academicJournals

Vol. 6(4), pp. 26-36, November, 2014
DOI 10.5897/JIDI2013.0127
Article Number: C8C2F2648704
ISSN 2141-2375

http://www.academicjournals.org/JIDI

Journal of Infectious Diseases and Immunity

Review

Cost effectiveness analyses of influenza A (H1N1) vaccination programs: How accurate were they?

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Received 16 September, 2013; Accepted 5 November, 2014

Three economic evaluations of pandemic influenza A (H1N1) vaccination campaigns in North America concluded that the mass vaccination campaigns would be, or were, highly cost-effective, if not cost-saving. This paper re-assesses each study's analysis and presents three arguments: 1) prediction of vaccine program cost-effectiveness is unrealistic, if not impossible, unless quality surveillance data is available; 2) even when surveillance data is available, vaccine cost-effectiveness calculations can still vary dramatically and need to undergo wider-ranging sensitivity analysis; 3) H1N1 vaccination campaigns in North America were likely not as cost-effective as previously thought. Several recommendations are then made for improving transparency, accuracy, portability, and sensitivity analysis in pharmacoeconomic studies more generally.

Key words: Pandemic, influenza, vaccination, immunization, cost-effectiveness, health economics, pharmaco-economics.

INTRODUCTION

Mass immunization programs in Canada and the United States during the 2009 Influenza A (H1N1) pandemic have been criticized as expensive and excessive (Waldie and Alphonso, 2009; Blackwell, 2010; Amico, 2009), with total costs in Canada and the US borne by all levels of government being estimated at CAD $1 billion (Blackwell, 2010) and USD $6.15 billion (Amico, 2009), respectively. Despite these expenditures, the question of cost and efficiency has received little attention in official reviews of the pandemic immunization programs. Three cost-effectiveness analysis (CEA) papers on H1N1 immunization programs in North America found the programs to be highly cost-effective in terms of expenditure per quality-adjusted life year (QALY) (Sander et al., 2010), if not cost-saving due to avoided influenza treatment costs (Durbin et al., 2011; Khazeni et al., 2009).

Evaluating pandemic vaccination programs is inherently difficult due to the number of unknown or uncertain modeling parameters. The three studies provided extensive acknowledgment of their modeling assumptions and parameter uncertainty, and conducted sensitivity analysis (SA). In Khazeni et al. (2009) and Sander et al. (2010), the SA was especially extensive. All three found their respective conclusions to be robust. However, careful assessment of the studies' methodologies, parameters and outputs reveals high levels of variation

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Table 1. Selected parameters and outcomes from the Khazeni (K), Sander (S), and Durbin (D) studies.

Parameter	K	S	D	Max. Difference
Population	8,300,000	13,069,182	13,077,256	
Case fatality ratio (%)	0.1 (0.01-1.0)	0.005	0.01	20×
Pr(hospitalized | symptoms)	0.033 (0.01-0.1)	0.00075	0.033	44×
Vacc. campaign length (days)	10	98	67	9.8×
QALYs lost per flu case	0.00548	0.0187	n/a	3.4×
(SA range)	(0.0027-0.0082)	(0.0065-0.023)		
Health events averted				
Symptomatic cases	2,051,000	895,114	1,780,491	3.61×
Primary case visits	-	105,080	533,069	5.07×
Emergency dept. visits	-	28,721	9,807	2.93×
Hospitalizations (ward)	60,915	427	3,567	225×
ICU admissions	6,768	80	810	133×
Deaths	2,051	52	154	62.1×

and possible over-estimation of vaccine cost-effectiveness. These findings highlight certain general challenges in the field of pharmacoeconomics, as well as issues specific to the economic evaluation of mass immunization programs for pandemic influenza. Following a comparative analysis of the three papers, we present recommendations for addressing these challenges.

The first study, written during the first-wave of H1N1 by Khazeni et al. (2009), aimed to predict the cost-effectiveness of the US immunization program during the second wave. It drew on first-wave surveillance data and assumptions from the US Centers for Disease Control and Prevention (CDC) published pre-pandemic to construct a compartmental epidemic model, and simulated mass vaccination in a large US city. The other two studies were retrospective rather than predictive. The second study (Sander et al., 2010), building on previous work published by the same authors in 2009, used post-pandemic surveillance data to simulate a pandemic in a medium-sized Canadian city and infer the vaccine campaign's impact for the Canadian province of Ontario. The third study, published in 2011 by Durbin et al., used agent-based simulation to model a pandemic in Ontario as well. The models Sander and Durbin used are described in separate publications (Gojovic et al., 2009; Aleman et al., 2011). For simplicity, we identify each study by first author. We analyze the variability between the studies with respect to four factors: predicted epidemiological outcomes; per capita costs and cost-savings; gains in QALYs; and the use of different accounting perspectives. Each model is then tested using certain parameters from the other studies, and from external sources, to illustrate the limitations of the SA and of the conclusions drawn. The analysis suggests that (1) prediction of vaccine program cost-effectiveness is unrealistic unless quality surveillance data are available; (2) even when surveillance data are available, cost-effectiveness calculations can still vary dramatically and need wider-ranging SA; and (3) H1N1 vaccination campaigns in North America were likely not as cost-effective as previously thought.

To ensure comparability, only papers that examined the cost-effectiveness of mass vaccination were considered; CEA papers on other interventions, such as school closures or anti-viral prophylaxis, were excluded from our analysis. We also excluded three other studies relating to H1N1 vaccine cost-effectiveness in North America; one for not modeling population-level disease transmission (Prosser et al., 2011), and two for insufficient detail to allow evaluation and comparison (Yarmand et al., 2010; Lee et al., 2010).

SOURCES AND COMPOSITION OF PARAMETER

Assumptions

Table 1 shows the extent of variation between key parameters used in each of the three papers, including both the baseline scenario values and the ranges tested in SA. Durbin did not present SA results for these parameters. Baseline values are shown, with the ranges tested in SA listed in parentheses. “Max Diff” is the maximum difference between the papers' parameter values or per capita outcomes in baseline scenarios, as a multiple of the row's smallest value. The 20-fold difference in case fatality ratios (CFRs) shows the extent of disagreement that can arise between early surveillance vs post-pandemic datasets. Likewise, the hospitalization rates used in Khazeni were based on a paper published before the H1N1 pandemic, whereas Sander's hospitalization rate, 44 times smaller, was calibrated to match

observed hospitalization rates in Canada during the pandemic. The variability of past influenza pandemics and limited early surveillance data make it difficult to estimate the properties of new virus strains at the time pandemic mitigation strategies need to be developed. Despite the generous SA range for Khazeni's CFR and hospitalization rates, neither interval captured Sander's baseline values.

All three studies found vaccination timing to be consequential; shorter deployment times greatly increased the expected impact of the programs. Unfortunately, distribution speed assumptions varied widely. In particular, Khazeni's assumption that 40% of citizens would be vaccinated in 10 days was overly optimistic; the programs ran for two months before getting close to 40% coverage.

Quality-adjusted life years

Despite major parameter differences, the studies reached fairly congruent conclusions: the H1N1 vaccination campaign would be either cost-saving (Durbin et al., 2011; Khazeni et al., 2009) or highly cost-effective (Durbin et al., 2011; Sander et al., 2010). However, the size and composition of health benefits, and the way they were counted, varied considerably. The QALY gains presented in the baseline vaccination scenarios were re-calculated from raw output. Several minor parameters not stated in the papers were inferred by back-solving with stated parameters and results. Durbin's paper presented raw output such as lives saved and emergency department (ED) visits prevented; its health gains were converted to QALYs using the other papers' QALY weightings. The gains are expressed in QALYs per 100,000 people.

Khazeni predicted a more severe pandemic and effective vaccination campaign than the Canadian studies, which themselves differed by 100 to 1000% on every health outcome. Khazeni did not state the number of infections prevented, but deaths avoided and the CFR were given, at 2,051 and 0.1%. The number of infections prevented was therefore estimated as 2,051,000, which was consistent with the reported QALY gains.

Khazeni assumed that 6.67% of the population had already been symptomatically infected by the start of the second wave, and that the vaccine would be administered two weeks before the pandemic's peak. For Khazeni's population of 8.3 million, if 6.67% became ill before the second wave, with a stated attack rate of 36%, then 29.33% of the population (2.43 million) would still be expected to fall ill in a scenario with no vaccination. By the time the first vaccines confer immunity, the second wave would have peaked.

Conservatively, one could assume that at least 40% of the 29.33% of the population expected to become infected during the second wave would become infected by the second wave's peak - roughly the wave's half-way point. Accordingly, there should be no more than 1.461 million cases of influenza that would still happen without any intervention. Khazeni's prediction that vaccination would prevent 2.051 million infections seems unlikely.

Similar analysis applies to Durbin, which had a non-intervention attack rate of 33.5%. The model initialized with 7,317 infected persons, and vaccinations began roughly two weeks prior to the peak of the second wave. Under the assumption that at least 45% of the 4,379,195 infections occurring in the non-intervention scenario would have happened by the peak of the second wave, the 1,780,491 cases prevented due to vaccination represent 74% of all cases that would be expected to happen thereafter without vaccination. Given that vaccination covered only 40% of the population over several weeks, starting in the middle of the second wave, and a 20-day delay in the onset of immunity was assumed, this prevention rate seems unrealistically high.

Differences in discount rates and in the QALY weights given to each prevented health outcome added further variation to the studies (Table 2). The value of 6.55 QALYs per death in Sander was the unique solution to the paper's claim that 2% of the 17,035 QALYs saved came from averting 52 deaths; it is lower than the 21.1 QALY loss per death in Khazeni because Sander used a 5% discount rate vs Khazeni's 3%, and attributed a greater fraction of deaths to older adults than Khazeni. Higher discount rates reduce the value of QALYs gained in the future; this is of little consequence when most QALY losses are from short-term morbidity, such as in Sander's analysis, but may create large differences in CEA studies when QALY losses are from long-term morbidity or death in younger and middle-aged people. There is active debate within health economics on whether and how health outcomes should be discounted (Claxton et al., 2011; Torgerson and Raftery, 1999; Severens and Milne, 2004). The 3 and 5% rates used by Khazeni and Sander, respectively, are the two rates most commonly recommended in government guidelines for CEA (Smith and Gravelle, 2001).

Sander and Khazeni both used peer-reviewed studies to obtain values for QALY losses per case due to morbidity, yet these values differed by a factor of 3.4 (Table 1). Such large differences underscore a major challenge in CEA: when morbidity is the dominant concern, QALYs for the same clinical outcome are not always comparable between studies, because there are a range of methods for comparing morbidity to lost life-years. QALY weights generated by different methods are often only weakly correlated (Arnesen and Trommald, 2004), and some methods have been found to give significantly more weight to morbidity than others (Salomon and Murray, 2004).

Prevented deaths represent nearly two-thirds of Khazeni's QALY gains, but only 2% for Sander. Khazeni assumed that all surviving intensive care unit (ICU) patients would live with life-long disability; the other studies

Table 2. QALY gains in Khazeni (K), Sander (S), and estimates for Durbin using K's and S's QALY weights.

Event averted	QALYs lost per event		QALYs gained per 100,000		% of QALYs gained		QALYs gained per 100,000		% of QALYs gained	
	K	S	K	S	K	S	Durbin-K	Durbin-S	Durbin-K	Durbin-S
Symptomatic cases	0.005479	0.01865	135.4	127.7	16.1	98	74.6	253.9	66.1	97.1
Hospitalization (ward)	0.007808	-	5.7	-	0.68	-	0.21	-	0.19	-
ICU	0.02	-	1.63	-	0.20	-	0.01	-	0%	-
Post-ICU disability	2.12	-	172.9	-	20.6	-	13.13	-	11.6	-
Death	21.2	6.55	523.9	2.6	62.4	2	39.39	7.72	34.8	2.9
Total burden	-	-	839.5	130.3	100	100	112.9	261.6	100	100

did not consider disability. Although disability prevention comprised most of Khazeni's non-death-related QALY gains, no source was given for the disability QALY value, which was varied in SA to the same degree as parameters with sources (33%). In both studies, preventing hospitalization resulted in tiny QALY gains.

QALY gains for Durbin were estimated using Khazeni's and Sander's QALY parameters. The results further illustrate how the estimated impact of health events can vary according to the QALY values chosen. The QALYs saved due to vaccination are 2.3 times greater using Sander's QALY parameters. The breakdown of where QALYs are gained also differs substantially.

Cost-savings and program costs

Each study counted vaccine program costs and savings differently. Khazeni and Durbin used a societal perspective by monetizing the time patients spent getting vaccinated. In one of two analyses, Durbin also considered the prevention of lost workdays. Both studies estimated total vaccine cost as the cost per vaccine times the number administered, thereby excluding the cost of unused vaccines. Sander considered the province of Ontario's total expenditure on vaccines, used and unused, but excluded the Canadian Federal Government's 60% contribution towards the vaccines' cost, as well as vaccination program advertising costs. The studies' cost estimates understated the programs' costs to taxpayers. All currency amounts are expressed in the currencies used in the studies (2009 USD for Khazeni and 2009-2010 CAD for Sander and Durbin). The currencies over this period were near parity.

Khazeni's cost-savings categories included “normal healthcare expenditures,” which had a unit value of $19.56, though it is unclear who incurs these costs. It was possible to replicate Khazeni's cost-savings figures for all scenarios by assuming that $19.56 is incurred per day for 3.7 days for every symptomatic case. This cost was placed under the “Other” category in Table 3, which summarizes expense sources. All cost-savings and program costs values in Table 3 are presented from the baseline vaccination program in each study's currency. Durbin included anti-viral drugs and laboratory costs, also listed under “Other.” ICU costs are an average, as Sander and Durbin considered costlier ICU interventions for certain patients. The studies' cost-savings differed greatly in magnitude and composition. The four-fold difference between the Canadian studies becomes an 18-fold gap when Durbin's workday savings are included. Program delivery costs varied less. All three papers considered costs for treating adverse vaccine reactions, which were negligible in Sander's paper and minor in Durbin's. The ICU stay for life-threatening adverse reactions in Khazeni's paper was assumed to be the same as ICU flu patients - 10 days.

Only Durbin's paper considered government advertising, though its estimate excluded Ontario's 38% share of the Canadian Government's $26 million advertising expenditure for H1N1 (Blackwell, 2010). Khazeni's vaccine administration costs excluded facility costs, administrative and IT staff, public health managers, and distribution and storage costs.

As shown in Table 3, savings exceeded program costs almost 12-fold in Khazeni's baseline case. Durbin's savings also exceeded program costs under a societal-perspective, but not when patient time and work absenteeism are excluded. Sander did not find the program cost-saving.

Table 3. Economic analysis of cost-savings and program costs from different accounting perspectives.

Event averted	Cost savings per event			Costs saved per 100,000 in pop.			% of savings		
	K	S	D	K	S	D	K	S	D
Cost savings from a healthcare provider/payer perspective									
PCP visit	-	57.34	34	-	46,103	136,685	-	29.5	21.9
ED visit	-	248.83	220	-	54,684	16,498	-	35.0	2.6
Hospitalizations	9,152.30	9,060.15	4,265	6,716,983	24,056	116,334	58.1	15.4	18.7
ICU	37,390	51,463	35,727	3,049,038	31,502	221,295	26.4	20.1	35.5
Other	19.56	-	26	1,788,196	-	132,305	15.5	0	21.2
Sub-total	-	-	-	11,554,217	156,345	623,117	100	100	100
Cost-savings from a societal perspective									
Lost workdays	-	-	204.47	-	-	2,192,446	-	-	-
Program costs from health provider perspective									
Vaccine	13.9	10.7	7.9	554,217	480,000	311,181	57	35	26
Administration	8.7	20	22.1	349,398	900,000	838,660	36	65	71
Advertising	-	-	0.52	-	-	19,882	0	0	2
Adverse events	1.93	-	0.32	77,108	-	12,249	8	0	1
Sub-total	-	-	-	980,723	1,380,000	1,181,971	100	100	100
Costs from a societal perspective									
Patient wait time	10.55	-	17.68	422,000	-	671,743	-	-	-

ALTERNATE SCENARIOS

The papers' SA may have underestimated their findings' sensitivity to key assumptions. The seemingly wide ranges tested for certain critical parameters were not wide enough to capture the parameter values the other studies used. This was especially significant for the QALY weightings, hospitalization rates, and the CFR. To re-test the robustness of each study's findings, the QALY and cost calculations were repeated for each study using parameters drawn from the other papers and/or from post-pandemic data sources. The impact of changing accounting perspectives is also tested. Separate analysis was done for each paper since they included different cost and health gain categories, and had different key assumptions. Health outcome numbers for Khazeni were drawn from Center for Disease and Control (CDC) (2010a), while Public Health Agency of Canada data were used for Durbin and Sander (PHAC, 2010).

Khazeni revisited: US vaccine campaign not cost-saving

Khazeni's analysis was affected by its high assumed rates of death, hospitalization and the number of infections prevented. A scenario closer to how the pandemic played out, as estimated by the CDC and by Sander's paper, which calibrated its results to Canadian surveillance data, was constructed to better estimate the cost-effectiveness of the US's H1N1 vaccination campaign. The

Table 4. Changes in costs and savings for Khazeni's analysis with adjusted health outputs and parameters.

Event averted	Cost per event	Costs per 100,000 in population			% of costs	
		Original	Adjusted	% change	Original	Adjusted
Adjusted cost-savings from baseline vaccination program*						
PCP visit	45.67	-	31,279	-	-	3.9
ED visit	234.42	-	40,138	-	-	5.0
Hospitalizations	9,152.30	6,716,983	202,132	(97.0)	58.1	25.0
ICU	37,390	3,049,038	37,775	(98.8)	26.4	4.7
Other	19.56	1,788,196	495,630	(72.3)	15.5	61.4
Sub-total		11,554,217	806,995	(93.0)	100	100
Additional savings from societal perspective*						
Workdays saved	204.5	-	1,102,899	-	-	-
Adjusted costs from healthcare payer perspective**						
Vaccine	13.9	554,217	554,217	0	56.5	37.1
Administration	21	349,398	841,400	141	35.6	56.4
Advertising	0.52	-	19,882	-	-	1.3
Adverse events	1.93	77,108	77,108	0	7.9	5.2
Sub-total	37.3	980,723	1,492,607	52.2	100	100
Additional costs from a societal and all-of-government perspective**						
Patient wait time	10.55	422,000	422,000	-	-	-
Unused vaccine (1)	21.00	-	839,896	-	-	-
Unused vaccine (2)	35.85	-	1,434,108	-	-	-
Sub-total	31.55-46.40	422,000	1.26M-1.86M	185-321	-	-

Negative values are in brackets. *Indicates cost-savings. ** Indicates new program costs.

number of cases prevented due to vaccination, as a percentage of the total population, was set to 6.8%, from Sander. The rate of visits to PCPs and to the ED per infection, which did not appear in Khazeni's original analysis, were set to the 10 and 2.5% rates in Sander, though these rates may be higher than the US rates because of Canada's universal health insurance.

Recalculating the number of hospitalizations avoided involved several steps. An estimate of 7,802 hospitalizations occurring under the revised vaccination scenario was obtained by multiplying the model's 8.3 million population by the mid-point of the CDC's estimated hospitalization rate for the USA: 0.094% of the population (CDC, 2010a). The number of hospitalizations that would have occurred without vaccination was calculated by assuming that the ratio of infections in the intervention and no-intervention scenarios would be the same as the ratio of hospitalizations in those two scenarios. The ratio of infections was calculated as (36 -6.8)/36, using the initial attack rate of 36% in the denominator and the intervention attack rate lowered by 6.8% of the population in the numerator. The number of hospitalizations without vaccination was therefore estimated to be 9,635, which is 1,833 more hospitalizations than in the vaccination scenario. A similar approach was used to estimate ICU admissions and deaths prevented. The estimated per capita Canadian ICU admission rate of 0.0043% (PHAC, 2010) had to be used in the absence of US figures; this number happened to equal the mid-point of the CDC's per capita mortality rate for the US (CDC, 2010a), which was used to estimate deaths prevented.

In the new cost analysis, unused vaccines were also taken into account. The CDC administered 97 million doses to 86 million people (CDC, 2010a) out of 147 million doses held in government distribution centers (CDC, 2010b), or out of 251 million doses paid for by the US government as of January 11, 2010 (Reuters, 2010). The excess vaccine cost was calculated using both the 147 and 251 million numbers. Where categories were omitted in the original analysis, such as advertising and workdays saved, they were added to the new analysis at the same per case or per capita cost as in Durbin or Sander. Since Khazeni's vaccine administration cost only reflected nurse wages, it was revised to equal $21, the average of the two Canadian studies. The new parameters and revised results are presented alongside the old results in Tables 4 and 5.

Under the new scenario, savings fell by 83.5% and

Table 5. Changes in cost-effectiveness for Khazeni's analysis using adjusted health outputs and parameters (continued).

Even averted	Cost per event	Costs per 100,000 in pop.			% of costs	
		Original	Adjusted	% change	Original	Adjusted
Net financial outcome (savings - program costs)						
Total cost savings	-	11,554,217	1,909,854	(83.5)	-	-
Total program costs	68.85-83.70	1,402,723	2.75 M-3.35 M	96-138	-	-
Payer perspective	-	10,573,494	(685,652)	(106.5)	-	-
Societal perspective	-	10,151,494	840 K-1.44 M	(108-114)	-	-
		Adjusted QALY gains from vaccination				
Event averted	**QALYs lost per event**	**QALYs gained per 100,000**			**% of QALYs gained**	
		Original	**Adjusted**	**% change**	**Original**	**Adjusted**
Symptomatic cases	0.005479	135.4	37.53	(72.3)	16.1	61.2
Hospitalization (ward)	0.007808	5.7	0.17	(97.0)	0.68	0.3
ICU	0.02	1.63	0.02	(98.8)	0.20	0.0
Post-ICU disability	2.12	172	2.14	(98.8)	20.6	3.5
Death	21.2	523.9	21.4	(95.9)	62.4	35.0
Total	-	839.5	61.3	(92.7)	100	100

* Indicates cost savings. ** Indicates new program costs. Negative values are in brackets.

Table 6. Changes to Sander's and Durbin's parameters in the revisited economic analysis.

Event/Item	Unit cost	Value per 100,000 pop.
Additions to Sander's economic analysis		
Workdays saved*	204.5	1,102,899
Patient wait time**	10.55	422,000
Gov. communications***	2.14	97,478
Federal vaccine costs***	16	720,000
Total	-	136,579
Additions to Durbin's economic analysis		
Fed gov. communications***	2.01	76,536
Wasted vaccines***	23.37	888,079
Total	25.38	964,615

* Indicates cost savings from societal perspective. ** Indicates costs from societal perspective. *** Indicates costs from all-of-government perspective.

healthcare provider costs rose 52%. When the cost of unused vaccines is considered, program costs roughly doubled. Including the cost of unused vaccines is essential to assessing average treatment costs accurately. The adjusted scenario is not cost-saving. Under a payer/government-only accounting perspective, the net program cost is $1.45 million to $2.12 million per 100,000, depending on the vaccine waste figure adopted. From a societal perspective, the programs cost $840,000 to $1.44 million per 100,000. The QALYs saved per 100,000 fell from 839.5 to 61.3. The proportion of QALY gains from preventing death and disability also fell. The incremental cost-effectiveness ratio (ICER), which was negative or small in all cases of one-way SA in Khazeni's original report, is $18,000 using the original cost categories, and $34,000 under a government-only perspective. These values still suggest cost-effectiveness, but differ greatly from the original estimates. These revised ICER values are not a worst-case scenario.

Sander revisited: Accounting perspectives shift results

The alternate scenario for Sander involved no changes to cost-savings or to program costs incurred from the healthcare provider's perspective (the Province). However, omitted program costs from a societal and whole-of-government perspective were considered (Table 6). Under a whole-of-government perspective, including the federal government's 60% share of the vaccine cost

Table 7. QALY gains from Sander's baseline vaccination campaign, using Sander's original QALY values (S-QALY) and Khazeni's QALY values (K-QALY).

Event averted	QALYs lost per event		QALYs gained per 100,000		% of QALYs gained	
	K-QALY	S-QALY	K-QALY	S-QALY	K-QALY	S-QALY
Symptopmatic cases	0.005479	0.01865	59.1	127.7	79.3	98.0
Hospitalizations (ward)	0.007808	-	0.04	-	0.1	-
ICU	0.02	-	0.02	-	0	-
Post-ICU disability	2.12	-	2.04	-	2.7	-
Deaths	21.2	6.55	13.28	2.61	17.8	2.0
Total	-	-	74.5	130.3	100	100

Table 8. QALY gains from Durbin's baseline vaccination campaign, using Khazeni's and Sander's QALY values.

Event averted	QALYs lost per event		QALYs gained per 100,000		% of QALYs gained	
	K-QALY	S-QALY	K-QALY	S-QALY	K-QALY	S-QALY
Symptopmatic cases	0.005479	0.01865	74.6	253.9	66.1	97.1
Hospitalizations (ward)	0.007808	-	0.21	-	0.2	-
ICU	0.02	-	0.01	-	0	-
Post-ICU disability	2.12	-	13.13	-	11.6	-
Deaths	21.2	6.55	39.33	7.72	34.8	2.9
Total			112.9	261.6	100	100

and the province's share of federal advertising, the program cost rises to $2.04 million per 100,000 from $1.22 million. From a societal perspective, the program cost falls to $1.61 million per 100,000. To test the sensitivity of Sander's expected QALY savings, the health gains were re-calculated using Khazeni's QALY weightings. Table 7 shows that the QALY gains are only 74.5 QALYs per 100,000 using Khazeni's weightings vs 130.3 in the original analysis. Considering federal expenditures, Sander's original $9,388 per QALY ICER estimate becomes $15,652. Using Khazeni's QALY value for flu cases, the ICER becomes $30,487. Using both full government expenditures and Khazeni's flu case QALY, the ICER reaches $50,839, over five times the original estimate. It is not necessary to run a worst-case scenario to obtain ICER values that are not cost-effective. Sander's SA considered administration costs as high as $100 per vaccine to account for various practical expenses. If the $100 upper range of Sander's administration cost is added to the previous calculation, the ICER reaches $140,526, which is not cost-effective. QALY weights in Sander's SA did not vary widely enough to capture the true range appearing in other pharmaco-economic studies. The choice of a provincial accounting perspective was questionable since the majority of the immunization program's costs were incurred at the federal level in Canada.

Durbin revisited

Durbin's economic analysis (Table 8) was tested in the same manner as Sander's. Since Durbin did not convert health outcomes to QALYs, the conversions were done using Khazeni's QALY values and again with Sander's. Program expenses were modified to include the cost of unused vaccines, since the federal government ordered 50.4 million doses (CBC News, 2009) with 19.4 million going to Ontario (Durbin et al., 2011) and only 40% of the province's 13 million residents receiving the vaccine. Considering unused vaccines and federal advertising, the program is no longer cost-saving from a societal perspective. When unused vaccines and federal advertising are added to the original cost and savings categories, which excluded sick days, the cost rises to $2.20 million per 100,000. When a government perspective is adopted, the cost is $1.52 million per 100,000. The ICERs under Sander's and Khazeni's QALY values and a government perspective were $5,823 and $13,491, respectively. If Khazeni's QALY value for normal flu cases is used alongside Sander's QALY values for the other health events, the ICER becomes $18,507. When patient time is monetized, the ICER becomes $26,667. These outcomes are all cost-effective. However, it is important to recall that the number of influenza cases prevented in Durbin's study seems high.

DISCUSSION

The differences in the CEA studies considered can be largely attributed to three types of variation: (1) differences in pandemic modeling methods; (2) uncertainty in pandemic model parameter inputs; and (3) different protocols for performing economic analysis on the health outcomes predicted. Pandemic modeling is an

area of active research that has produced a range of methodologies. To our knowledge, no systematic comparative study of the predictive differences or dispositions of these methodologies has been conducted. Until such an analysis is performed, it will be hard to know how much variation in predictions between models is due to differences in their parameter inputs vs model structure.

Uncertainty in pandemic model inputs, such as the case fatality ratio, incubation period, and transmission risk, can lead to inaccurate health outcome predictions. Consequently, those conducting CEA studies must consider two basic problems: how long to wait for quality pandemic data before performing CEA, and how to ensure that SA conveys the extent of uncertainty in the findings.

Influenza vaccine CEA studies will be of limited value for real-time pandemic decision-making unless quality surveillance data allow key parameters to be estimated with accuracy and precision. This is especially important since the possible range for several of these parameters, such as the case fatality ratio, can span a few orders of magnitude. Khazeni's paper greatly overestimated influenza deaths for this reason. Conducting CEA too early will hurt accuracy; by contrast, conducting CEA too late, albeit with better data, risks producing recommendations after the window for meaningful action has closed. The timing of CEA during a pandemic must therefore strike a balance between accuracy and expediency. Influenza pandemics with two-wave structures could facilitate this balance. Towards the end of the first wave of H1N1 in 2009, additional data from jurisdictions with strong public health surveillance systems caused the original Mexican CFR estimates for H1N1 to be revised downwards by one or more orders of magnitude (Wilson and Baker, 2009). These new estimates were available several months before the second wave's peak - early enough to influence vaccine procurement decisions.

The way in which uncertainty is modeled and communicated is another area of CEA requiring careful attention. Most CEA conclusions are based on the ICER obtained using the set of parameter values that are deemed to be most plausible, even if these parameters' estimates are highly uncertain. Instead of calculating the most likely ICER estimate, a more valuable pursuit would be constructing a histogram of ICER values generated by Monte Carlo sampling on the uncertain input parameters. Such a histogram would provide a much richer picture of the range and probability of different cost-effectiveness levels. We recommend that assertions of cost-effectiveness be made only when a sufficiently large proportion of Monte Carlo sampling scenarios show cost-effectiveness.

Khazeni's paper shows how focusing on the base case instead of the overall distribution of simulated outcomes can produce very different conclusions. The paper stated that in 55% of Monte Carlo simulations a November vaccination campaign would not be cost-saving; but using the base case, the authors still concluded that large-scale vaccination would be cost-saving. Strong cost-effectiveness claims were also made even though 29% of Khazeni's simulations yielded ICERs above $100,000 per QALY. We would recommend scientific norms be developed for interpreting Monte Carlo simulation output in CEA, whereby notions of inconclusive, weak, moderate, and strong evidence are associated with progressively larger proportions of Monte Carlo simulations surpassing the cost-effectiveness threshold. The probability distributions assigned to each unknown model parameter can have a large impact on the histograms produced by Monte Carlo sampling. Constructing such distributions requires synthesizing knowledge of the historic range of a parameter's value in past pandemics with limited data from the current pandemic. In some cases the distributions may justifiably center around the base case value, while other parameters, such as the CFR, might initially require extremely wide distributions until extensive surveillance data is available. The range of CFR values tested in Khazeni's SA did not include the actual CFR for H1N1 because the baseline exceeded the true value by roughly two orders of magnitude. Consequently, even the lowest mortality scenario greatly overestimated mortality.

The third source of variation in CEA studies comes from differences in CEA protocols - that is, the subjective choices about discount rates, perspectives, time horizons, and methods for determining QALY weights. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has published a comparative table summarizing differences in government guidelines for economic evaluations of health technologies across 33 countries (ISPOR, 2014). While a case could be made for further standardizing CEA guidelines, this may not be a realistic goal; moreover, guideline differences may reflect differing national values and priorities, or differences in the most relevant target audience (for example, governmental vs. healthcare provider vs. insurer).

An alternative to standardizing CEA protocols is to publish enough intermediary information to allow results to be recalculated under other protocols. The following recommendations, largely drawn from Canada's Guidelines for the Economic Evaluation of Health Technologies (Canadian Agency for Drugs and Technology in Health (CADTH), 2006), are likely sufficient to enable such recalculation. First, the main results and SA output should be stated for per capita QALY gains and net costs (Loper et al., 2003; CADTH, 2006), in addition to the ICER ratio. QALY gains should be broken down by length of life and quality of life gains, or ideally by health outcome prevented, before presenting aggregated QALY gains. Although a particular cost perspective may be adopted, costs that fall under broader perspectives should be stated, especially if their impact is under other perspectives is substantial (CADTH, 2006).

Following these practices would provide greater comparability with other studies, and allow readers to select the subset of outcomes or costs relevant to their local CEA practices.

CEA for mass vaccination can provide greater value when ICERs are used to represent the cost-effectiveness of incremental program changes rather than program averages (Loper et al., 2003). The first 30% of vaccines delivered around the pandemic's peak likely had more value than the final 10%. Examining the incremental cost-effectiveness of expanding vaccination coverage in steps of 10% would lead to better assessments of the economic value of different vaccine procurement quantities and coverage targets. For example, if increasing vaccination coverage from 40 to 50% in the middle of the second wave was shown not to be cost-effective, then significant resources could be saved.

The ICER calculated from average population outcomes may also differ from the ICERs for specific groups, based on age and other risk-factors (Prosser et al., 2011). Group-specific analysis is especially appropriate for pandemics, since policies that prioritize vaccine access for certain groups were adopted in many jurisdictions.

CONCLUSIONS

Although all three evaluations of the H1N1 vaccine found public immunization campaigns in Canada and the US to be cost-saving or highly cost-effective, careful review of these studies shows that the programs were not cost-saving once additional expenses and post-pandemic data were incorporated. While it is possible that the campaigns were cost-effective, the extent of the cost-effectiveness was likely overestimated, or was at least a product of particular decisions about which accounting perspective to adopt and which studies to cite for QALY values.

Unless an official estimate of the full cost of administering the vaccination program becomes available, including the fraction of public health agency operating budgets and staff time consumed, it will not be possible to know with certainty whether the H1N1 vaccination program was cost-effective.

Each study modeled the health outcomes of the same pandemic, yet differed substantially in the parameters used, the magnitude of outcomes predicted, the QALY-weighting of those outcomes, and the composition of predicted health gains from vaccination. The potential range for case fatality ratios, hospitalization rates, and usage of healthcare resources is exceptionally wide due to variation between pandemics, and data inadequacy. This variation is symptomatic of a set of more general challenges and diverse approaches in pharmaco-economics. In response to these challenges, SA procedures should be sufficiently wide-ranging, and should report the parameter variation effects on the individual components of cost and QALY gains to facilitate transparent analysis and interpretation. Basing recommendations and risk-assessments off Monte Carlo simulation histograms instead of single “maximum likelihood” ICER estimates will result in more nuanced appraisals that reflect the limitations of our knowledge at the time CEA is conducted. Sufficient intermediary information, such as non-discounted health events averted, and costs from all accounting perspectives, should be provided where possible so that analysis can be replicated or adjusted by readers who operate under different national CEA proto-cols. Providing such information allows comparability between studies and broadens the set of audiences for which a particular CEA study is relevant and useable.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Chris Longo for providing valuable feedback on the manuscript. This work was supported by the Natural Sciences and Engineering Research Council of Canada Discovery Grant (grant number 1359-2008), the Canadian Institutes for Health Research (CIHR), and the CIHR Strategic Training Program in Public Health and the Rural and Agricultural Ecosystem.

Conflict of interest

The authors have no conflicts of interest to declare.

Abbreviations: CDC, Centers for Disease Control and Prevention; **CEA,** cost-effectiveness analysis; **CFR,** case fatality ratio; **ED,** emergency department; **ICER,** incremental cost-effectiveness ratio; **ICU,** intensive care unit; **PCP,** primary care provider; **QALY,** quality-adjusted life year; **SA,** sensitivity analysis.

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