ORIGINAL ARTICLE

Cost effectiveness of infant vaccination for rotavirus in Canada

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INTRODUCTION: Rotavirus is the main cause of gastroenteritis in Canadian children younger than five years of age, resulting in significant morbidity and cost. The present study provides evidence on the cost effectiveness of two alternative rotavirus vaccinations (RotaTeq [Merck Frosst Canada Ltd, Canada] and Rotarix [GlaxoSmithKline, Canada]) available in Canada.

METHODS: Analysis was conducted through a Markov model that followed a cohort of children from birth to five years of age. Analysis used pertinent data on the natural history of rotavirus and the effects of vaccination. Estimates of heath care costs for children requiring hospitalizations and emergency department visits were derived from the Canadian Immunization Monitoring Program, Active (IMPACT) surveillance, emergency department studies, as well as other Canadian studies. The model estimated the effect of vaccination on costs and quality-adjusted life years (QALYs).

RESULTS: The incremental cost per QALY gained from the health care system perspective was $122,000 for RotaTeq and $108,000 for Rotarix. From the societal perspective, both vaccination strategies were dominant – both cost saving and more effective. The cost-effectiveness of vaccination is dependent on the mode of administration, the perspective adopted and the cost of the vaccine.

CONCLUSIONS: From a societal perspective, a universal vaccination program against rotavirus will be both cost saving and more effective than no vaccination. Becasue the majority of rotavirus infections do not require emergency department visits or hospital admission, from a health care system perspective, a program would not be considered cost effective.

Le rapport coût-efficacité de la vaccination des nourrissons contre le rotavirus au Canada

INTRODUCTION : Le rotavirus est la principale cause de gastroentérite chez les enfants canadiens de moins de cinq ans, ce qui s'associe à une morbidité et à des coûts considérables. La présente étude expose des données probantes sur le rapport coût-efficacité de deux vaccins contre le rotavirus (RotaTeq [Merck Frosst Canada Ltée, Canada] et Rotarix [GlaxoSmithKline, Canada]) offerts au Canada.

MÉTHODOLOGIE : Les chercheurs ont effectué l'analyse au moyen d'un modèle de Markov qui consistait à suivre une cohorte d'enfants entre la naissance et cinq ans. L'analyse faisait appel à des données pertinentes sur l'évolution naturelle du rotavirus et sur les effets de la vaccination. Les évaluations des coûts de santé à l'égard des enfants devant être hospitalisés et consulter à l'urgence étaient tirées de la surveillance du Programme canadien de surveillance active de l'immunisation (IMPACT), d'études des départements d'urgence et d'autres études canadiennes. Le modèle a permis d'évaluer l'effet de la vaccination sur les coûts et les années de vie ajustées en fonction de la qualité (AVAQ).

RÉSULTATS : Le coût incrémentiel par AVAQ épargné par le système de santé s'élevait à 122 000 $ à l'aide du vaccin RotaTeq et à 108 000 $ à l'aide du vaccin Rotarix. Sur le plan sociétal, les deux stratégies vaccinales étaient dominantes, c'est-à-dire qu'elles étaient à la fois rentables et plus efficaces. Le rapport coût-efficacité de la vaccination dépend du mode d'administration, de la perspective adoptée et du coût du vaccin.

CONCLUSIONS : Sur le plan sociétal, un programme de vaccination universel contre le rotavirus sera à la fois rentable et plus efficace que l'absence de vaccination. Puisque la majorité des infections à rotavirus n'exigent pas de consultation à l'urgence ou d'hospitalisation, le programme ne serait pas rentable pour le système de santé.

Key Words: *Cost effectiveness; Rotavirus; Vaccination*

Rotavirus is the main cause of gastroenteritis in children (1). It is estimated to be responsible for approximately 570,000 deaths worldwide each year (2). Although mortality due to rotavirus is rare in Canada, it remains the most common cause of gastroenteritis among children younger than five years of age and results in significant morbidity and resource utilization (3,4). Estimates of the percentage of children infected with rotavirus by five years of age range from 35% to 100% (1,5).

Despite the low mortality rate, the economic and societal burden of this common illness in developed countries is estimated to be substantial. A recent study performed in the United States (6) estimated that there were three million cases of rotavirus each year resulting in 213,000 emergency room visits, 67,000 hospitalizations and 30 deaths. Evidence from a recent Canadian study (7) suggested that the societal costs of rotavirus, in terms of both lost productivity and direct costs to parents, are much greater than the associated health care costs.

The Canadian Immunization Monitoring Program, Active (IMPACT) is a national surveillance initiative managed by the Canadian Paediatric Society and conducted by the IMPACT network of pediatric investigators. IMPACT has collected data relating to community-acquired rotavirus infections requiring hospitalization and hospital-acquired infections at 12 pediatric hospitals from January 1, 2005, to December 31, 2007. The data from the IMPACT analysis (8) facilitated the present cost utility analysis.

Two vaccines for prevention of rotavirus gastroenteritis have been licensed in Canada: RotaTeq (Merck Frosst Canada Ltd, Canada) and Rotarix (GlaxoSmithKline, Canada) (9,10). These vaccines have been shown in clinical trials to be efficacious in reducing the incidence of rotavirus infections (11-15). Given the anticipated costs of vaccinating a high proportion of Canadian infants, there is a need to conduct a formal economic evaluation to assess whether government funding for these vaccines is warranted.

METHODS

Study objective

The objective of the present study was to assess the cost effectiveness of rotavirus vaccination of infants in Canada.

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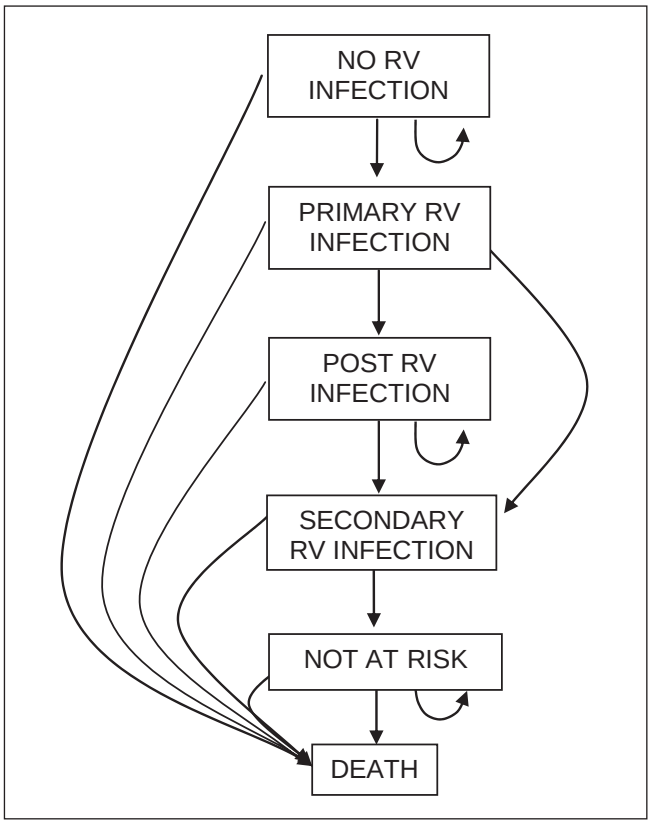

Figure 1) *Schematic of Markov model. RV Rotavirus*

Study perspective

Analysis was conducted from the perspective of both the Canadian health care system and from a societal perspective following guidance documents for health economics studies relating to immunization practices (16,17) and general Canadian guidelines for health economic evaluation (18). The societal perspective includes both the health care system costs as well as costs directly incurred by the patient and caregivers.

Intervention strategies

The analysis compared three strategies with respect to the prevention of rotavirus in children: no vaccination, vaccination with RotaTeq and vaccination with Rotarix.

RotaTeq is a live, attenuated, oral, pentavalent vaccine containing reassortant human bovine-derived rotaviruses. Rotarix contains live, attenuated, monovalent, human rotavirus. A complete series using RotaTeq vaccine consists of three oral doses, and a complete series using Rotarix vaccine consists of two doses.

To minimize the use of additional resources for administration of the vaccine, it would be beneficial to time the vaccine delivery within current vaccination schedules either through well-baby routine visits with a family physician or public health program. All rotavirus vaccinations must be started before 15 weeks of age and be completed by eight months of age. The Rotarix vaccine can be administered at two and four months of age, and the RotaTeq vaccine can be administered at two, four and six months of age. Therefore, vaccination could result in minimal additional health care system costs for administration. Hence, the base analysis was conducted assuming that there would be no additional health care system costs for administration, although additional scenarios are considered in the sensitivity analysis.

Analytical framework

Analysis was conducted through a Markov model that followed a cohort of children from birth to five years of age with a cycle length of one month (19). The model was developed within an Excel (Microsoft Corporation, USA) spreadsheet. Patients enter the model at birth in a state of being at risk of infection with rotavirus and are able to transition through a number of health states over time. The health states within the model include first infection, recovered from first infection, second infection, not at risk and death (Figure 1).

By weighing the proportion of children in each health state each month according to associated costs and quality of life weights, the model enables the calculation of the current economic burden of disease and the costs and quality-adjusted life years (QALYs) associated with each alternate intervention. Data incorporated into the economic model are detailed in Table 1.

In the base analysis, the QALYs were measured focusing only on the quality of life of the children. Within a sensitivity analysis, the quality of life effects of infection on a caregiver were also included.

TABLE 1
Data elements of the economic model

	Base analysis	Source, reference
Monthly probability of primary RV infection	0.0299	23
Relative risk reduction for secondary infection versus primary infection	0.93	26
Probability of death from RV per case of RV	0.00001	6,27
Monthly probability of death from other causes		21
Age <1 year	4.36×10^{-4}	
Age ≥1 to <2 years	2.93×10^{-5}	
Age ≥2 to <3 years	1.72×10^{-5}	
Age ≥3 to <4 years	1.50×10^{-5}	
Age ≥4 to <5 years	1.33×10^{-5}	
Distribution of RV infections without vaccination, %		24,25
Not requiring medical management	80.70	
General practitioner visit	13.60	
Emergency department visit	3.20	
Hospitalization	2.50	
Vaccine efficacy: RotaTeq*, %		12
All RV infections	74	
Hospitalizations	96	
Emergency department visit	94	
General practitioner visit	86	
Vaccine efficacy: Rotarix†, %		11,13-15
All RV infections	76	
Hospitalizations	96	
Emergency department visit	84	
General practioner visit	84	
Vaccine uptake	94	28
Utility values		24
Healthy child	0.986	
Healthy caregiver	0.967	
Child with rotavirus	0.927	
Caregiver of child with rotavirus	0.91	
Vaccine costs per dose, $		30
RotaTeq	69.84	
Rotarix	93.43	
Health care system costs, $		8,32
Hospitalization	3,057.12	
Emergency department visit	367.22	
General practitioner visit	62.65	
Societal costs, $		7,8,32
Hospitalization	3,658.47	
Emergency department visit	537.98	
General practitioner visit	406.50	
No formal visit	373.72	

**RotaTeq, Merck Frosst Canada Ltd, Canada; †Rotarix, GlaxoSmithKline, Canada. RV Rotavirus*

Time horizon and discounting

For the base analysis, outcomes are assessed over the five-year period of the model. In sensitivity analysis, the quality adjusted life expectancy for children alive at five years of age was included to allow consideration of a lifetime horizon (20,21). Costs and benefits were discounted at 5% in the base case analysis and alternative rates of 0% and 3% within a sensitivity analysis (18).

Natural history

The design of the Markov model requires four specific data elements: the monthly probability of primary infection with rotavirus for an unvaccinated child; the relative risk of secondary infection versus primary infection; the monthly probability of death from other causes; and the probability of death due to rotavirus. To identify each of these data elements, an extensive search of the literature was conducted, and wherever possible, data from Canadian sources were incorporated in the model. In cases where Canadian data were not available, probabilities from other countries, which are comparable with Canada, were incorporated.

The monthly rate of primary rotavirus infection was obtained from a reanalysis of data from a study conducted in Winnipeg, Manitoba (22,23). A Canadian study (24) was used to estimate the distribution of primary episodes between family physicians' care, emergency rooms and hospitalizations. In the absence of reliable data regarding the proportion of rotavirus episodes, which do not result in any medical consultation within Canada, United Kingdom study data (25) were extrapolated and applied to the Canadian situation. A sensitivity analysis was conducted where it was assumed a greater proportion of rotavirus episodes require medical consultation.

The transition probabilities of secondary infections are 93% lower than the probabilities of primary infection (26). All secondary infections are assumed to be mild and to not result in medical consultation. The age-specific probability of death from other causes was estimated from Statistics Canada data derived for the Canadian population (21).

Epidemiological data from the United States reported estimates of 20 to 40 rotavirus-related deaths among children younger than five years of age (27). This translates to a death rate of 0.00001 per rotavirus case (6). This estimate is similar to other rates used in previous economic analyses (5).

Effects of vaccination on natural history

Vaccination affects both the probability that a child will be infected with rotavirus and the distribution of rotavirus cases in terms of severity and clinical management.

The efficacy of RotaTeq was examined in a multicentre, double-blind, randomized controlled study involving 69,274 children (12). The reported efficacy of the vaccine against all severities of rotavirus gastroenteritis was 73.8% (95% CI 67.2% to 79.3%). The efficacy of the vaccine in reducing hospitalizations (95.8% rate reduction, 95% CI 90.5% to 98.2%), emergency department visits (93.7%, 95% CI 88.8% to 96.5%) and general practitioner (GP) visits (86.0%, 95% CI 73.9% to 92.5%) were also obtained from the clinical trial.

Three multicentre, double-blind trials centred in Europe, Finland and Latin America examined the efficacy of Rotarix (11,13-15). A meta-analysis of the three trials was conducted and estimated a combined efficacy rate of 76.3% (95% CI 47.8% to 89.2%). The European trial reported the efficacy of the vaccine in reducing hospitalizations (96.0%, 95% CI 83.8% to 99.5%) and other medical attention (83.8% 95% CI 76.8% to 88.9%), which was applied to emergency room and GP visits in the model.

In the base-case scenario, it was assumed that 94% of children would be fully immunized. This was based on vaccine coverage rates in Canada for vaccines given on a similar schedule (eg, Diphtheria, pertussis and tetanus) which is 94% (28). This assumption is tested within the sensitivity analysis using rates of 70% and 100% as well as allowing for the proportion of infants who will receive only partial coverage.

Quality of life

Analysis required an estimate of a utility value with and without rotavirus. For the present report, data from a recently published study by Brisson et al (24) was used. The Brisson et al study was a substudy of the MIRAGE study, a prospective, multicentre, observational study of children with gastroenteritis. Utility values were obtained for 182 rotavirus-infected children and their patients using the HUI2 and EQ-5D questionnaires, respectively.

Costs

The cost of RotaTeq was based on the Canadian list price sourced from the Ontario Drug Benefit Formulary ($58.19), plus the associated 8% pharmacy mark up and $7.00 dispensing fee (29). This leads to a cost of $69.84 per dose, corresponding to $209.52 over the course of treatment. The cost of Rotarix ($78.57) to private payers was obtained directly from the pharmaceutical company (Nigel Rawson, Glaxo Smith Kline, personal communication). This leads to a cost of $93.43 per dose, including pharmacy costs, corresponding to $186.86 over the course of treatment. In sensitivity analysis, the costs of vaccinations were reduced by 30%, 50% and 70% to allow consideration of the potential discounts in costs should universal vaccination strategies be implemented.

Costs associated with rotavirus infections were derived from either the IMPACT study (8) or from a recent Canadian rotavirus costing study by Jacobs et al (7). Both studies involved calculation of the costs of health care resources associated with rotavirus infection. Societal costs were derived as the summation of health care associated costs and costs to patients and caregivers. The Jacobs et al study (7) provided estimates of the costs to families from prescription medications, transportation, lost work and other out of pocket expenses obtained through a survey of 421 parents of rotavirus patients in the Toronto and Peel (Ontario) regions. All costs were adjusted to 2009 values using the Bank of Canada inflation calculator (30).

Analysis

The analysis presented the total costs and QALYs associated with each of the three separate interventions on a per child basis and the associated incremental cost per QALY gained with vaccination.

Sensitivity analysis

A range of sensitivity analyses were conducted relating to model structure, natural history, effects of vaccination, utility values and costs. Specific analyses of note were related to assuming a higher proportion of rotavirus infections require medical management, alternative methods of managing and financing vaccine administration and the impact of partial coverage.

There is evidence that rotavirus is poorly diagnosed (31). The Canadian Emergency Department IMPACT study (children who were seen due to acute gastroenteritis) demonstrated that one-third of stool samples from symptomatic children that were negative by antigen testing and electron microscopy locally were positive by molecular testing (32). This suggests that routine diagnostic testing, even at paediatric centres, underestimates infection by as much as one-third. Thus, a sensitivity analysis was conducted where it was assumed that the proportion of rotavirus infections potentially requiring medical management was increased by 33%.

In the base analysis, it was assumed that vaccination would be conducted through an existing family physician or public health programs with no additional costs to the system other than the cost of the vaccine. Sensitivity analysis assumed additional scenarios. First, analysis assumed that vaccination would be conducted within current vaccination programs but there would be small increases in costs due to the incremental work involved ($4.10 for family physician vaccination [33] and $3.80 for public health administration [34]). Second, it was assumed that vaccination would be given as an additional visit rather than as part of routine care ($9 or $32.35 for family physician vaccination [32] and $25.05 for public health administration [35]).

For assessing the impact of partial coverage, data from British Columbia relating to the percentage of children commencing rotavirus

TABLE 2
Costs and quality-adjusted life years (QALYs) associated with rotavirus vaccination strategies

	Vaccination		
	None	with RotaTeq*	with Rotarix†
Costs			
Health care system perspective	$69.29	$206.85	$199.41
Societal perspective	$351.89	$321.99	$304.28
QALYs	4.352	4.353	4.353
Incremental cost per QALY gained versus no vaccination			
Health care system perspective		$122,000	$108,000
Societal perspective		Dominant	Dominant
Incremental cost per per QALY gained versus vaccination with RotaTeq			
Health care system perspective			Dominant
Societal perspective			Dominant

**RotaTeq, Merck Frosst Canada Ltd, Canada; †Rotarix, GlaxoSmithKline, Canada*

vaccination (93.2%) and the percentage that completed all doses of RotaTeq (68.9%) and Rotarix (86.4%), were used (Monika Naus, personal communication).

In addition to the univariate sensitivity analysis, probabilistic sensitivity analysis was conducted using a Monte Carlo simulation (36). For the Monte Carlo simulation, probability distributions related to transition probabilities, relative risks, cost and utilities were incorporated into the analysis. Estimates of incremental costs and QALYs were obtained by rerunning the model using values from the related probability distributions. In the present study, 5000 replications were conducted (ie, a set of 5000 outcome estimates was obtained). Cost-effectiveness acceptability curves (CEACs) were derived, which present the probability that vaccination is optimal given different values of willingness to pay for an additional QALY (36).

RESULTS

Base analysis

Assuming a birth cohort of 354,617, up to five years of age without vaccination, there would be 302,746 cases of rotavirus. The majority (247,900, 81.9%) will not require medical management: 38,809 will require only a GP consultation; 8981 will require an emergency deparment visit; and there will be 7056 hospitalizations, with 2.8 deaths from rotavirus in each birth cohort. A vaccination strategy using RotaTeq will lead to fewer overall rotavirus infections (125,000), resultign in fewer cases requiring GP consultations (10,900), emergency deparment visits (1400) and hospitalizations (900). Vaccination with Rotarix would lead to fewer overall infections than RotaTeq (112,700) but with higher numbers of cases requiring GP consultations (15,900) or hospitalizations (2800). Both vaccination strategies would lead to approximately two fewer rotavirus-related deaths.

From a health care system perspective, assuming no additional costs associated with administration, the cost of implementing a rotavirus vaccination program with either RotaTeq ($207 per individual birth) or Rotarix ($199 per individual birth) in Canada is substantially higher than the costs associated with no vaccination program ($69 per individual birth) (Table 2).

Vaccination results in slightly greater QALYs compared with no vaccination, with a gain of 0.001 per individual live birth for both vaccines. The incremental cost per QALY gained for RotaTeq versus no vaccination was $122,000, and for Rotarix versus no vaccination was $108,000 (Table 2). Rotarix is dominant over RotaTeq because it is slightly less expensive, primarily due to lower vaccine costs (fewer doses) and equal effectiveness.

The results of the analysis were different when conducted from the societal perspective. The costs associated with both vaccination strategies were lower than no vaccination if administration occurred without any additional costs ($322 for RotaTeq and $304 for Rotarix versus $352 for no vaccination). Thus, in these scenarios, vaccination is dominant (ie, clearly cost effective) over no vaccination because it is both less costly and more effective. Rotarix remains dominant over RotaTeq from the societal perspective.

TABLE 3
Sensitivity analysis: Health care system perspective

	Incremental cost per QALY		
Scenario	RotaTeq* vs no vaccination	Rotarix† vs no vaccination	Rotarix vs RotaTeq
Base case	$122,000	$108,000	Dominant
Discount rate of 3%	$115,000	$102,000	Dominant
Discount rate of 0%	$105,000	$94,000	Dominant
Life time horizon	$115,000	$102,000	Dominant
70% of children have primary infection by 5 years of age	$146,000	$27,000	Dominant
95% of children have primary infection by 5 years of age	$98,000	$93,000	Dominant
33% increase in cases requiring medical management	$104,000	$100,000	Dominant
Death rate of 1 per 50,000 RV cases	$120,000	$107,000	Dominant
Zero death rate in RV cases	$123,000	$109,000	Dominant
50% reduction in costs of hospitalized RV with vaccination	$119,000	$99,000	Dominant
70% uptake of the vaccine	$122,000	$108,000	Dominant
100% uptake of the vaccine	$122,000	$108,000	Dominant
Include disutility of caregiver	$62,000	$55,000	Dominant
Disutility from RV lasts 7 days	$241,000	$213,000	Dominant
Allowance for proportion not fully vaccinated	$143,000	$109,000	Dominant
30% reduction in cost of vaccine	$75,000	$67,000	Dominant
50% reduction in cost of vaccine	$43,000	$41,000	Dominant
70% reduction in cost of vaccine	$12,000	$14,000	$38,000

**RotaTeq, Merck Frosst Canada Ltd, Canada; †Rotarix, GlaxoSmithKline, Canada. RV Rotavirus; QALY Quality-adjusted life year; vs Versus*

Univariate sensitivity analysis

Table 3 presents the results of the detailed univariate sensitivity analysis conducted from the health care system perspective. For the same sensitivity analyses from the societal perspective there were no changes in the results, and vaccination strategies dominated no vaccination for all scenarios explored.

The interpretation of the results was insensitive to assumptions concerning discount rates, the time horizon, death rates from rotavirus and the uptake of the vaccine.

Analysis was sensitive to the assumptions relating to the proportion of rotavirus episodes that required medical consultation. Assuming an increase of one-third in the cases requiring medical management led to lower incremental cost per QALY from the health care system perspective, although none were lower than $40,000 to $60,000, which are considered typical threshold levels for the value of a QALY (37).

Inclusion of the disutility of rotavirus to caregivers leads to a lower incremental cost per QALY gained, approximately $60,000 for both RotaTeq and Rotarix. However, reducing the duration of the disutility to children from rotavirus significantly increases the incremental cost per QALY gained from the health care system perspective, although from the societal perspective, vaccination was still dominant.

Assuming only modest additional costs to current family physician or public health administration does not significantly increase the cost-effectiveness ratios from the health care system perspective, and

TABLE 4
Scenario analysis relating to costs of vaccine administration

	Incremental cost per quality-adjusted life year			
	Health care system perspective		Societal perspective	
Scenario	RotaTeq* versus no vaccination	Rotarix† versus no vaccination	RotaTeq versus no vaccination	Rotarix versus no vaccination
Base-case	$122,000	$108,000	Dominant	Dominant
Family physician administration				
Additional fee for vaccine ($4.10 per dose)	$132,000	$114,000	Dominant	Dominant
Additional visit for vaccine ($9 per dose)	$144,000	$122,000	Dominant	Dominant
Additional consultation for vaccine ($32.35 per dose)	$203,000	$159,000	$54,000	$11,000
Public health administration				
Incremental cost of additional vaccine ($13.89 per dose)	$131,000	$114,000	Dominant	Dominant
Incremental cost of additional visit for vaccine ($25.05 per dose)	$184,000	$143,000	$36,000	Dominant

**RotaTeq, Merck Frosst Canada Ltd, Canada; †Rotarix, GlaxoSmithKline, Canada*

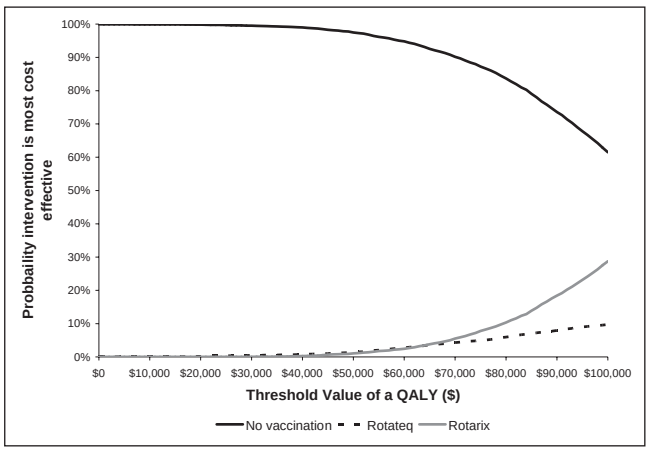

Figure 2) *Cost-effectiveness acceptability curve for the health care system perspective. QALY Quality-adjusted life year. RotaTeq, Merck Frosst Canada Ltd, Canada; Rotarix, GlaxoSmithKline, Canada*

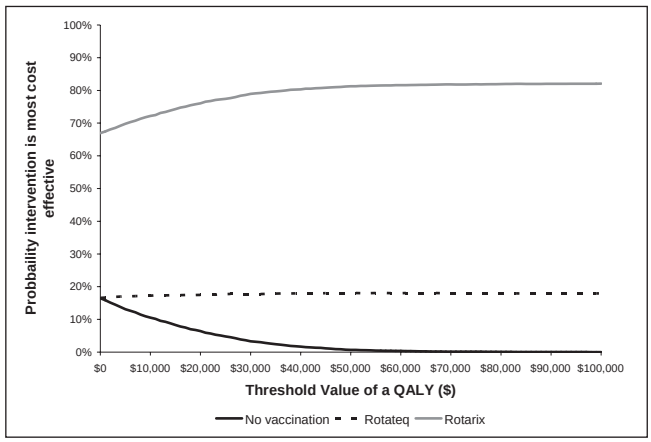

Figure 3) *Cost-effectiveness acceptability curve for the societal perspective. QALY Quality-adjusted life year. RotaTeq, Merck Frosst Canada Ltd, Canada; Rotarix, GlaxoSmithKline, Canada*

vaccination remains cost effective from the societal perspective (Table 4). Assuming additional visits and consultations does, in some situations, lead to vaccination being more costly than no vaccination from the societal perspective, although the incremental cost per QALY gained remained less than $60,000 in all scenarios.

Analysis was sensitive to assumptions relating to the proportion of children who do not receive all the required doses of the vaccine, with higher incremental cost-effectiveness ratios from the health care system perspective. From the societal perspective, the incremental cost per QALY gained for RotaTeq versus no vaccination was $26,000, while Rotarix remained dominant over both no vaccination and RotaTeq.

Results are very sensitive to reductions in vaccine costs, with vaccination becoming cost-effective if the costs were reduced substantially. If vaccine costs were reduced by 50%, incremental cost per QALY gained versus no vaccination would be $43,000 for RotaTeq and $41,000 for Rotarix. Under all scenarios, Rotarix remained cost-effective compared with RotaTeq. The cost of the vaccine where the program would become cost saving (dominant) was $31.42 (a reduction of 46%) for RotaTeq and $44.79 (a reduction of 43%) for Rotarix.

Probabilistic sensitivity analysis

The CEAC represents the probability that an intervention will be cost-effective at alternative values placed on a QALY. The CEAC based on the health care system perspective (Figure 2) highlights the limited likelihood of vaccination being cost-effective from this perspective. The probability that either vaccination is cost-effective when a QALY is worth $50,000 was 2.5% (1.4% for RotaTeq versus 1.1% for Rotarix) when vaccine was administered with no additional cost. However, from the societal perspective, the probability that either vaccination is cost effective when a QALY was worth $50,000 was greater than 99% (18% for RotaTeq versus 81% for Rotarix) when vaccine is administered with no additional cost (Figure 3).

DISCUSSION

Our results suggest that from a societal perspective, the economic burden of rotavirus is large ($125 million over five years for each birth cohort) and that vaccination against rotavirus would be both cost saving and more effective if administered without additional costs either through public health delivery or through family practice within existing immunization programs.

The cost effectiveness of rotavirus vaccination is sensitive to both the perspective adopted and whether additional administrative costs for vaccination will be required. There is a lack of consensus in the economic literature regarding the appropriateness of including societal costs in health care decision making, primarily due to concerns over the accuracy and applicability of estimates of lost productivity. Analyses from the health care perspective reach a much different conclusion. The incremental costs per QALY gained for vaccination would not be considered cost effective under standard decision criteria, where a ratio of between $40,000 and $60,000 is considered to be typical threshold level (37). However, inclusion of the impact of rotavirus infection on parents' quality of life led to vaccination being on the margins of being cost effective from the health care system perspective. Furthermore, in many instances, the high societal costs of disease are the specific justification for the introduction of vaccination programs. Thus, analysis from the societal perspective may best represent society's preferences with respect to the implementation of vaccination programs (16,17). However, the funding decision for a

universal immunization program must consider the other health care programs that would not be funded, given the limited resources available. Thus, if decision makers were solely concerned with health care system resources, the case for funding a universal vaccination program would not be strong. However, the analysis may have underestimated the health care costs associated with rotavirus vaccination because other developed and developing countries have noted dramatic decreases in health care resources for diarrheal illnesses following the introduction of routine infant rotavirus immunization (38,39).

Analysis was sensitive to assumptions relating to the costs of vaccine administration. If it is assumed that vaccination could be given either during a regular visit to the family physician or through existing public health vaccination clinics, assuming no additional costs in either setting, vaccination would be cost saving from the societal perspective. However, if vaccine administration requires additional fees resulting from physician consultations or additional costs to the public health system, it may be more costly, although it appears to remain cost effective from the societal perspective.

Results are very sensitive to the cost of the vaccine. Assuming the full cost of vaccines found vaccination to be cost effective only from the societal perspective. However, a reduction in vaccine costs of 46% for RotaTeq and 43% for Rotarix would lead to both therapies being cost effective from both the health care system and societal perspectives.

There have been a number of previous analyses examining the cost effectiveness of universal childhood vaccination against rotavirus in different countries (5). These studies have come to divergent conclusions. In all studies, results appeared particularly sensitive to the perspective adopted (ie, whether costs from the societal perspective were included) and to the costs of administration (ie, how the vaccine was delivered), both similar findings to the present analysis.

Our study has several limitations relating to both the natural history of rotavirus infection and the associated costs and quality of life effects. Our analysis does not include the effects of rotavirus in patients older that five years of age, although the number of clinically significant infections beyond five years of age will be limited and the benefits and costs savings will be heavily discounted.

Analysis assumed there would be no herd immunity arising as a result of vaccination, even though the impact of assumptions relating to herd immunity had little impact on cost effectiveness in a previous analysis based on publicly funded vaccination and was argued to be unnecessary to include (40). Despite this limitation, it is possible that herd immunity may be a significant contributor to the decrease in rotavirus cases in areas where vaccine uptake is not complete, especially in areas where vaccination is not publicly funded (41).

There were limited data on the proportion of rotavirus infections that required medical care, with evidence of underdiagnosis of cases receiving medical management. However, if the rate of episodes that require medical management was greater than assumed by one-third (given the potential underdiagnosis), then vaccination would still not be cost effective strictly from the health care system perspective.

Analysis found that Rotarix was likely to be more cost effective than the use of RotaTeq because it was estimated to lead to less costs and similar QALYs. While two doses of Rotarix is considered complete, there are not formal data available on the efficacy of two doses of RotaTeq. Given parental concern over the number of vaccines delivered to infants (42) and the significant reduction of cost effectiveness when vaccination with RotaTeq is not complete, a vaccination program that requires only two doses compared with three doses and that is more cost-effective may be appealing if equivalent safety data are present.

Our analysis assumed that the costs of hospitalized cases would be the same for vaccinated and unvaccinated cases. Non-Canadian studies conducted more than 10 years ago, using a rotavirus vaccine that is no longer available, suggested that the costs of hospitalization for rotavirus infection of vaccinated children were lower than for unvaccinated children (43,44). However, results of an additional sensitivity analysis assuming that the costs of hospitalizations for rotavirus were 50% lower for vaccinated children were essentially no different than the base analysis.

A major concern that has not been addressed in any previous economic analysis is the cost of prevention of hospital-acquired rotavirus infections. The IMPACT data estimates that up to one-quarter of children who are in hospital with rotavirus infections represent hospital-acquired cases, likely acquired from children admitted to hospital for community-acquired rotavirus infections (45). Our analysis does not incorporate the costs associated with hospital-acquired infections. The costs of hospital-acquired infection would be higher than the general cost of rotavirus infection, with evidence of significant increased length of stay due to health care-associated rotavirus infection (46). The proportion of rotavirus episodes that involve hospitalization in Canada is low. Thus, the proportion of all rotavirus cases (ie, including those not requiring medical management) that are nosocomial infections that are a subset of these cases will be even lower. Thus, inclusion of nosocomial infections would reduce the incremental costs associated with vaccination but is likely to make only a modest difference in the cost effectiveness of vaccination.

Analysis was based on the efficacies found within the existing clinical trials, which were conditional on the distribution of circulating virus strains at the time the trials were performed. Should the distribution of the strains shift, it would change the cost effectiveness of vaccination, although the direction of this change is unknown.

Finally, our analysis adopted a similar death rate from rotavirus infections as adopted in a previous study performed in the United States (47). This produced an estimated number of deaths per birth cohort from rotavirus infection of three. This was much higher than suggested by reports of deaths. However, the number of deaths due to rotavirus infection may be an underestimate due to the lack of routine testing and the nonreportable nature of the infection. Sensitivity analysis confirmed that the death rate had no significant effect on the results of the analysis given its rarity.

Although there were a number of data limitations, the extensive sensitivity analysis found that none were likely to undermine the results of our analysis. From a health care system perspective alone, a universal vaccination program against rotavirus would not be considered cost effective. However, based on the current evidence, from a societal perspective, a universal vaccination program against rotavirus would be both cost-saving and more effective than no vaccination, assuming there were limited additional costs of administration.

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