine effectiveness				
	0.5	0.6	0.7	0.8	0.9
In IDU					
300	630	430	280	160	80
250	470	300	170	80.0	10
200	300	170	70	0	-60
150	140	40	-30	-90	-120
100	-20	-90	-140	-170	-190
50	-190	-220	-240	-250	-260
25	-270	-280	-290	-290	-300
Average risk 12 year old					
300	171,400	142,500	121,900	106,400	94,400
250	143,300	119,100	101,800	88,800	78,700
200	115,200	95,600	81,700	71,200	63,000
150	87,000	72,200	61,600	53,600	47,500
100	58,900	48,700	41,500	36,000	31,800
50	30,700	25,300	21,400	18,500	16,200
25	16,600	13,500	11,300	9700	8400

Incremental cost per quality-adjusted life year gained for the vaccination strategy.

vaccine costs of less than \$150 generally resulted in a universal vaccination strategy being cost effective.

We explored the effects of changing the age distributions as well as overall HCV incidence, as both may change with vaccination. For the IDU group, decreasing incidence by 50% prior to age 35, and increasing by 50% after age 35 had minimal effect on the analytic result. Shifting the age distribution 20 years to the right increased the cost-utility ratio to \$77,895 per QALY gained in the general population cohort.

Finally, probabilistic (Monte-Carlo) sensitivity analyses incorporating the joint effects of uncertainty within all model parameters showed that for the IDU population, the model was very robust. The 95% confidence bound for incremental cost per QALY was \$ -740 to \$340, suggesting a high degree of confidence (>99%) that a universal vaccination strategy would be economically attractive. Among average risk 12 year olds, the 95% confidence bound was \$6949 to \$66,691. Our simulations suggest that, at baseline efficacy values, there is approximately a 93% probability that an effective vaccine would be economically attractive (ICER < \$50,000/QALY).

3. Discussion

Our analysis suggests that a vaccine of even moderate efficacy would substantially reduce the both the lifetime risk of HCV infection and the adverse effects of HCV sequelae. Among the approximately 100,000 IDUs in Canada, a vaccine with 80% efficacy would reduce the risk of HCV infection by 35–50% and reduce HCV-related deaths by 32–45%. A more durable vaccine whose efficacy declines more slowly over time (our baseline rate = 2.5% loss of protection per year) would prevent an even larger proportion of HCV-related events. Our analysis also suggests that a vaccine of even moderate efficacy would be cost saving in high-risk groups and quite economically attractive (\$18,000/QALY, 93% probability of being <\$50,000/QALY) in lower risk general population cohorts. Few health interventions reduce costs and improve health. Those that do should be implemented forthwith. Interventions that increase costs and improve health require judgments about whether additional expenditures represent good value for money. In the case of population hepatitis C vaccination, \$18,000/QALY gained is well below conventional cost effectiveness thresholds of \$50,000 and \$100,000/QALY [44,59]. It is also comparable to the economic attractiveness of vaccines for pneumococcal pneumonia (~\$12,000/life year [60,61], hepatitis B vaccine in adolescents (\$2100/QALY [24] and hepatitis A vaccine in adolescents (\$34,000/QALY) [62].

Our analysis has several limitations. Chief among these is the highly speculative nature of some of the parameter values. For example, estimating vaccine efficacy for a vaccine that does not yet exist is a process associated with considerable uncertainty. This analysis was conceived, however, as an exploratory study that would indicate in a general way the conditions under which a new vaccine was likely to be

economically attractive. It cannot therefore be considered a definitive study.

In addition, this is a cohort simulation study. Like other published cohort simulation studies of vaccination programs [63–67], it cannot capture the full benefits of vaccination such as preventing secondary and tertiary infection to non-cohort members. A full population simulation run over many generations would be required to estimate the full health and economic effects of an ongoing vaccination program [68]. Nonetheless, cohort simulation models often have greater fidelity to clinical events within the cohort, and generally approximate simulations of dynamic models. When results differ, cohort models tend to underestimate the economic attractiveness of vaccination policies [68], because the benefits of preventing additional infections in contacts of the vaccines are not fully captured. Thus, we believe that this model, while conservative, provides significant insight into the future economic and health consequences of vaccination at current levels of HCV infection risk.

Finally, the generalizability of this model to other settings will depend on the degree to which the HCV epidemiology and HCV health care costs in other countries are similar to those of Canada. It is likely to be the case that vaccinating high-risk groups will be cost effective irrespective of setting (see Table 3). However, for general populations in other health care settings, the economic attractiveness will depend heavily on the local burden of disease, the cost of caring for individuals with HCV infection and, notably, the cost of reaching vaccinees and administering vaccine.

4. Conclusion

At conservative estimates of vaccine cost and efficacy, an HCV vaccine will likely be highly economically attractive. As vaccine development progresses, additional studies should be performed to update these predictions. The results of this study should provide encouragement to vaccine developers that a vaccine that is moderately effective and reasonably priced should not face economic barriers to implementation, and will be attractive to third party payers, in settings where the burden of disease and costs of HCV-related health care are similar to those of Canada.

Acknowledgements

This work was supported by a project grant from the Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Diseases (CANVAC). Dr. Krahn's contribution was supported by an Investigator Award from the Canadian Institutes for Health Research. Dr. Friedman's contribution was supported by US National Institute on Drug Abuse grants R01 DA13128 (Networks, norms, and HIV risk among youth) and P30 DA11041 (Center for Drug Use and HIV Research).

References

- [1] Remis R, et al., Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960–1985 and 1990–1992; Report to Health Canada. June 1998 (http://www.phac-aspc.gc.ca/hcai-iamss/bbp-pts/pub_e.html).
- [2] Alter HJ. Epidemiology of hepatitis C. *Hepatology* 1997;26(3 Suppl 1):62s–5s.
- [3] Armstrong GL, et al. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000;31(3):777–82.
- [4] Wong JB, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000;90(10):1562–9.
- [5] Inchauspe G, Feinstone S. Development of a hepatitis C virus vaccine. *Clin Liver Dis* 2003;7(1):243–59, xi.
- [6] Forns X, Bukh J, Purcell RH. The challenge of developing a vaccine against hepatitis C virus. *J Hepatol* 2002;37(5):684–95.
- [7] Naimark D, et al. Primer on medical decision analysis: Part 5—Working with Markov processes. *Med Decis Making* 1997;17(2):152–9.
- [8] Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13(4):322–38.
- [9] Krahn M, et al., Estimating the prognosis of Canadians infected with the hepatitis C virus through the blood supply, 1986–1990 first revision of prognostic model incorporating data from the compensation claimant cohort. Toronto: University of Toronto; 2002. p. 133.
- [10] Krahn M, et al., Estimating the Prognosis of Hepatitis C Patients Infected by Transfusion in Canada between 1986 and 1990; Report to the Joint Committee, Hepatitis C, January 1, 1986–July 1, 1990 Class Actions Settlement, 1999. Available on request from the author.
- [11] Gold MR, et al. Identifying and valuing outcomes. In: Gold MR, et al., editors. *Cost effectiveness in health and medicine*, New York: Oxford University Press; 1996.
- [12] Brisson M, Edmunds WJ. Varicella vaccination in England and Wales: cost-utility analysis. *Arch Dis Child* 2003;88(10):862–9.
- [13] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *J Am Med Soc* 2003;290(6):781–9.
- [14] Prakash C. Crucial factors that influence cost-effectiveness of universal hepatitis B immunization in India. *Int J Technol Assess Health Care* 2003;19(1):28–40.
- [15] Vamvakas EC, Taswell HF. Mortality after blood transfusion. *Transfus Med Rev* 1994;8(4):267–80.
- [16] Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (The DEALE). *Am J Med* 1982;73:883–8.
- [17] Dobson S, Scheifele D, Bell A. Assessment of a universal school-based hepatitis B vaccination program. *J Am Med Assoc* 1995;274:1209–13.
- [18] Krahn M, Detsky AS. Should Canada and the United States universally vaccinate infants against hepatitis B? A cost-effectiveness analysis. *Med Decis Making* 1993;13(1):4–20.
- [19] Quaglio G, et al. Compliance with hepatitis B vaccination in 1175 heroin users and risk factors associated with lack of vaccine response. *Addiction* 2002;97(8):985–92.
- [20] Lugoboni F, et al. Hepatitis A virus vaccination among injecting drug users: do we have to change the vaccination schedule? *Clin Infect Dis* 2000;31(3):847–8.
- [21] Lugoboni F, et al. Immunoresponse to hepatitis B vaccination and adherence campaign among injecting drug users. *Vaccine* 1997;15(9):1014–6.
- [22] Mezzelani P, et al. High compliance with a hepatitis B virus vaccination program among intravenous drug users. *J Infect Dis* 1991;163(4):923.
- [23] Des Jarlais DC, et al. Providing hepatitis B vaccination to injection drug users: referral to health clinics vs on-site vaccination at a syringe exchange program. *Am J Public Health* 2001;91(11):1791–2.
- [24] Krahn M, et al. Costs and cost-effectiveness of a universal, school-based hepatitis B vaccination program. *Am J Public Health* 1998;88(11):1638–44.
- [25] Alter MJ, et al. The natural history of community-acquired hepatitis C in the United States. The sentinel counties chronic non-A, non-B hepatitis study team [see comments]. *N Engl J Med* 1992;327(27):1899–905.
- [26] Miller CL, et al. Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. *Hepatology* 2002;36(3):737–42.
- [27] Garfein RS, et al. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;18(Suppl 1):11–9.
- [28] Patrick DM, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. *Can Med Assoc J* 2001;165(7):889–95.
- [29] Villano SA, et al. Incidence and risk factors for hepatitis C among injection drug users in Baltimore. *Maryland J Clin Microbiol* 1997;35(12):3274–7.
- [30] Concool B, Smith H, Stimmel B. Mortality rates of persons entering methadone maintenance: a seven-year study. *Am J Drug Alcohol Abuse* 1979;6(3):345–53.
- [31] Eskild A, et al. Differences in mortality rates and causes of death between HIV positive and HIV negative intravenous drug users. *Int J Epidemiol* 1993;22(2):315–20.
- [32] Ghodse AH, et al. Deaths of drug addicts in the United Kingdom, 1967–81. *Br Med J (Clin Res Ed)* 1985;290(6466):425–8.
- [33] Bargagli AM, et al. Mortality among problem drug users in Rome: an 18-year follow-up study, 1980–97. *Addiction* 2001;96(10):1455–63.
- [34] Perucci CA, et al. Mortality of intravenous drug users in Rome: a cohort study. *Am J Public Health* 1991;81(10):1307–10.
- [35] McAnulty JM, et al. Underreporting of AIDS, New South Wales, 1988–1989. *Med J Aust* 1992;156(7):452–5.
- [36] Joe GW, Lehman W, Simpson DD. Addict death rates during a four-year post-treatment follow-up. *Am J Public Health* 1982;72(7):703–9.
- [37] Goedert JJ, et al. Cause-specific mortality associated with HIV and HTLV-II infections among injecting drug users in the USA. *AIDS* 2001;15(10):1295–302.
- [38] Pezzotti P, et al. Direct comparison of time to AIDS and infectious disease death between HIV seroconverter injection drug users in Italy and the United States: results from the ALIVE and ISS studies. *AIDS link to intravenous experiences. Italian seroconversion study. J Acquir Immune Defic Syndr Hum Retrovirol* 1999;20(3):275–82.
- [39] Mezzelani P, et al. A multicentre study on the causes of death among Italian injecting drug users. *AIDS has overtaken overdose as the principal cause of death. AIDS Care* 1998;10(1):61–7.
- [40] Tyndall MW, et al. Impact of HIV infection on mortality in a cohort of injection drug users. *J Acquir Immune Defic Syndr* 2001;28(4):351–7.
- [41] Van Haastrecht HJ, et al. Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *Am J Epidemiol* 1996;143(4):380–91.
- [42] Zaccarelli M, et al. Impact of HIV infection on non-AIDS mortality among Italian injecting drug users. *AIDS* 1994;8(3):345–50.
- [43] Remis R, Consortium to characterize injection drug users in Canada. Division of HIV/AIDS and STD, Toronto: Laboratory Centre for Disease Control, Health Canada; 1998. p. 73.
- [44] Gold MR, et al. *Cost-effectiveness in health and medicine*. New York: Oxford University Press Inc.; 1996.
- [45] Finkler SA. The distinction between cost and charges. *Ann Intern Med* 1982;96:102–9.
- [46] Brandeis J, et al. A nationwide charge comparison of the principal treatments for early stage prostate carcinoma. *Cancer* 2000;89(8):1792–9.
- [47] Mushinski M. Average charges for hip replacement surgeries: United States, 1997. *Stat Bull Metrop Insur Co* 1999;80(2):32–40.

- [48] Hayman JA, et al. A comparison of two methods for estimating the technical costs of external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2000;47(2):461–7.
- [49] Myers RP, Gregor JC, Marotta PJ. The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C. *Hepatology* 2000;31(4):834–9.
- [50] Ontario M.O.H. Schedule of benefits. Physician services under the Health Insurance Act, 1995. Ontario: Ministry of Health.
- [51] Chong CA, et al. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003;98(3):630–8.
- [52] Mittman N, et al. Utility scores for chronic conditions in a community-dwelling population. *Pharmacoeconomics* 1999;15:369–76.
- [53] Ware J, et al. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. *J Am Med Assoc* 1999;282(3):221–2.
- [54] Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology* 1998;27(1):209–12.
- [55] Siebert U, et al., Health related quality of life in chronic hepatitis C patients: a comparison of different utility assessment methods. *Med Decis Making*; 2002.
- [56] Bayoumi AM, Redelmeier DA. Economic methods for measuring quality of life associated with HIV infection. *Qual Life Res* 1999;8(6):471–80.
- [57] Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol questionnaire. *Health Econ* 1993;2:237–46.
- [58] Hurst NP, et al. Validity of Euroqol—a generic health status instrument—in patients with rheumatoid arthritis. *Br J Rheumatol* 1994;33:655–62.
- [59] Laupacis A, et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;146:473–81.
- [60] Ament A, et al. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries. *Clin Infect Dis* 2000;31(2):444–50.
- [61] De Graeve D, Lombaert G, Goossens H. Cost-effectiveness analysis of pneumococcal vaccination of adults and elderly persons in Belgium. *Pharmacoeconomics* 2000;17(6):591–601.
- [62] Krahn M, et al. Universal hepatitis A vaccination for adolescents and children in Canada: a cost effectiveness analysis. Toronto: Health Canada; 2001. p. 42.
- [63] Krahn M, Detsky AS. Universal vaccination against hepatitis B in North America: a cost effectiveness analysis. *Clin Res* 1991;39:379a.
- [64] Krahn M, Guasparini R, Sherman M. Costs and cost effectiveness of a universal, school-based, adolescent hepatitis B vaccination program. *Am J Public Health* 1998;88:1638–44.
- [65] Bloom BS, et al. A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. *Ann Intern Med* 1993;118(4):298–306.
- [66] Lieu TA, et al. Cost-effectiveness of a routine varicella vaccination program for US children. *J Am Med Assoc* 1994;271(5):375–81.
- [67] Lieu TA, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. *J Am Med Assoc* 2000;283(11):1460–8.
- [68] Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. *Stat Med* 1999;18(23):3263–82.
- [69] Savage RB, Hussey MJ, Hurie MB. A successful approach to immunizing men who have sex with men against hepatitis B. *Public Health Nurs* 2000;17(3):202–6.
- [70] Younossi ZM, et al. Cost effectiveness of interferon alpha2b combined with ribavirin for the treatment of chronic hepatitis C. *Hepatology* 1999;30(5):1318–24.
- [71] Taylor MC, et al. Factors associated with the high cost of liver transplantation in adults. *Can J Surg* 2002;45(6):425–34.
- [72] Group TMC. Inter- and intra-observer variation in the assessment of liver biopsy of chronic hepatitis C. *Hepatology* 1996;20:15–20.