REVIEW ARTICLE

Pharmacoeconomics 2008; 26 (1): 17-32
1170-7690/08/0001-0017/$48.00/0

Cost-Effectiveness Analyses of Hepatitis A Vaccine

A Systematic Review to Explore the Effect of Methodological Quality on the Economic Attractiveness of Vaccination Strategies

Andrea M. Anonychuk,[1,2,3] *Andrea C. Tricco*,[4,5] *Chris T. Bauch*,[6] *Ba' Pham*,[3,4,7] *Vladimir Gilca*,[8,9] *Bernard Duval*,[8,9] *Ava John-Baptiste*,[3,7,10] *Gloria Woo*[1,3] and *Murray Krahn*[1,3,7,10]

1 Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
2 Statistics and Epidemiology, GlaxoSmithKline Canada, Mississauga, Ontario, Canada
3 Toronto Health Economics and Technology Assessment Collaborative, Toronto, Ontario, Canada
4 Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
5 Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada
6 Department of Mathematics and Statistics, University of Guelph, Guelph, Ontario, Canada
7 Department of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
8 Institut National de Santé Publique du Québec, Québec City, Québec, Canada
9 Centre Hospitalier Universitaire de Québec (CHUQ) Research Centre, Québec City, Québec, Canada
10 University Health Network, Toronto, Ontario, Canada

Contents

Abstract

Hepatitis A vaccines have been available for more than a decade. Because the burden of hepatitis A virus has fallen in developed countries, the appropriate role of vaccination programmes, especially universal vaccination strategies, remains unclear. Cost-effectiveness analysis is a useful method of relating the costs of vaccination to its benefits, and may inform policy. This article systematically reviews the evidence on the cost effectiveness of hepatitis A vaccination in varying populations, and explores the effects of methodological quality and key modelling issues on the cost-effectiveness ratios.

Cost-effectiveness/cost-utility studies of hepatitis A vaccine were identified via a series of literature searches (MEDLINE, EMBASE, HSTAR and SSCI). Citations and full-text articles were reviewed independently by two reviewers. Reference searching, author searches and expert consultation ensured literature saturation. Incremental cost-effectiveness ratios (ICERs) were abstracted for base-case analyses, converted to $US, year 2005 values, and categorised to reflect various levels of cost effectiveness. Quality of reporting, methodological issues and key modelling issues were assessed using frameworks published in the literature.

Thirty-one cost-effectiveness studies (including 12 cost-utility analyses) were included from full-text article review (n = 58) and citation screening (n = 570). These studies evaluated universal mass vaccination (n = 14), targeted vaccination (n = 17) and vaccination of susceptibles (i.e. individuals initially screened for antibody and, if susceptible, vaccinated) [n = 13]. For universal vaccination, 50% of the ICERs were <$US20 000 per QALY or life-year gained. Analyses evaluating vaccination in children, particularly in high incidence areas, produced the most attractive ICERs. For targeted vaccination, cost effectiveness was highly dependent on the risk of infection.

Incidence, vaccine cost and discount rate were the most influential parameters in sensitivity analyses. Overall, analyses that evaluated the combined hepatitis A/hepatitis B vaccine, adjusted incidence for under-reporting, included societal costs and that came from studies of higher methodological quality tended to have more attractive cost-effectiveness ratios. Methodological quality varied across studies. Major methodological flaws included inappropriate model type, comparator, incidence estimate and inclusion/exclusion of costs.

Hepatitis A virus is a common cause of acute hepatitis and is responsible for a substantial societal economic burden.[1] It is one of the most frequently reported vaccine-preventable diseases, even though vaccines have been available since 1994. The safety and immunogenicity profile of hepatitis A vaccines is excellent.[2] These vaccines have been used for universal childhood immunisation programmes in the US, parts of Spain and Italy, and Israel, and as a result, a substantial reduction of hepatitis A incidence has been observed in these regions of the world.[3-7]

In Canada (and many other industrialised countries), the current immunisation strategy to control hepatitis A is to vaccinate groups at risk.[8] Candidates for the vaccine include travellers to hepatitis A endemic countries, members of closed communities, and people with lifestyle risks of infection (e.g. illicit intravenous drug use).[8-10] Deciding how to apply the national guidelines for vaccine use in

Canada has been difficult because hepatitis A epidemiology in Canada is poorly defined, complex and changing.[2] The appropriate role of vaccination programmes remains unclear.[2]

With competing priorities and limited budgets, decision makers have a wide range of issues to consider.[11,12] Cost-effectiveness analyses are needed to justify or provide guidance for new programmes, especially because long-term, recurrent expenditures are involved.[12,13] However, results of economic evaluations often vary considerably as a result of different methodologies[14] and varying quality.[15-17] As such, generating conclusions about the cost effectiveness of a programme may be challenging.

Methodological issues specific to the economic evaluation of vaccination programmes need to be considered because of the unique features of infectious disease and vaccination.[14] For example, there are two types of models that can be used in an analysis: cohort and dynamic. In a cohort model, the force of infection, i.e. the rate at which a susceptible individual becomes infected, is constant over time.[18] However, vaccination not only reduces incidence in the vaccinated population, but it indirectly protects unvaccinated people, an effect known as 'herd immunity'.[19] Unlike cohort models, dynamic (transmission) models capture the herd immunity effects. If these effects are large, these two models may result in important differences in cost-effectiveness results. This is likely the case for hepatitis A virus, as previous studies have indicated that herd immunity accounts for 67% of vaccine effectiveness in mass childhood immunisation against the virus in the US.[20]

The way in which disease incidence is represented in the model may also affect the cost-effectiveness ratio. Hepatitis A incidence is generally underestimated because asymptomatic hepatitis A cases and many symptomatic cases are not reported to public health authorities. The true incidence rate of hepatitis A in Canada and the US has been estimated to be between 7 times[21] and 10 times[22] the reported incidence rate.

Another issue applicable to all economic evaluations is that of systematic bias. A recent systematic review of cost-effectiveness studies found that industry-funded studies were more likely to produce favourable cost-effectiveness ratios.[23] Exactly how this effect is mediated remains unclear.

The objective of our work was to systematically review the literature on cost effectiveness of hepatitis A vaccination, in order to collate what is known about the economic attractiveness of hepatitis A vaccination strategies in varying populations, and to explore effects of methodological quality and key modelling issues on the economic attractiveness of hepatitis A vaccination.

1. Literature Review and Assessment

1.1 Methods

1.1.1 Search Strategy

MEDLINE (1966 to week 36 Sep 2006), EMBASE (1980 to week 36 Sep 2006), HealthSTAR (1966 to Sep 2006), Social Sciences Citation Index (1965 to Sep 2006) and Econlit (1969 to Sep 2006) were searched. The full MEDLINE search strategy was as follows: ('cost' OR 'cost-benefit' OR 'cost-effectiveness' OR 'decision analysis') AND 'hepatitis A'. In order to ensure literature saturation, the reference lists of relevant reports were searched. The authors of relevant reports were contacted for further information when required. Authors of potentially relevant abstracts identified from the search were also contacted to identify unpublished material.

1.1.2 Eligibility Criteria

A study report was included if it was a cost-effectiveness or cost-utility study of hepatitis A vaccine. We excluded studies that reported only costs (descriptive costing studies), studies that did not report primary data and publications that were written in languages other than English.

1.1.3 Screening

The abstracts and titles retrieved from the electronic databases were screened by two independent reviewers. Disagreements were resolved through discussion or the involvement of another member of the team. The kappa statistic was used to calculate the inter-observer agreement between the two reviewers for the first level of screening.[24] Studies that were deemed relevant at this first screening level were retrieved in full-text format and screened

by one reviewer to confirm eligibility. Reasons for exclusion at the title and abstract and full-text screening levels were noted.

1.1.4 Data Abstraction

Two investigators independently abstracted detailed information using a prespecified 34-item data extraction form. The abstracted data included study characteristics (e.g. design, population, perspective, funding source), key aspects of analysis (e.g. vaccination strategies, costs, discount rate) and key parameters in the sensitivity analysis (e.g. hepatitis A incidence, vaccine cost, discount rate). Incremental cost-effectiveness ratios (ICERs) were abstracted for base-case analyses (i.e. not for sensitivity analyses). Disagreements regarding the extracted data were resolved through discussion or the involvement of a third reviewer.

1.1.5 Data Synthesis

In order to compare cost effectiveness across studies, ICERs and costing data were converted to $US, 2005 values using purchasing power parities,[25] and inflated to 2005 values using the consumer price index for all urban consumers, medical care.[26] In studies where monetary year was not reported, year of publication was used.

To explore the potential impact of various study characteristics and methodological issues on cost-effectiveness ratios, ICERs that were reported as cost per QALY or cost per life-year (LY) were stratified into three categories that represent thresholds of cost effectiveness: <$US20 000 per QALY (or LY); $US20 000–100 000 per QALY (or LY); and >$US100 000 per QALY (or LY).[27-29] The association between vaccination strategy (e.g. universal, targeted), population (e.g. children, adults), study characteristics (e.g. location, year of publication), methodological issues (e.g. quality, work-loss costs) and corresponding cost-effectiveness thresholds was explored descriptively. If the cost-effectiveness distributions across different levels of a characteristic were equivocal, a Fisher's exact test was used to formally evaluate the association, subject to data availability. Finally, in order to compare results across studies and explore the impact of various parameters on ICERs, a table for each of the major vaccination strategies (e.g. universal, targeted, vaccination of susceptibles) showing all base-case ICERs and their related model parameters are shown in the supplementary material ('ArticlePlus' at http://pharmacoeconomics.adisonline.com [see tables AI–III]).

1.1.6 Quality Assessment

The quality of reporting was appraised using a 21-item quality assessment tool developed by Neumann et al.[15] Items appraised included study framing, adequate reporting of costs, appropriate reporting of results and discussion comprehensiveness. An overall quality score was assigned to each study, ranging from 1 (low) to 7 (high) based on methods, quality of reporting and assumptions. Study quality was assessed independently by two reviewers. Disagreements were resolved through discussion.

Methodological issues specific to hepatitis A vaccine economic evaluations were appraised using recommendations by Beutels et al.[14] These included more transparency and validation, careful choice of model and study design, appropriate discounting and extensive sensitivity analysis. Key modelling issues were examined using a framework for the assessment of decision-analytic models established by Philips et al.[30] The Philips et al.[30] assessment tool includes the following three key themes: structure, data and consistency. A model structure must reflect real-life events of individuals affected by the decision, and must be consistent with current clinical theory of the health conditions under evaluation. Data identified for use in the model should represent unbiased and optimal estimates, and uncertainty appropriately assessed in sensitivity analysis. Consistency relates to the quality of the model overall, including a combination of structure, assumptions and data. Reviewers assessed each of the 61 items, giving a score of 0 = no, 1 = yes, 9 = cannot tell or n/a = not applicable.

A model was categorised as 'dynamic' if it could project temporal changes in transmission patterns (e.g. reduction in the force of infection due to herd immunity brought on by vaccination programmes) by incorporating transmission mechanisms in the model. A model was characterised as 'static' if such temporal changes could not be accommodated for in the model structure. It was considered appropriate to use a dynamic model when evaluating universal

vaccination strategies or targeted vaccination of travellers.[18]

1.2 Results

1.2.1 Literature Review

A total of 570 titles and abstracts were identified and screened. There was strong agreement at the title and abstract level of screening between reviewers (kappa statistic = 0.71). Fifty-eight studies were retrieved in full-text format, as they were potentially relevant. After the full-text screening, 31 studies[7,11,31-59] met the inclusion criteria and were included in the systematic review (figure 1).

1.2.2 Study Characteristics

Of the 31 included studies, four were published before vaccine licensure, between 1990 and 1995 (table I). The rest were published in 1996–2000 (n = 10), and 2001–7 (n = 17). Studies evaluated vaccination in the US (n = 12), European countries (n = 13) [The Netherlands = 3; Spain = 2; France = 2; Germany = 2; UK = 2, Italy = 1, all Europe = 1], Canada (n = 2) and other (n = 4).

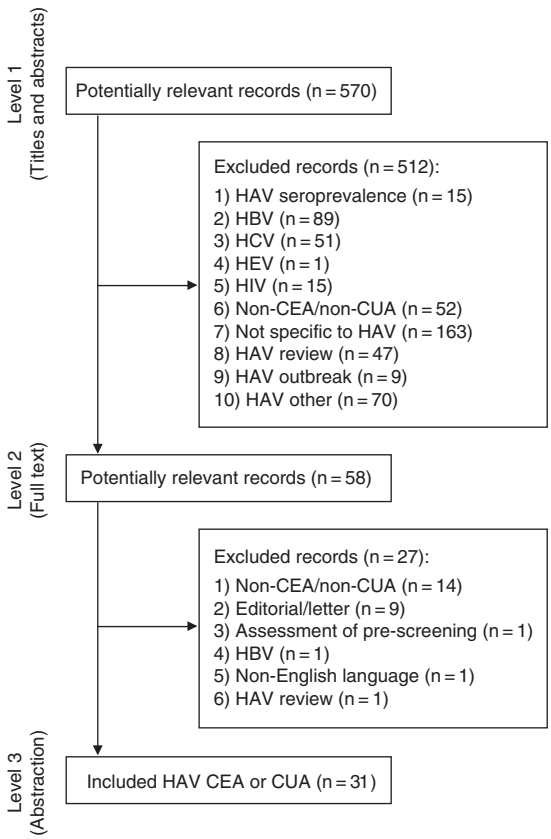

Fig. 1. Study flow. **CEA** = cost-effectiveness analysis; **CUA** = cost-utility analysis; **HAV** = hepatitis A virus; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HEV** = hepatitis E virus.

Universal vaccination strategies were evaluated in 45% (14/31) of studies, including universal vaccination of infants (n = 5), children or adolescents (n = 7), and adults (n = 3). Targeted vaccination was evaluated in 55% (17/31) of studies while 42% (13/31) of studies evaluated vaccination of susceptibles (i.e. individuals initially screened for antibody and, if susceptible, vaccinated). These two vaccination approaches were assessed in various populations including healthcare workers (n = 5), travellers (n = 3), patients with chronic hepatitis C (n = 3), military (n = 3), general population or adults (n = 3), infants (n = 2) and others (n = 6).

Most (87%) of the 31 cost-effectiveness studies evaluated vaccination with monovalent hepatitis A vaccine. The combined hepatitis A/hepatitis B vaccine was evaluated in 26% (8/31) of studies, and 19% (6/31) of studies evaluated passive vaccination with immunoglobulin.

2. Cost Effectiveness of Hepatitis A Vaccination

A summary of cost-effectiveness ratios stratified by vaccination strategy, population and intervention is shown in table II. Individual cost-effectiveness comparisons and associated ICERs are shown in the supplementary material.

2.1 Cost Effectiveness by Population, Intervention and Vaccination Strategy

Overall, universal vaccination strategies had a higher proportion of lower cost-effectiveness ratios (i.e. more economically attractive) than targeted vaccination or other vaccination (i.e. individuals initially screened for antibody and, if susceptible, vaccinated). Results for universal, targeted, and 'other' (respectively) were as follows: 51% vs 43% vs 11% (<$US20 000), 25% vs 19% vs 50% (≥$US20 000 and <$US100 000), and 25% vs 38% vs 39% (≥$US100 000) [p = 0.029; table II]. Analyses that assessed vaccination strategies with the

Table I. Characteristics of reviewed studies

Study characteristic	Total number studies (%) [n = 31]
Year of publication	
1990–95	4 (13)
1996–2000	10 (32)
2001–7	17 (55)
Population[a]	
Infants	8 (26)
Children/pre/adolescent	8 (26)
Adults/general population	6 (19)
Healthcare workers	5 (16)
Travellers	3 (10)
Patients with chronic hepatitis C virus	3 (10)
Military	2 (6)
Other high risk[b]	3 (10)
Vaccination strategy[a]	
Universal	14 (45)
Targeted	17 (55)
Other	13 (42)
Study funding	
Industry	13 (42)
Non-industry	4 (13)
Not reported	14 (45)
Region	
US	12 (39)
Canada	2 (6)
Europe[c]	13 (42)
Other	4 (13)
Methodological quality[d]	
1.0–4.0	14 (45)
4.5–5.0	10 (32)
5.5–7.0	7 (23)

a A study could assess more than one population and strategy; therefore, the percentages in these categories do not add to 100%.

b College students, prison inmates, food service workers, patients attending a sexually transmitted disease clinic, personal contacts of hepatitis A case.

c One study was included here and for the quality assessment component, but not for tables II–III or in the supplementary material (available at http://pharmacoeconomics.adisonline.com).

d According to an assessment tool by Neumann et al.[15]

combined hepatitis A/hepatitis B vaccine tended to produce lower cost-effectiveness ratios (i.e. more economically attractive) than those that assessed the monovalent hepatitis A vaccines: 60% vs 37% (<$US20 000), 40% vs 26% (≥$US20 000 and <$US100 000) and 0% vs 37% (≥$US100 000) [p = 0.007]. The following sections summarise results by major vaccination strategy: universal, targeted and other.

2.1.1 Universal Vaccination

Among 13 studies assessing universal strategies, the combined hepatitis A/hepatitis B vaccine was evaluated in six studies, while passive immunisation was assessed in two studies. All others evaluated strategies with hepatitis A vaccine. Two studies[33,53] compared universal childhood vaccination with targeted approaches, two studies compared with screening for hepatitis A antibodies before vaccination[36,49] and the rest compared with no vaccination.

Overall, 27 of the 53 ICERs (51%) were <$US20 000 per QALY or LY. Thirteen ICERs (25%) were between $US20 000 and $US100 000 although most (11/13) were <$US45 000. Thirteen (25%) were >$US100 000, mostly adult vaccination strategies[36,49] and childhood vaccination in low incidence regions in the US[53] and Canada.[33] The median cost per case prevented for universal vaccination was $US5335 (mean = $US69 021; range <$US0–399 337) [table II].

In adults or the general population, all ICERs were >$US100 000 (table II). ICERs ranged from $US7 million to $US34 million per QALY or LY, and the mean cost per case prevented was $US297 485[33,49,52] (see the supplementary material).[33,53,58]

For infant vaccination, 63% of the ICERs reporting by QALY or LY gained were <$US20 000. Four (13%) were >$US100 000; however, these all came from one study.[53] The median cost per case prevented was $US390 (range $US284–71 532). For childhood/adolescent vaccination, 41% of the ICERs were <$US20 000 and 29% were between $US20 000 and $US100 000, although all ICERs were <$US35 000. The rest (29%) were over the threshold of $US100 000, and all belonged to one study.[33] The median cost per case prevented was $US5335 (mean $US22 996, range <$US0–112 245).

Universal vaccination in higher incidence areas including Chile,[58] Spain[7] and parts of the US[39,42,53] resulted in cost savings. This was further demonstrated by two studies from the US where varying incidence in the country produced various cost-effectiveness estimates.[42,53] In the first study,

Table II. Summary of cost effectiveness ($US, year 2005 values) of hepatitis A (HA) vaccine, by vaccination strategy, population and intervention[a]

Study characteristic	Cost per LY or QALY					Cost per case prevented		
	total no. studies	total no. comparisons	<$20 000 [no. (%)]	$20 000–100 000 [no. (%)]	≥$100 000 [no. (%)]	total no. studies	total no. comparisons	median ($)
Vaccination strategy								
Universal	9	53	27 (51)	13 (25)	13 (25)	6	13	5 335
infant	4	32	20 (63)	8 (25)	4 (13)[b]	3	4	390
children/pre/adolescent	4	17	7 (41)	5 (29)	5 (29)[c]	3	7	5 335
adults	2	4	0 (0)	0 (0)	4 (100)	1	2	297 485
Targeted	8	21	9 (43)	4 (19)	8 (38)	9	23	18 258
travellers	NR	NR	NR	NR	NR	3	6	26 046
healthcare workers	3	9	1 (11)	2 (22)	6 (67)	2	3	129 757
military	NR	NR	NR	NR	NR	2	6	16 332
other high risk[d]	5	12	8 (67)	2 (17)	2 (17)	3	8	2 303
Other[e]	6	18	2 (11)	9 (50)	7 (39)	7	17	19 033
travellers	NR	NR	NR	NR	NR	3	4	23 555
healthcare workers	2	8	0 (0)	4 (50)	4 (50)	2	3	133 591
patients with chronic HCV	2	8	1 (13)	5 (63)	2 (25)	1	1	479 024
adults/general population	1	1	0 (0)	0 (0)	1 (100)	2	6	5 227
other groups[f]	1	1	1 (100)	0 (0)	0 (0)	1	2	6 672
Population								
Infants	4	33	21 (64)	8 (24)	4 (12)[b]	3	4	390
Children/pre/adolescent	4	17	7 (41)	5 (29)[g]	5 (29)[c]	3	9	5 832
Travellers	NR	NR	NR	NR	NR	3	10	25 836
Healthcare workers	3	17	1 (6)	6 (35)	10 (59)	2	6	131 674
Adults/general population	3	7	2 (29)	0 (0)	5 (71)	3	12	6 653
Patients with chronic HCV	2	10	1 (10)	5 (50)	4 (40)	1	1	479 024
Military (all case prevented)	NR	NR	NR	NR	NR	2	7	11 474
Other high risk[h]	3	7	5 (71)	2 (29)	0 (0)	1	5	≤0
Intervention								
HA vaccine	12	76	28 (37)	20 (26)	28 (37)	12	37	10 271
HA/HB vaccine	8	15	9 (60)	6 (40)	0 (0)	1	2	≤0
Immunoglobulin	NR	NR	NR	NR	NR	6	15	26 979

a One study is not included in this table due to extremely poor quality and inability to understand the data related to the ICERs. One study (Rein et al.[53]) did not have similar ICERs for cost per LY and cost per QALY for the same comparisons, and therefore only the cost per QALY is reported in this table. The other ICERs can be found in table AI of the supplementary material (available at http://pharmacoeconomics.adisonline.com).

b All ICERs from one study (Rein et al.[53]).

c All ICERs from one study (Bauch et al.[33]).

d 'Other high risk' included patients with chronic HCV, college students, infants, prison inmates, food service workers, patients attending a sexually transmitted disease (STD) clinic, personal contacts of an HA case.

e This is a strategy of screening for HA antibodies, then vaccinating only susceptibles. This would include travellers and healthcare workers. The universal strategy suggests vaccination of all travellers regardless of prior knowledge of antibody status.

f 'Other groups' included military and children.

g All were from Krahn et al.[11]

h Includes prison inmates, patients attending an STD clinic, food service workers and household or school contacts of HA cases.

HB = hepatitis B; **HCV** = hepatitis C virus; **ICERs** = incremental cost-effectiveness ratios; **LY** = life-year; **NR** = no ICERs were reported in this particular category.

Table III. Summary of cost effectiveness ($US, year 2005 values) of hepatitis A (HA) vaccine, by study characteristic and methodological factors[a]

Study characteristic	Cost per LY or QALY					Cost per case prevented		
	total no. studies	total no. comparisons	<$20 000 [no. (%)]	$20 000–100 000 [no. (%)]	>$100 000 [n (%)]	total no. studies	total no. comparisons	median ($)
Year of publication								
1990–5	NR	NR	NR	NR	NR	4	16	25 836
1996–2000	5	14	7 (50)	2 (14)	5 (36)	5	28	6 456
2001–7	13	77	30 (39)	24 (31)	23 (30)	4	10	390
Location								
US	12	47	20 (43)	14 (30)	13 (28)	1	2	390
Canada	2	16	4 (25)	5 (31)	7 (44)			
Europe	1	1	1 (100)	0 (0)	0 (0)	11	51	13 344
Other	3	27	12 (44)	7 (26)	8 (30)	1	1	479 024
Funding								
Industry	10	48	29 (60)	10 (21)	9 (19)	3	12	9 594
Non-industry	3	17	1 (6)	8 (47)	8 (47)	1	14	5 584
Not reported	5	26		8 (31)	11 (42)	9	28	26 769
Model type								
Cohort	17	79	33 (42)	25 (32)	21 (27)	10	46	9 595
Dynamic	1	12	4 (33)	1 (8)	7 (58)	1	2	91 889
NR	NR	NR	NR	NR	NR	2	6	16 330
Work loss cost								
Yes	14	43	23 (53)	10 (23)	10 (23)	7	19	19 033
No	13	48	14 (29)	16 (33)	18 (38)	5	27	5 335
Public health costs								
Yes	5	37	13 (35)	11 (30)	13 (35)	3	7	19 033
No	12	54	24 (44)	15 (28)	15 (28)	10	47	11 474
Under-reporting of HA								
Adjusted	13	64	34 (53)	14 (22)	16 (25)	2	4	142
Did not adjust	4	24	0 (0)	12 (50)	12 (50)	10	46	12 409
Unsure	1	3	3 (100)	0 (0)	0 (0)	1	4	45 306
Methodological quality								
1.0–4.0	5	23	4 (17)	6 (26)	13 (57)	8	26	49 255
4.5–5.0	7	34	15 (44)	11 (32)	8 (24)	4	14	5 234
5.5–7.0	7	34	18 (53)	9 (26)	7 (21)	1	14	5 584

a One study is not included in this table due to extremely poor quality and inability to understand the data related to the ICERs. One study (Rein et al.[53]) did not have similar ICERs for cost per LY and cost per QALY for same comparisons, and therefore only the cost per QALY is reported in this table. The other cost per life-years can be found in table AI of the supplementary material (available at http://pharmacoeconomics.adisonline.com).

ICERs = incremental cost-effectiveness ratios; **LY** = life-year; **NR** = no ICERs were reported in this particular category.

infant vaccination was shown to be cost saving when the incidence was >100% of the national average, and $US15 617 and $US71 294 per QALY when the incidence was 50–100% and <50% of the national average, respectively.[42] Similarly, the cost per QALY gained was <$US0, $US45 000 and $US132 000 for vaccination in high-incidence US regions, overall US and low-incidence regions, respectively[53] (see the supplementary material).

Studies that employed a lower cost of vaccine tended to report more favourable cost-effectiveness ratios. The mean cost of vaccine (per dose) for studies that reported ICERs of <$US20 000, $US20 000–100 000 and >$US100 000 was $US16, $US21 and $US30, respectively (because of a small sample size, a statistical test could not be conducted to determine if the difference was statistically significant). For example, in Canada, a low endemic country, childhood vaccination with the combined hepatitis A/hepatitis B vaccine was cost saving in more than one strategy assessed,[33] and this appears to be related to the low incremental cost of the vaccine (e.g. $US7–8). In another Canadian study,[11] the cost effectiveness of childhood vaccination ranged from $US20 151 to $US30 226 per QALY; however, the cost of the vaccine was much higher than in many of the studies (e.g. $US35) [see the supplementary material].

Cost-effectiveness ratios associated with the evaluation of universal vaccination of children with the combined hepatitis A/hepatitis B were all below ~$US35 000 per QALY (or LY), and 50% were <$US0 (see the supplementary material).

Additionally, all except one ICER that reported cost-saving results were generated by analyses using a societal perspective, taking into account both direct and other costs (e.g. time costs, out-of-pocket costs). In some studies, this had a large impact on results where the same vaccination strategy produced vastly different cost-effectiveness results when a societal or health system perspective was taken[33,53,58] (see the supplementary material).

Although a statistical test was not conducted, it appeared that analyses with a lower discount rate compared with a higher discount rate (3% vs 5%) tended to report lower ICERs: 50% vs 36% (<$US20 000/QALY or LY), 22% vs 57% (>$US100 000/QALY or LY).

2.1.2 Targeted Vaccination

Seventeen studies assessed vaccination in selected target populations (table II). Just under half (43%) of the ICERs were <$US20 000 per QALY or LY gained. Four (19%) were between $US20 000 and $US100 000, and the remaining eight (38%) were >$US100 000. The median cost per case prevented was $US18 258 (mean = $US41 423, range <$US0–265 241) [table II]. In most cases, targeted vaccination was compared with no vaccination, but in some cases it was compared with immunoglobulin (see the supplementary material for specific comparators).

Travellers

Three European studies[54,57,59] assessed hepatitis A vaccination in travellers. The median cost per case prevented was $US26 046 (mean $US37 365, range $US8918–89 309). All studies used a 5% discount rate for their analysis. Studies of vaccination in travellers to higher incidence areas tended to result in better cost effectiveness.[57,59] Less favourable results were seen with a higher cost of vaccine,[54] and the use of immunoglobulin as opposed to hepatitis A vaccine[57,59] (see the supplementary material).

Healthcare Workers

Five studies assessed hepatitis A vaccination in healthcare workers.[35,45,52,54,55] The majority of the nine ICERs were >$US100 000 per QALY or LY, and the median cost per case was $US129 046. The exception was a study in the US[45] that evaluated vaccination of healthcare and public safety workers with the combined hepatitis A/hepatitis B vaccine, which was found to be cost saving from the perspective of the employer. The cost of the vaccine used in this study was less expensive, approximately half the price of those used in other studies (see the supplementary material).

Military

The median cost per case prevented was $US16 332 (range <$US0–187 000) [table II]. Military vaccination was cost effective only when military personnel were assumed to be exposed to high-endemic areas. For example, vaccination of the military in The Netherlands was cost saving when they were exposed to areas where the attack rate for hepatitis A is very high.[34] For the UK military, cost

effectiveness was more favourable when deployments were to areas with incidences of 200 per 100 000, but not when the incidence was <21 per 100 000[47] (see the supplementary material).

Other High-Risk Groups

The cost effectiveness of hepatitis A vaccination in patients with chronic hepatitis C virus (HCV) infection ranged from $US16 386 to $US4 million per LY saved ($US5 million per QALY gained). Vaccination of food service workers in the US, prison inmates in higher incidence areas in US, and hepatitis A/hepatitis B vaccination of patients attending a sexually transmitted disease clinic resulted in ICERs of <$US25 000 per QALY or LY gained.[40,43,46] Vaccination of household and school contacts of cases in France in high-incidence areas resulted in ICERs <$US1500 per case prevented.[50]

2.1.3 Other Vaccination Strategies: Vaccination of Susceptibles

In this strategy, individuals are initially screened for antibody and, if susceptible, vaccinated. In most cases, vaccination was compared with no vaccination, but in some cases it was compared with immunoglobulin (see supplementary material for specific comparators).

Of the 18 ICERs for this strategy, two (11%) were <$US20 000, nine (50%) were in the range $US20 000–100 000 and seven (39%) were >$US100 000 per QALY or LY. The median cost per case prevented was $US19 033 (mean $US1 604 844, range <$US0–25 802 250) [table II].

Studies reporting cost savings were those that evaluated vaccination in adolescents, high-risk young and older adults in Spain where the incidence was very high.[32]

For healthcare workers in Israel,[35] the US[55] and Ireland,[52] screening before vaccination (vs no vaccination or immunoglobulin) resulted in ICERs >$US60 000 per QALY, LY or case prevented. Similarly, a high cost-effectiveness ratio (>$US100 000) was observed for healthy adults in North America[49] and for the general population in Ireland[52] (see the supplementary material).

For patients with chronic HCV infection, although none of the strategies resulted in cost savings, younger age at time of vaccination appeared to result in more favourable cost-effectiveness ratios. In a study by Jacobs et al.,[41] vaccination of patients at ages 30, 45 and 65 years resulted in costs per LY saved of $US16 386, $US51 623 and $US121 015, respectively, from a societal perspective. Screening before vaccination of chronic HCV-infected patients was extremely costly from a third party payer perspective in North America (e.g. up to $US25 million per case prevented)[48] [see the supplementary material].

3. Methodological Issues, Study Quality and Key Modelling Issues

Factors influencing the cost-effectiveness ratios included funding source, work loss, under-reporting and study quality. Other factors such as the country/region where vaccination was assessed, year of publication and inclusion of public health costs did not have an impact on cost-effectiveness ratios. Influential factors are described below and are reported in table III.

- Funding sources: studies funded by industry were more likely to report attractive cost-effectiveness ratios than those non-industry funded or those that did not report funding sources: 60% vs 6% vs 27% (<$US20 000), 21% vs 47% vs 31% (≥$US20 000 and <$US100 000) and 19% vs 47% vs 42% (≥$US100 000; p = 0.0004).
- Work loss: studies that took into account the cost for work loss seemed to be more likely to report attractive cost-effectiveness ratios than those that did not: 53% vs 29% (<$US20 000), 23% vs 33% (≥$US20000 and <$US100 000) and 23% vs 38% (≥$US100 000; p = 0.068).
- Under-reporting of hepatitis A: studies that adjusted reported incidence for under-reporting were more likely to report attractive cost-effectiveness ratios than those that did not: 53% vs 11% (<$US20 000), 22% vs 44% (≥$US20000 and <$US100 000) and 25% vs 44% (≥$US100 000; p < 0.001).
- Study quality: on average, high-quality studies were more likely to report attractive cost-effectiveness ratios than moderate and lower quality studies: 53% vs 44% vs 17% (<$US20 000), 26% vs 32% vs 26% (≥$US20000 and <$US100 000) and 21% vs 24% vs 57% (≥$US100 000; p = 0.0004).

3.1 Key Factors in Sensitivity Analyses

One study did not report results of a sensitivity analysis. Of the 30 studies that did, cost-effectiveness ratios were most sensitive to hepatitis A incidence (63%), cost of the vaccine (57%), discount rate (23%), long-term vaccine immunity or efficacy (17%), hepatitis A prevalence (10%) and vaccine coverage (10%) [figure 2].

3.2 Assessment of Quality of Reporting

Overall, the reviewer's quality score on the 21-item tool was a mean of 4.1 (out of 7). This is similar to scores found in other cost-effectiveness studies in other clinical areas.[15] In addition, studies that did a cost-utility analysis performed better on the overall quality score (4.9 vs 3.8, $p = 0.014$) than those that did not. Whereas most studies listed model assumptions, just under one-half (15/31) augmented this description with a diagram of the model or event pathways (table IV). Overall, 26% of studies did not report the year of monetary units. Half of the cost-utility analyses reported sensitivity analysis of preference weights. Only 67% of cost-utility and 37% of cost-effectiveness analyses reported sensitivity analysis of vaccine effectiveness.

3.3 Methodological Issues Specific to Vaccination

Methodological issues specific to vaccination were assessed using recommendations by Beutels et al.[14] The majority of studies (23/31, 74%) compared vaccination with the current practice in the country or region. Potential bias was identified with the comparators chosen in six (21%) of the studies, mostly because they compared vaccination with no vaccination when a targeted vaccination policy was in place.

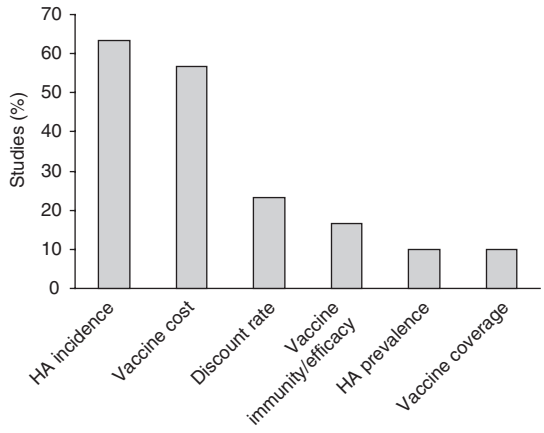

Fig. 2. Percentage of studies that indicated cost-effectiveness ratios were sensitive to key model parameters. **HA** = hepatitis A.

In this review, only two of the nine studies that assessed universal vaccination used a dynamic transmission model, taking into account herd immunity effects. Of studies that did not use a dynamic model, 40% acknowledged the use of a dynamic transmission model as an alternative modelling approach in their discussion. Herd immunity was partially taken into account in two studies by using a decision-analysis model parameterised with personal contact patterns to estimate a lower bound for herd immunity effects.[42,58]

The majority of studies (19/31, 61%) used a societal perspective for their analysis, taking into account work loss or other indirect costs. Just over half (17/31, 55%) of studies included relevant costs associated with the chosen perspective.

3.4 Quality Assessment of Key Modelling Issues

A limited number of studies performed consistently well on the items from Philips et al.[30] (supplementary material, table BI). Although most studies (81%, 25/31) had a clear statement of the decision problem, the primary decision maker was not specified in 68% (21/31) of the studies. Evidence regarding model structure was not provided by 45% (14/31); however, the structure of the model was consistent with a coherent theory of hepatitis A for 55% (17/31) of studies. The process of selecting key parameters was justified and systematic for only 39% (12/31) of studies; however, 77% (24/31) adequately described and justified their choice of baseline data. Assumptions regarding long-term efficacy/immunogenicity was documented and justified for 42% (13/31), and alternate values were explored in the sensitivity analysis for 30% (9/30) of studies. Sensitivity analysis was conducted to address parameter uncertainty in 73% (22/30), methodological uncertainty in 53% (16/30) and structural uncertainty in 30% (9/31) of studies.

Table IV. Assessment of quality of reporting of economic analysis of hepatitis A vaccination[15]

Items	CEA [n = 19 (%)]	CUA [n = 12 (%)]	Overall [n = 31 (%)]
Study funding source disclosed?	9 (47)	8 (67)	17 (55)
Framing			
Study perspective clearly stated?	15 (79)	11 (92)	26 (84)
Modelling assumptions listed?	14 (74)	11 (92)	25 (81)
Diagram of model or event pathway provided?	9 (47)	6 (50)	15 (48)
Discount rate for future costs and QALY reported?	16 (84)	11 (92)	27 (87)
Reporting of costs			
Net costs reported?	17 (89)	10 (83)	27 (87)
Source of valuation for all cost items reported?	13 (68)	10 (83)	23 (74)
Authors clearly state the year of monetary units?	15 (79)	8 (67)	23 (74)
Preference weights			
Reporting of preference weights?	NA	11 (92)	NA
Preference measurement technique reported?	NA	8 (67)	NA
Source of preferences listed?	NA	10 (83)	NA
Reporting of results			
Incremental analyses appropriately reported?	15 (79)	12 (100)	27 (87)
Sensitivity analyses reported?	18 (95)	12 (100)	30 (97)
for costs?	14 (74)	12 (100)	26 (84)
for preference weights?	NA	6 (50)	NA
for estimates of effectiveness?	7 (37)	8 (67)	15 (48)
for discount rate?	10 (56)	9 (75)	19 (61)
Discussion			
Study limitations discussed?	11 (58)	11 (92)	22 (71)
Results compared with those of related CUA?	14 (74)	8 (67)	22 (71)
Ethical implications discussed?	9 (47)	3 (25)	12 (39
Mean overall rating	3.8/7	4.8/7	4.1/7

CEA = cost-effectiveness analysis; **CUA** = cost-utility analysis; **NA** = not applicable.

Internal consistency was validated in two (7%) studies, as there was evidence that the mathematical logic of the model was tested before use. Only one study provided evidence that their model was calibrated against independent data. Half (55%, 17/31) compared their model results with those of previous models.

4. Discussion

Our systematic review suggests that universal vaccination of infants, children and adolescents is likely to be cost effective, especially in high-incidence areas. The cost effectiveness was robust against a range of factors. Adult vaccination was not economically attractive. Incidence was one of the major determining factors for the cost effectiveness of universal vaccination. Cost-effectiveness ratios in lower incidence areas, such as Canada and certain parts of the US can be highly influenced by vaccine cost and the inclusion of societal costs. A change in these parameters can have a dramatic effect on the ICER in both directions. Cost effectiveness in high incidence areas appears to be more robust to changes in vaccine cost or other costs.

For targeted vaccination, economic attractiveness seemed to be less dependent on the population type itself, and more likely to be influenced by the risk of hepatitis A. Vaccination of populations living in or exposed to high incidence areas and/or at increased risk of infection due to lifestyle or occupation were more likely to be economically attractive.[32,34,40,43,44,46,47,50,57,59] This was similar for strategies that vaccinated only susceptible individuals,[32,41] although generally this strategy was not found to be very cost effective.

The relative cost effectiveness of hepatitis A vaccination can in part be explained by those factors

that were tested and shown to be influential in sensitivity analyses (e.g. incidence, vaccine cost, discount rate). Additionally, our results indicate that using the combined hepatitis A/hepatitis B vaccine tended to produce more favourable cost-effectiveness ratios. This is likely because in most cases the combined hepatitis A/hepatitis B vaccine replaced a pre-existing programme with the hepatitis B vaccine and only the incremental cost of the vaccine was used.[7,11,33,45,46] The inclusion of the costs associated with work loss or other societal costs was also important in determining economic attractiveness of a programme.

We were also interested in exploring less obvious methodological or other factors that may influence certain outcomes. We found that studies of higher quality, studies funded by industry and studies that adjusted hepatitis A incidence for under-reporting tended to produce more economically attractive results. These results are somewhat inconsistent with a recent systematic review of 494 cost-effectiveness studies.[23] Although this study found an association between industry-funded studies and favourable cost-effectiveness ratios, they also found this to be true for studies of lower methodological quality.[23] In addition, they found that industry-funded studies tended to be of lower methodological quality. In contrast, our data may suggest that studies funded by industry may be of higher quality (a statistical test could not be conducted to confirm this because of a very small sample size). Conclusions based on funding source should be interpreted with caution as sample sizes were very small, and almost half of the studies did not report funding source (see final paragraph of this section).

Abstracting and consolidating the ICERs from various studies is useful to make conclusions about the cost effectiveness of hepatitis A vaccination programmes. However, uncertainties remain in the reliability of these estimates. This largely depends on the quality of the studies, and the methodological choices made by the investigators. While quality assessment checklists are helpful, they generally do not distinguish between major flaws and simple weaknesses. In our view, there are certain features of a model that represent major flaws. For example, using a cohort model (which tends to underestimate cost effectiveness),[18,19] when a dynamic model is more appropriate is one such flaw.

Only two studies that assessed universal vaccination used a dynamic model.[33,38] Although most economic evaluations of vaccination programmes using cohort models may argue that their analysis is conservative or biased against vaccination, this is not always the case.[19] A reduced force of infection also increases the mean age at infection.[60,61] Because disease morbidity increases significantly with age, cohort models may also overestimate cost effectiveness of hepatitis A vaccination programmes.[18] A third aspect of real-world epidemiology that cohort models fail to capture is the transient phase following initiation of a new vaccination programme. Cost effectiveness of a universal policy evolves over time as herd immunity accumulates.[24] Since cohort models cannot capture these multiple effects, the use of dynamic models is recommended for the assessment of universal programmes.[14,18] An exception occurs when coverage is close to 100%, in which case herd immunity does not apply because almost all individuals are vaccinated. However, in practice, 100% coverage is only possible for a few strategies. Thus, for most realistic universal vaccination strategies, dynamic models are still a necessity in cost-effectiveness analysis. Other exceptions occur when assessing targeted vaccination in groups that do not contribute significantly to hepatitis A transmission, and when the decision maker is interested solely in the health benefits of that group and not others in the population.[18] In this case, a cohort model is sufficient. In other cases, for example when targeting a group responsible for significant transmission, a cohort model is not sufficient.[18]

Using under-reported incidence data is another example of a methodological weakness. Many studies did not adjust incidence for under-reporting of hepatitis A. Although knowledge of the true incidence of hepatitis A virus infection is essential for immunisation programme evaluation, this information is unknown for most regions of the world. Modelling can rectify this problem, if data exist to do so. Catalytic modelling is a simple technique using integral equations to reconcile case reporting data with seroprevalence data.[22,62] This technique was used to determine the true incidence of hepatitis

A (including subclinical infection) in the US and Canada, which was estimated at approximately 10 and 7.7 times the reported incidence, respectively.[21,22] Under-reporting of only symptomatic infection is smaller but still significant, ranging from 1.5 : 1 in Switzerland[63] to 3 : 1 in the US.[64] Although under-reported cases may not directly consume healthcare resources, they are important in the chain of transmission because they contribute to the circulation of the virus without detection.[21]

Just over half of studies included in this review did not include all relevant costs associated with the chosen perspective. An important costing component that was not captured by the quality assessment tools, but in our view deserves some attention, is the inclusion of public health costs (i.e. costs associated with hepatitis A outbreaks and intervention). Public health costs were estimated to account for approximately 23% of the total direct cost per hepatitis A case in Canada.[33,65] Very few studies included in this review account for these costs, yet this is important because of the large costs associated with interventions. For example, one single case of an infected food handler working at a grocery store in Canada resulted in the vaccination of 19 208 patrons and cost local public health $Can658 000.[66] In the US, the estimated cost of an outbreak involving 43 cases in the 1990s was $US689 314.[67]

According to our assessment, using the framework by Philips et al.,[30] studies should provide more justification of their methods, to allow the reader to make an informed judgment about the relevance, coherence and usefulness of their analysis. In a time when many or most journals allow online supplementary material, space limits are no longer a reason to limit descriptions of methodology. Valid comparisons of cost-effectiveness ratios across studies require that the ratios be reported in similar terms and be obtained by using comparable methods.[68] Although standards for conducting and reporting cost-effectiveness analyses have been proposed as a way of improving consistency and clarity,[47,69] adherence to recommended protocols has generally been lacking.[15,47] In general, we found that reporting practices have improved over time, which is consistent with findings from other studies.[15] We also found that reporting practices and the overall quality of cost-utility analyses were better than other analyses. This may be due to the improvement in studies over time, as the cost-utility analyses were conducted in later years.

There were limitations to this systematic review. First, the results from analyses conducted in tables II and III should be interpreted with caution, as the appropriate statistical tests to check for confounding of model parameters could not be conducted. The cost per QALY is not likely affected by one factor, but a combination of several factors. Currently, consensus on this type of analysis has not been reached. Systematic review of cost-effectiveness studies is in its infancy and this is a methodological issue worthy of further investigation. Second, although we used validated quality assessment tools and two reviewers per study, assessment of quality can be subjective, was not blinded, and was therefore susceptible to bias. Third, some of these articles were judged against recommendations that were developed after the studies were conducted and published. Fourth, it is possible that researchers may tend to evaluate programmes most applicable to their region and those that are more likely to be cost effective. For example, in very low incidence regions, universal infant vaccination may not be evaluated if it is not likely to be cost effective, and if decision makers are not interested in this option. Therefore, this type of bias should be kept in mind when making conclusions about the cost effectiveness of a programme based on the comparison of a number of studies. Finally, the majority of the studies included in our review were published and therefore our results may be affected by publication bias, as published literature tends to report statistically favourable results.[70-72]

5. Conclusions

We conducted a systematic review of cost-effectiveness studies of hepatitis A vaccine to explore the effects of methodological quality and key modelling issues on the economic attractiveness of vaccination programmes. Cost effectiveness of universal childhood vaccination is likely to be an economically attractive option, particularly in high-incidence countries. The cost effectiveness of targeted vaccination appears to be dependent on the risk of infection, and vaccinating only susceptibles generally does not appear to be economically attractive. The

reliability of these estimates, however, is influenced by the overall quality and other methodological choices made by the analyst. Therefore, perhaps the least contentious way to summarise and interpret cost-effectiveness studies is to pay attention to the factors that appear to influence the cost-effectiveness ratios, rather than relying on the absolute ICER values themselves to indicate cost effectiveness of vaccination programmes.

Acknowledgements

This study was part of a research grant to C. Bauch funded by the Canadian Institutes of Health Research Industry-Partnered Operating Grant and GlaxoSmithKline, Canada. A. Tricco, A. John-Baptiste and G. Woo have held research contracts with GlaxoSmithKline, Canada. A. Anonychuk is currently employed by GlaxoSmithKline, Canada and B. Pham was an employee at the time of this project. M. Krahn is sponsored, in part, by an Investigator Award from CIHR and the F. Norman Hughes Chair in Pharmacoeconomics, Faculty of Pharmacy, University of Toronto. A. Tricco is sponsored, in part, by a CIHR Doctoral Research Award.

We would like to thank Carmen Ng for her assistance with the preparation of the manuscript.

References

1. Di Giammarino L, Dienstag JL. Hepatitis A: the price of progress. N Engl J Med 2005 Sep 1; 353 (9): 944-6
2. Scheifele DW, Ochnio J. Hepatitis A vaccine: is it being used to best advantage? CMAJ 2002 Jul 9; 167 (1): 44-5
3. Dagan R, Leventhal A, Anis E, et al. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA 2005 Jul 13; 294 (2): 202-10
4. Dominguez A, Bruguera M, Plans P, et al. Prevalence of hepatitis A antibodies in schoolchildren in Catalonia (Spain) after the introduction of universal hepatitis A immunization. J Med Virol 2004 Jun; 73 (2): 172-6
5. Germinario C, Lopalco PL, Chirona M, et al. From hepatitis B to hepatitis A and B prevention: the Puglia (Italy) experience. Vaccine 2000 Feb 18; 18 Suppl. 1: S83-5
6. Jenson HB. The changing picture of hepatitis A in the United States. Curr Opin Pediatr 2004 Feb; 16 (1): 89-93
7. Navas E, Salleras L, Gisbert R, et al. Efficiency of the incorporation of the hepatitis a vaccine as a combined A + B vaccine to the hepatitis B vaccination programme of preadolescents in schools. Vaccine 2005; 23 (17-18): 2185-9
8. Health Canada. Canadian immunization guide. 6th ed. Ottawa: Canadian Medical Association, 2002
9. Andre FE. Universal mass vaccination against hepatitis A. Curr Top Microbiol Immunol 2006; 304: 95-114
10. Wasley A, Fiore A, Bell BP. Hepatitis A in the era of vaccination. Epidemiol Rev 2006; 28: 101-11
11. Krahn M, Remis R, Hogg R, et al. Universal hepatitis A vaccination for adolescents and children in Canada: a cost effectiveness analysis [online]. Available from URL: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/dr3115eb.html [Accessed 2007 Oct 31]
12. Mason J, Eccles M, Freemantle N, et al. A framework for incorporating cost-effectiveness in evidence-based clinical practice guidelines. Health Policy 1999; 47 (1): 37-52
13. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. BMJ 2004; 329 (7459): 224-7
14. Beutels P, Edmunds WJ, Antonanzas F, et al. Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics 2002; 20 (1): 1-7
15. Neumann PJ, Stone PW, Chapman RH, et al. The quality of reporting in published cost-utility analyses, 1976-1997. Ann Intern Med 2000 Jun 20; 132 (12): 964-72
16. Davies L, Coyle D, Drummond M. Current status of economic appraisal of health technology in the European Community: report of the network. The EC Network on the Methodology of Economic Appraisal of Health Technology. Soc Sci Med 1994; 38 (12): 1601-7
17. Drummond M, Cooke J, Walley T. Economic evaluation under managed competition: evidence from the UK. Soc Sci Med 1997; 45 (4): 583-95
18. Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. Stat Med 1999 Dec 15; 18 (23): 3263-82
19. Brisson M, Edmunds WJ. Economic evaluation of vaccination programs: the impact of herd-immunity. Med Decis Making 2003 Jan; 23 (1): 76-82
20. Samandari T, Bell BP, Armstrong GL. Quantifying the impact of hepatitis A immunization in the United States, 1995-2001. Vaccine 2004 Oct; 22 (31-32): 4342-50
21. Chen H, Bauch C, Foty R, et al. Use of catalytic modeling to estimate hepatitis A incidence in a low endemicity country: implications for modeling immunization policies [abstract]. Available from URL: http://smdm.confex.com/smdm/2004ga/techprogram/P1609.htm [Accessed 2007 Oct 31]
22. Armstrong GL, Bell BP. Hepatitis A virus infections in the United States: model-based estimates and implications for childhood immunization. Pediatrics 2002 May; 109 (5): 839-45
23. Bell CM, Urbach DR, Ray JG, et al. Bias in published cost effectiveness studies: systematic review. BMJ 2006 Mar 25; 332 (7543): 699-703
24. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics 1977 Jun; 33 (2): 363-74
25. Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP) [online]. Available from URL: http://www.oecd.org/std/ppp/ [Accessed 2007 Jan 1]
26. US Department of Labor. US labor statistics data [online]. Available from URL: http://data.bls.gov/PDQ/servlet/SurveyOutputServlet [Accessed 2007 Jan 1]
27. Evans C, Tavakoli M, Crawford B. Use of quality adjusted life years and life years gained as benchmarks in economic evaluations: a critical appraisal. Health Care Manag Sci 2004 Feb; 7 (1): 43-9
28. Laupacis A, Feeny D, Detsky AS, et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992 Feb 15; 146 (4): 473-81
29. Owens DK. Interpretation of cost-effectiveness analyses. J Gen Intern Med 1998 Oct; 13 (10): 716-7
30. Philips Z, Bojke L, Sculpher M, et al. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics 2006; 24 (4): 355-71
31. Arguedas MR, Heudebert GR, Fallon MB, et al. The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C viral infection in the United States. Am J Gastroenterol 2002 Mar; 97 (3): 721-8

32. Arnal JM, Frisa O, Garuz R, et al. Cost effectiveness of hepatitis A virus immunisation in Spain. Pharmacoeconomics 1997; (3): 361-73
33. Bauch CT, Anonychuk AM, Pham BZ, et al. Cost-utility of universal hepatitis A vaccination in Canada. Vaccine 2007; 25 (51): 8536-48
34. Buma AH, Beutels P, Van DP, et al. An economic evaluation of hepatitis A vaccination in Dutch military personnel. Mil Med 1998 Aug; 163 (8): 564-7
35. Chodick G, Lerman Y, Wood F, et al. Cost-utility analysis of hepatitis a prevention among health-care workers in Israel. J Occup Environ Med 2002; 44 (2): 109-15
36. Das A. An economic analysis of different strategies of immunization against hepatitis A virus in developed countries. Hepatology 1999; (2): 548-52
37. Demicheli V, Carniglia E, Fucci S. The use of hepatitis A vaccination in Italy: an economic evaluation. Vaccine 2003 Jun 2; 21 (19-20): 2250-7
38. Diel R, Rappenhoner B, Schneider S. Cost-effectiveness of hepatitis A immunization of children and adolescents in Germany. Hepac Health Econ Prev Care 2001; 2 (3): 96-103
39. Jacobs RJ, Margolis HS, Coleman PJ. The cost-effectiveness of adolescent hepatitis A vaccination in states with the highest disease rates. Arch Ped Adolesc Med 2000; 154 (8): 763-70
40. Jacobs RJ, Grover SF, Meyerhoff AS, et al. Cost effectiveness of vaccinating food service workers against hepatitis A infection. J Food Protect 2000 Jun; 63 (6): 768-74
41. Jacobs RJ, Koff RS, Meyerhoff AS. The cost-effectiveness of vaccinating chronic hepatitis C patients against hepatitis A. Am J Gastroenterol 2002; 97 (2): 427-34
42. Jacobs RJ, Greenberg DP, Koff RS, et al. Regional variation in the cost effectiveness of childhood hepatitis A immunization. Pediatr Infect Dis J 2003; 22 (10): 904-14
43. Jacobs RJ, Meyerhoff AS. Cost-effectiveness of hepatitis A/B vaccine versus hepatitis B vaccine in public sexually transmitted disease clinics. Sex Transm Dis 2003 Nov; 30 (11): 859-65
44. Jacobs RJ, Saab S, Meyerhoff AS. The cost effectiveness of hepatitis immunization for US college students. J Am Coll Health 2003 May; 51 (6): 227-36
45. Jacobs RJ, Gibson GA, Meyerhoff AS. Cost-effectiveness of hepatitis A-B vaccine versus hepatitis B vaccine for healthcare and public safety workers in the Western United States. Infect Control Hosp Epidemiol 2004; 25 (7): 563-9
46. Jacobs RJ, Rosenthal P, Meyerhoff AS. Cost effectiveness of hepatitis A/B versus hepatitis B vaccination for US prison inmates. Vaccine 2004 Mar 12; 22 (9-10): 1241-8
47. Jefferson TO, Behrens RH, Demicheli V. Should British soldiers be vaccinated against hepatitis A? An economic analysis. Vaccine 1994; 12 (15): 1379-83
48. 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
49. O'Connor JB, Imperiale TF, Singer ME. Cost-effectiveness analysis of hepatitis A vaccination strategies for adults. Hepatology 1999; 30 (4): 1077-81
50. Pechevis M, Khoshnood B, Buteau L, et al. Cost-effectiveness of hepatitis A vaccine in prevention of secondary hepatitis A infection. Vaccine 2003; 21 (25-26): 3556-64
51. Postma MJ, Bos JM, Beutels P, et al. Pharmaco-economic evaluation of targeted hepatitis a vaccination for children of ethnic minorities in Amsterdam (The Netherlands). Vaccine 2004; 22 (15-16): 1862-7
52. Rajan E, Shattock AG, Fielding JF. Cost-effective analysis of hepatitis A prevention in Ireland. Am J Gastroenterol 2000; 95 (1): 223-6
53. Rein DB, Hicks KA, Wirth KE, et al. Cost-effectiveness of routine childhood vaccination for hepatitis A in the United States. Pediatrics 2007 Jan; 119 (1): e12-21
54. Severo CA, Fagnani F, Lafuma A. Cost effectiveness of hepatitis A prevention in France. Pharmacoeconomics 1995; 8 (1): 46-61
55. Smith S, Weber S, Wiblin T, et al. Cost-effectiveness of hepatitis A vaccination in healthcare workers. Infect Control Hosp Epidemiol 1997 Oct; 18 (10): 688-91
56. Szucs T. Cost-effectiveness of hepatitis A and B vaccination programme in Germany. Vaccine 2000; 18 (S1): S86-9
57. Tormans G, Van DP, Van DE. Cost-effectiveness analysis of hepatitis A prevention in travellers. Vaccine 1992; 10 (S1): S88-92
58. Valenzuela MT, Jacobs RJ, Arteaga O, et al. Cost-effectiveness of universal childhood hepatitis A vaccination in Chile. Vaccine 2005; 23 (32): 4110-9
59. Van Doorslaer E, Tormans G, Van DP. Cost-effectiveness analysis of vaccination against hepatitis A in travellers. J Med Virol 1994; 44 (4): 463-9
60. Anderson RM, May RM. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. J Hyg 1985 Jun; 94 (3): 365-436
61. Ukkonen P, von Bonsdorff CH. Rubella immunity and morbidity: effects of vaccination in Finland. Scand J Infect Dis 1988; 20 (3): 255-9
62. Muench H. Catalytic models in epidemiology. Cambridge (MA): Harvard University Press, 1959
63. Mutsch M, Spicher VM, Gut C, et al. Hepatitis infection in travellers 1988–2004. Clin Infect Dis 2006 Feb 15; 42 (4): 490-7
64. Berge JJ, Drennan DP, Jacobs RJ, et al. The cost of hepatitis A infections in American adolescents and adults in 1997. Hepatology 2000 Feb; 31 (2): 469-73
65. Anonychuk A, Krahn M, Gilca V, et al. The cost of hepatitis A in Canada: ministry and societal perspectives [abstract]. Society for Medical Decision Making Conference; 2006 Oct 14-18; Boston [online]. Available from URL: http://smdm.confex.com/smdm/2006ma/techprogram/P3122.htm [Accessed 2007 Oct 1]
66. Tricco AC, Pham B, Duval B, et al. A review of interventions triggered by hepatitis A infected food-handlers in Canada. BMC Health Serv Res 2006; 6: 157
67. Dalton CB, Haddix A, Hoffman RE, et al. The cost of a foodborne outbreak of hepatitis A in Denver, Colo. Arch Intern Med 1996 May 13; 156 (9): 1013-6
68. Gold M, Siegel J, Russell L, et al. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996
69. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996 Oct 16; 276 (15): 1253-8
70. Song F, Eastwood AJ, Gilbody S, et al. Publication and related biases. Health Technol Assess 2000; 4: 1-115
71. Dickersin K. Publication bias: recognizing the problem, understanding its origins and scope, and preventing harm. In: Rothstein H, Sutton AJ, Borenstein M, editors. Publication bias in meta-analysis: prevention, assessment and adjustments. Chichester: John Wiley & Sons Ltd, 2005
72. Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 2000; 263: 1385-9

Correspondence: Dr *Murray Krahn*, Toronto General Hospital, 200 Elizabeth St, Eaton 14th Floor Rm 14E207, Toronto, Ontario M5G 2C4, Canada.
E-mail: murray.krahn@uhn.on.ca