Costs and Cost-Effectiveness of a Universal, School-Based Hepatitis B Vaccination Program

ABSTRACT

Objectives. This study evaluated the costs and cost-effectiveness of a school-based grade 6 universal vaccination program against hepatitis B.

Methods. We performed a descriptive cost study and cost-effectiveness analysis of British Columbia's vaccination program for 1994 and 1995. Since 1992, public health nurses have administered hepatitis B vaccine to grade 6 students in schools. We measured costs of vaccine, vaccine administration, and net program costs and used a validated Markov model to calculate the cost-effectiveness of the program.

Results. Vaccinating each student cost $44, $24 of which was the cost of vaccine administration. The net cost was $9 per person; considering productivity costs, net savings were $75 per person. Marginal cost per life year gained was $2100. Universal adolescent vaccination is also economically attractive in the United States but less attractive in regions with incidence rates below 3 cases per 100 000 per year.

Conclusions. Hepatitis B vaccine can be delivered in North American schools at a reasonable cost. Adolescent vaccination is economically attractive in North American regions of high and average incidence rates. Our analysis supports vaccination in adolescents who remain at risk for hepatitis B virus infection. (*Am J Public Health.* 1998;88:1638–1644)

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In the last 10 years, advisory groups in the United States and Canada have recommended alternate forms of universal hepatitis B vaccination as components of a comprehensive strategy to eliminate hepatitis B virus transmission. US advisory groups have selected universal neonatal vaccination as a centerpiece of this strategy. The role of universal vaccination of school-age children, adolescents, and adults who have not been previously vaccinated remains uncertain.

Canadian advisory groups have selected universal adolescent vaccination as the main component of their national hepatitis B virus control strategy, opting to leave non–high-risk neonates and children unvaccinated.[1,2] However, the economic attractiveness of vaccinating all school-age children and adolescents has not been well established.[3,4] In this study, we report the actual costs of implementing the first large-scale, school-based vaccination program in North America and estimate the economic attractiveness of this program.

British Columbia's School-Based Hepatitis B Vaccination Program

During the 1980s, reported hepatitis B virus infections increased throughout North America, but selected regions such as Washington State and British Columbia experienced particularly dramatic increases in incidence. Driven by immigration and intravenous drug use, British Columbia's rate increased from 1 to 30 per 100 000.[5] In 1992, British Columbia's minister of health announced a Can $3.5 million program targeting all grade 6 students. The entire cohort of 46 000 grade 6 students were offered the vaccine in the 1992–1993 school year in a program administered by visiting public health nurses.

Methods

Design

The analysis consists of 2 components. We performed a descriptive cost study and a cost-effectiveness analysis using a Markov cohort analytic model.

Cost study. Utilization and unit cost estimates were derived from 1994 data. Costs are expressed in 1994 US dollars, using the median 1994 currency exchange rate (US $0.7234 = Can $1). The cost-effectiveness analysis was performed from both societal and third-party payer perspectives. Thus, costs for each health state related to hepatitis were calculated, both including and excluding productivity losses. Future costs and life years were discounted at 3%.[6,7]

The number of sixth graders who were candidates for vaccination and the number of vaccine doses actually administered were tabulated by program personnel. Vaccine cost per dose was the contract price paid in 1994 by the British Columbia Ministry of Health. The cost of pamphlets and supplies and of ongoing surveillance was estimated by the Ministry of Health. The time spent giving the vaccine was calculated from

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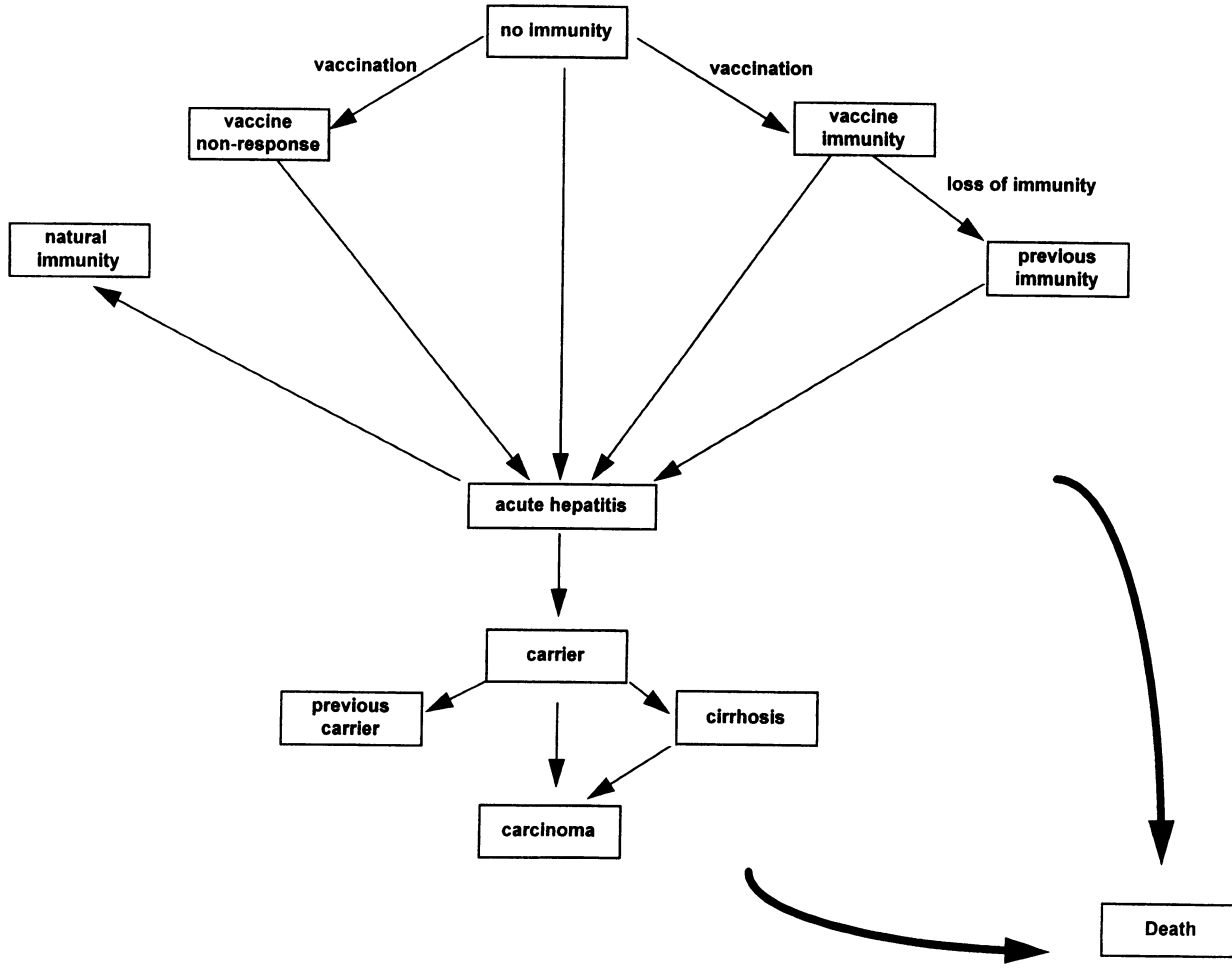


Note. Each rectangle represents a health state. The cohort is distributed among the health states at the start of the simulation. With each cycle, transitions occur between health states.

FIGURE 1—Markov cohort model of health states related to hepatitis B immune status and to hepatitis B infection.

activity reports completed by public health nurses in all areas of the province except part of the Greater Vancouver area. Vaccine administration time included counseling and teaching activities but excluded travel and organizational activities. We estimated nursing time spent in travel by using a time study at the Central Fraser Valley Health Unit, which serves a mixed urban and rural region of the province. The amount of aide and clerical time consumed by the program was estimated from a 1994 survey of 9 of the 21 health units.

The cost of nursing and clerical services includes salaries and benefits paid by the Ministry of Health, transportation and isolation allowances, and all overhead costs.

Cost-effectiveness analysis. We compared 2 strategies in the cost-effectiveness analysis. The first strategy was that used by the grade 6 program. All eligible students are offered 3 vaccinations free of charge. The alternate strategy represents the policy in place prior to the new program: no vaccination for adolescents, but maternal screening and vaccination of offspring born to carrier mothers, in addition to vaccination of high-risk individuals.

The decision model is structured as a Markov cohort analysis. Potential outcomes are defined as specific health states (Figure 1), and transitions between these states are modeled over time. The Markov cohort model consists of a set of 5 health states related to hepatitis B immune status and a set of 6 health states related to acute and chronic outcomes of hepatitis B infection. Potential transitions between health states are shown schematically in Figure 1.

Using a methodology described in a previous publication,[8] we used 3 techniques to assess resource utilization. First, 4 hepatologists completed a questionnaire describing scenarios for 4 acute and 4 chronic hepatitis states. We then reviewed charts describing inpatient and outpatient care provided to 148 individuals with 6 hepatitis-related diagnoses. Finally, we reviewed all hepatitis B–related admissions to Canadian hospitals over a 10-year period by using the Canadian Institute for Health Information hospital discharge database.

Inpatient unit costs (hotel costs for medical and intensive care unit beds, laboratory tests, imaging, procedures, drugs, and blood products) were estimated by using 1994 data from the Patient Costing System at the Greater Victoria Hospital Society, a large community hospital in coastal British Columbia. By using a standardized methodology to allocate overhead costs,[9] this system provides accurate estimates of direct inpatient costs. Costs for inpatient and outpatient physician services were estimated from the 1994 British Columbia Medical Services Plan Fee Schedule.

Indirect costs (the loss of productive time incurred because of hospitalization, convalescence, physician visits, and premature death) were estimated by using the industrial aggregate of average weekly earnings in British Columbia for 1994.[10] We generated age- and sex-specific estimates of the value of productivity loss by using published data about workforce participation (by age and sex) in British Columbia.[11] Average weekly earnings for those employed in full-time domestic work, adjusted for the differential in number of hours worked between domestic workers in and out of the labor force,[12,13] were used to estimate the productivity value of housekeeping services ($201/week). These estimates were further adjusted to reflect the age- and sex-related distribution of chronic hepatitis B virus infection.[14]

Data Sources

We performed a series of MEDLINE searches using acute and chronic hepatitis B–related indexing terms and examined the bibliographies of all retrieved articles. We also used a clinical database at the Toronto Hospital describing outcomes in 1066 hepatitis B virus carriers with an average of 2.95 years of follow-up per carrier to provide supplementary estimates for sensitivity analysis. Where published data were not available or were unreliable, we obtained estimates from a panel with expertise in hepatitis B epidemiology and hepatitis B immunization (see Acknowledgments).

To estimate probabilities related to immune status at time of vaccination, vaccine response, and compliance with vaccination in grade 6 students, we used program data and a 1992 seroprevalence survey carried out among 259 students enrolled in the grade 6 program.[15]

The data used in our model of the natural history of hepatitis B infection are listed in Table 1 and are described in greater detail in a document available from the authors. The document describes the validation process and offers predictions of the model that can be compared with predictions of other models of the natural history of hepatitis B virus infection.[3,16–19] The expert panel reviewed all epidemiologic data in the model, in addition to providing estimates for parameters for which no published data exist. We validated our model of the natural history of hepatitis B infection by comparing predictions of the model against external data sets describing population exposure to hepatitis B infection[20,21] and the long-term prognosis of chronic hepatitis B infection.[16,22]

Vaccine Efficacy

We modeled loss of vaccine efficacy by calculating the annual proportion of immunocompetent children and adults in published studies whose antibody levels dropped below 10 IU/L (assuming an initial vaccine response). We calculated the annual rate of loss from reported studies, using the following relationship:

$$\text{Annual Rate} = (-1/t) \times \ln (S_t/S_0),$$

where t is the mean duration of follow-up in years and S_t/S_0 is the proportion of the cohort initially responding to vaccination (hepatitis B surface antigen [HBsAb] titer > 10 IU/L) who maintained protective antibody levels at time t. Assumptions about vaccine efficacy are summarized in Table 1 and described in further detail in the supplementary document available from the authors.

Results

Program Costs

We estimated the cost of vaccinating each child to be $44, almost evenly split between the cost of vaccine ($20) and the cost of administering vaccine ($24) (Table 2). This compares reasonably well with the estimated total cost of vaccinating neonates ($35; 1994 British Columbia Ministry of Health budget projections [unpublished]). Delivery costs are similar in adolescent and neonatal programs ($25 vs $24), and nearly all cost savings in neonatal vaccination are achieved through lower costs of vaccine ($11 vs $20).

Effectiveness, Cost Comparison, and Cost-Effectiveness

Our model predicts that without vaccination, 4100 of the 46 000 grade 6 students in British Columbia who were at risk for hepatitis B virus infection (8.9%) would, at some point in their lives, become infected with hepatitis B virus, and 400 (0.89%) would become chronically infected (Table 3). We predict that the program will prevent 63% of all acute infections, 47% of chronic infections, and 51% of all hepatitis B virus–related deaths. The program prevents a greater proportion of the events that are avoidable at age 12 (85%, 86%, and 88%, respectively).

Although $44 is spent vaccinating each child, future health expenditures are decreased by $35 per child. When the value of productivity losses (indirect costs) is considered, the program results in cost savings of $75 per person vaccinated, or $3.5 million for the entire cohort.

A cost-effectiveness analysis was performed for key clinical outcomes. For this analysis, we assumed that a program with an incremental cost-effectiveness ratio (not quality adjusted) of less than $50 000 per life year can be considered economically attractive.[23,24]

Considering direct costs only, vaccination results in incremental costs of $161 and $2135 for each acute and chronic infection prevented, respectively, and $2145 for each additional life year gained. We consider the program to be economically attractive because the costs per event averted seem reasonable, the cost for each life year gained falls well below the thresholds of economic attractiveness offered above, and the program generates net cost savings when productivity losses are considered.

Sensitivity Analysis

We performed extensive sensitivity analyses by varying epidemiologic and economic variables singly and multiply across their plausible ranges. From the societal perspective, the model was insensitive to changes in all variables. When direct costs only were included in the analysis, analytic results varied most with changes in the underreporting rate, the probability of chronic infection following acute infection, the discount rate, and the cost of vaccination. However, the analysis was insensitive to even these parameters, since changing any single parameter did not increase the cost-effectiveness ratio above $50 000 per life year. We evaluated the model under worst-case assumptions that biased the analysis against vaccination (duration of vaccine efficacy = 10 years, underrreporting factor = 7.5, and probability of chronic infection = 0.5 × baseline rate) and the analytic results remained remarkably robust.

We also performed simulations using incidence rates from other locations to determine the economic attractiveness of universal hepatitis B vaccination in regions with a lower disease burden (Figure 2). At the Canadian average incidence rate of 11.4 per 100 000, this strategy remained dominant from a societal perspective and retained a still-attractive cost-effectiveness ratio of $6200 per life year using the third-party payer perspective. Because reporting standards across provinces are not uniform, however, the true Canadian rate is probably lower, in keeping with US and Northern European rates, which are low and have been falling for the past 10 years.[25,26] At a vaccination cost of $44, the incremental cost-effec-

TABLE 1—Epidemiologic Data and Assumptions

Variable	Age	Estimate	Ranges	Source	Costs (Direct/Indirect)
Immune status at age 12					
Carrier	12	0.004	. . .	LIT	
Already immunized[a]	12	. . .	. . .		
Previously exposed	12	0.023	. . .	LIT	
Compliance with adolescent vaccination	12	0.94	0.80–1.00	LIT	
No immunity/vaccine nonresponse states					$0/0
Probability of inducing immunity with vaccine	12	0.99	0.95–1.00	LIT	
Reported incidence of new infection[b]	10–14	7.2	1.2–13.2	BC Ministry of	$284/$595
	30–34	52.7	15.2–90.1	Health, unpublished	
	65+	7.2	1.1–13.3	EE, NC	
Underreporting factor	All	10	4–20	LIT	
Probability of death from fulminant hepatitis, given acute infection	<15	0		EE	
	>15	0.0007	0–0.004	LIT	
Probability of chronic infection after acute infection	12	0.14	. . .	LIT	
	20	0.08	. . .		
	>25	0.05	0–15%	LIT	
Vaccine immunity/previous immunity states					$0/0
Annual rate of loss of vaccine immunity[c]	All	0.045	0.006–0.159	LIT	
Vaccine protective efficacy, HBV infection					
Prior vaccination, nonresponse[d]	All	baseline	. . .	EE	
Prior vaccination, HBsAb>10 IU/L	All	95%	80–100%	EE	
Prior vaccination, HBsAb<10 IU/L	All	50%	0–90%	EE, LIT	
Vaccine protective efficacy, acute fulminant hepatitis					
Prior vaccination, nonresponse[d]	All	baseline	. . .	LIT*	
Prior vaccination, HBsAb>10 IU/L	All	100%	80–100%		
Prior vaccination, HBsAb<10 IU/L	All	100%	80–100%		
Vaccine protective efficacy, carrier postinfection					
Prior vaccination, nonresponse[d]	All	0%	. . .	EE	
Prior vaccination, HBsAb>10 IU/L	All	100%	. . .	EE	
Prior vaccination, HBsAb<10 IU/L	All	75%	. . .	EE	
Carrier state	<20				$140/$0
	>20				$236/$127
Annual rate of developing cirrhosis, HBsAg carrier	10–19	0	0	LIT	
(per 100 000/y)	20–49	100	100–550	(Sherman,	
	>50	441	441–890	unpublished data)	
	Overall	102	102–636		
Annual overall rate of developing HCC, HBsAg carrier (per 100 000/y)	10–19	263[a]	263	LIT	
	20–49	230	0–230	(Sherman,	
	>50	701	560–890	unpublished data)	
	Overall	254	254–528		
Annual rate of developing HCC directly (without developing cirrhosis), HBsAg carrier (per 100 000/y)	10–19	262	. . .	Derived	
	20–49	209			
	>50	617			
Annual rate of developing HCC, previous carrier (per 100 000/y)	All	0	. . .	EE	

(Continued)

tiveness of adolescent vaccination dramatically increases at reported hepatitis B virus infection rates below 3 per 100 000. Some regions (Prince Edward Island, Saskatchewan, and Newfoundland) currently report rates below this threshold, and the US national average will approach this figure in the near future if current trends continue.

Finally, we evaluated the attractiveness of adolescent vaccination in the United States, using US incidence data (lifetime exposure risk = 4.8%)[4] and cost data (vaccination = $85,[4] interferon = $5500 per course,[20] treatment costs of chronic disease increased by 50%). Universal adolescent vaccination remained attractive at $26 000 per life-year gained.

Discussion

The results of our analysis strongly support the economic attractiveness of universal hepatitis B vaccination of school-age children and adolescents. In geographic regions with a high burden of hepatitis B virus infection and vaccination costs similar to those observed in this program, vaccination is economically attractive and results in a net cost saving when the productivity losses of hepatitis B virus–related morbidity and mortality are considered.

The extent to which the results of this analysis are generalizable to other geographic regions depends largely on 3 factors: the incidence rate of new infection, vaccination costs, and health care costs of treating hepatitis B virus–related illness. In regions with similar vaccination and health care delivery costs, adolescent vaccination may be economically attractive at incidence rates as low as 2 to 3 reported cases per 100 000 per year. Lower vaccination costs

TABLE 1—*Continued*

Variable	Age	Estimate	Ranges	Source	Costs (Direct/Indirect)
Cirrhosis state					$5858/$9019
Annual aggregate disease-specific mortality rate, cirrhosis	All	0.057[a]	0.039–0.092	LIT	
Annual rate of developing HCC, given cirrhosis	All	0.057	0.010–0.149	LIT	
Annual disease-specific mortality rate, cirrhosis, (due to decompensated cirrhosis)	All	0.014	. . .	Derived	
Hepatocellular carcinoma state[e]					$9159/$21 783
Annual disease-specific mortality rate, HCC	All	0.56	. . .	LIT	
Annual probability of losing HBsAg, HBsAg carrier	All	0.01	0.005–0.023	LIT	
Proportional reduction in annual progression	<20	0%	. . .	NC	
rate from carrier state to cirrhosis due to interferon therapy	>20	29.8%		Derived	
Proportional reduction in annual progression rate	<20	0%	. . .	NC	
from carrier state to HCC due to interferon therapy	>20	15.8%		Derived	

Note. LIT = data derived from published literature; EE = expert opinion; HCC = hepatocellular carcinoma; NC = not candidates for interferon therapy.
[a]Some proportion of this cohort will already have been immunized because of maternal screening, or because they belong to high-risk groups.[15] The seroprevalence study from which our data was derived evaluated HBsAb only after vaccination and was therefore unable to distinguish between primary responders and those who had been exposed to the virus. We assume that the presence of HBsAb at age 12 indicates natural (i.e., lifelong) immunity.
[b]Reported incidence includes all reported "acute" cases (expressed as a rate per 100 000) and 50% of the "undetermined" cases. The range of incidence includes, at the lower end, only cases reported as acute cases, and at the upper end, all "acute" and "undetermined" cases.
[c]Mean of values obtained from cited studies, weighted by person-years of observation.
[d]Successful vaccination is defined as an initial anti-HBsAb response exceeding 10 IU/L.
[e]Costs for this health state are summed costs from diagnosis to death.

TABLE 2—Cost of Vaccination, 1994 Grade 6 Program

Variable	Estimate	Source
Target population (number eligible for immunization)	45 915	BC immunization program
% of target successfully immunized[a]	94.3%	BC immunization program
Vaccine cost/dose	$6.37	BC immunization program
Pamphlet cost/person	$0.04	Ministry of Health estimate
Syringe supplies/person	$0.58	Ministry of Health estimate
Surveillance cost/dose	$0.27	Ministry of Health estimate
Nursing minutes/dose (vaccine administration)	10.4	1992–1993 time study, BC immunization program (unpublished)
Travel time as a proportion of vaccine administration time	0.32	Maple Ridge travel time study (unpublished)
Total nursing minutes/dose	13.73	Calculated
Nursing FTEs required for program[b]	19.1	Calculated
Clerical-aide FTEs required for program	3.2	Calculated
Cost/nursing FTE	$42 700	BC Ministry of Health[c]
Cost/clerical-aide FTE	$29 200	BC Ministry of Health[c]
Total FTE costs	$910 300	Calculated
Total vaccine cost	$869 500	Calculated
Total cost of syringes, supplies, surveillance	$110 100	Calculated
Total program cost	$1 890 000	
Cost/dose of vaccine given	$14.52	
Cost/person successfully vaccinated (3 doses of vaccine)	$43.62	
Cost of vaccine/person successfully vaccinated	$20.07	
Cost of vaccine administration/person successfully vaccinated	$23.55	

Note. BC = British Columbia.
[a]Includes the 92.1% who received 3 doses of vaccine, 66% of the 3% who received 2 doses, and 25% of the 0.8% who received 1 dose of vaccine.
[b]FTE = full time equivalent, the number of full-time nurses or clerical support personnel required to perform a given amount of work.
[c]Includes benefits, transportation and isolation allowance, supplies, equipment, and overhead.

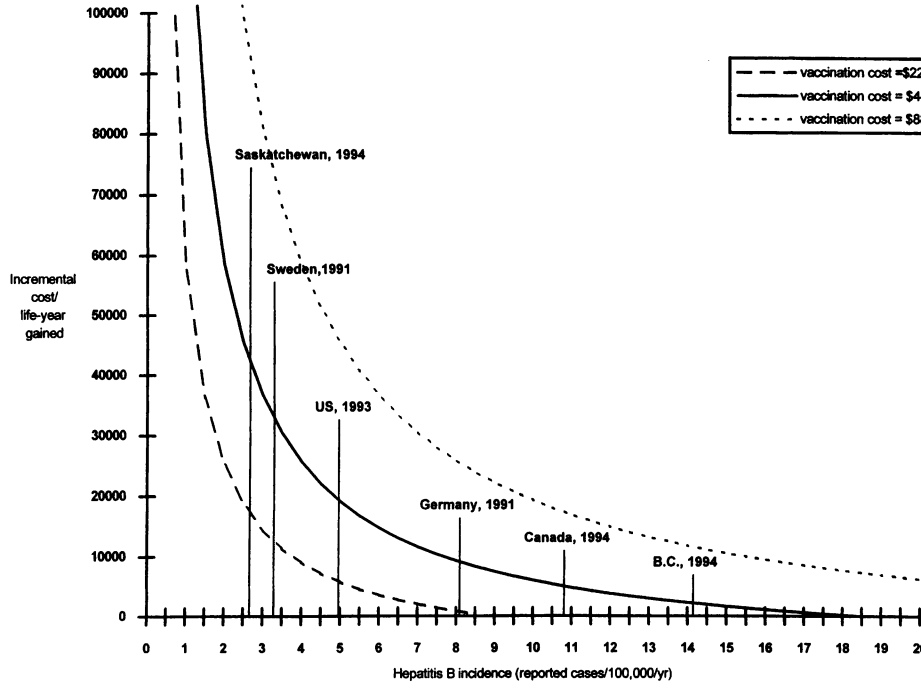
and higher health care costs may reduce further the threshold of disease burden at which vaccination is attractive. Allowing for differences in the epidemiology of disease and health care costs, our analysis suggests that vaccinating all adolescents who remain at risk for hepatitis B infection is cost-effective in both Canadian and US contexts, although regional variations in health care costs, cost of vaccination, and burden of disease may alter the attractiveness of this program in specific regions.

What does this analysis add to our existing knowledge? First, this study provides accurate costs of vaccine delivery from the first large-scale, adolescent hepatitis B vaccination program in North America. Vaccine can be delivered to adolescents at a cost of

TABLE 3—Baseline Results: Program Effectiveness, Net Costs, and Cost-Effectiveness Analysis

	No Vaccine	BC Grade 6 Program	Difference
Predicted lifetime cases of acute hepatitis[a,b]	4077	1515	−2562
Predicted lifetime cases of chronic infection[a,b]	409	216	−193
HBV-related deaths[a,c]	73	37	−37
Average life expectancy (y, not discounted)	63.2984	63.3168	0.0183
Life years, entire cohort	2 906 346	2 907 191	845
Net direct cost/person[d]	$67	$75	$9
Net total cost/person[d] (direct and indirect)	$23 730	$23 655	−$75
Lifetime direct costs, entire cohort[d]	$3 048 000	$3 525 000	$477 000
Lifetime indirect costs, entire cohort[d]	1 089 623 000	$1 086 132 000	−$3 491 000
Cost/acute infection prevented[e]			
Direct	...	...	$161
Total	...	...	DS[f]
Cost/chronic infection prevented[e]			
Direct	...	...	$2135
Total	...	...	DS[f]
Cost/life year gained[g]			
Direct	...	...	$2145
Total	...	...	DS[f]

Note. BC = British Columbia; HBV = hepatitis B virus.
[a]In screening cohort of 45 915 sixth graders.
[b]Includes infections occurring before age 12. Approximately 184 students are already carriers, and 1056 are HBsAb positive, some of whom may have been vaccinated.
[c]Includes an estimated 32 HBV-related deaths in HBsAg carriers that acquired infection prior to age 12.
[d]Net cost, in discounted 1994 US dollars.
[e]Costs are discounted, clinical events are not.
[f]Dominant strategy. Vaccination results in fewer clinical events as well as cost saving.
[g]Discounted costs and life years.



Note. The incremental cost-effectiveness of adolescent vaccination at various rates of reported hepatitis B virus incidence and cost of providing vaccination (cost of vaccine and administration) to susceptible adolescents are shown.

FIGURE 2—Sensitivity analysis for hepatitis B virus incidence and total cost of vaccination.

$24 per person, similar to the costs of neonatal vaccine delivery.

It also suggests that adolescent vaccination may be more economically attractive than previously believed, particularly in regions with higher than average hepatitis B virus incidence rates. By considering productivity losses in addition to direct medical costs, we have demonstrated that vaccinating adolescents may result in a net cost saving.

Our study may overcome some methodological shortcomings of earlier work. Our estimates of program cost, compliance, and program effectiveness are grounded in primary data, as opposed to expert opinion or secondary data. Our analysis uses neither unduly pessimistic[10] nor insupportably optimistic[11] assumptions about the duration of vaccine efficacy. It incorporates the costs and clinical effects of treating patients with interferon and the costs of ongoing care for patients with chronic hepatitis B virus illness, as well as disease- and sex-specific costs of hepatitis B virus productivity losses. Compared with previous models, our validated prognostic model of the natural history of chronically infected HBsAg carriers may have a higher degree of clinical fidelity and prognostic accuracy.

This analysis does not resolve the debate about which is the most appropriate age for universal vaccination, because it does not explicitly compare universal adolescent vaccination with universal neonatal or childhood vaccination. It does, strongly support the economic attractiveness of adolescent vaccination, either as the centerpiece of hepatitis B control efforts (as in Canada) or as a supplemental strategy (as in the United States) for unvaccinated individuals who remain at risk for hepatitis B infection. □

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