Budget Impact and Cost-Effectiveness of Including a Pentavalent Rotavirus Vaccine in the New Zealand Childhood Immunization Schedule

Richard J. Milne, PhD,1 Keith Grimwood, MD, FRACP2

1School of Population Health, University of Auckland, Auckland, New Zealand; 2Queensland Paediatric Infectious Disease Laboratory, Queensland Children’s Medical Research Institute, Royal Children’s Hospital, Discipline of Paediatrics and Child Health, University of Queensland, Brisbane, Australia

ABSTRACT

Objectives: To estimate: 1) rotavirus disease burden in New Zealand children aged under 5 years, and 2) health benefits, budget impact, and cost-effectiveness of incorporating a pentavalent rotavirus vaccine (PRV) into the national immunization schedule.

Methods: A static equilibrium model was developed to evaluate health benefits and budget impact of vaccinating five successive birth cohorts with PRV at $50 per dose and 85% coverage (three doses). Cost-effectiveness was estimated from the societal perspective in year 5 of the program, with future health benefits discounted at 3.5% per annum.

Results: By the age of 5 years, one in five children will have sought medical advice for rotavirus gastroenteritis and one in 43 will have been hospitalized. In 2009, we estimate 1506 hospitalizations (476 per 100,000; 95% confidence interval 451, 502), 3086 Emergency Department (ED) presentations not requiring hospitalization, plus 10,120 cases of rotavirus gastroenteritis managed solely in primary care. The annual societal cost is $7.07 million, including 41% from hospitalization and 25% from caregiver income loss. Health benefits will increase and the cost of illness will decline by 78% in year 5 as successive birth cohorts are immunized. In the fifth year, 1191 hospitalizations, 2442 ED treated cases, 9762 primary care consultations, and 0.8 deaths will be averted. It requires six vaccinated children to avoid one primary care consultation, 49 to avert one hospitalization, and 73,357 to prevent one death. The incremental cost is $2.99 million and the break-even price per vaccine dose is $32.39 at 2006 prices. The cost is $2509 to avert one hospitalization and $305 to prevent one case seeking health-care assistance. The cost per life-year gained in year 5 is $143,097 and the cost per quality-adjusted life-year (QALY) gained is $46,092 (US$26,774). The cost per QALY is sensitive to incidence rates, vaccine price and efficacy, loss of quality of life by the child, case fatality, and caregiver income loss.

Conclusions: From a societal perspective, addition of PRV to the New Zealand childhood immunization schedule would confer important clinical gains at a modest cost per QALY gained.

Keywords: cost-effectiveness, gastroenteritis, immunization, rotavirus, vaccine.

Introduction

Rotaviruses are the most common cause of severe gastroenteritis in infants and young children worldwide. Virtually all children are infected by the age of 5 years. Annually, rotaviruses cause 114 million episodes of diarrhea, 25 million clinic visits, 2.4 million hospital admissions, and more than 500,000 deaths in children up to age 5 years [1,2]. Although most deaths are in developing countries, every year, more than 220,000 children living in industrialized countries are hospitalized because of rotavirus gastroenteritis [1,3]. This includes 60,000 children hospitalized in the United States [4], 87,000 in the European Union [5], and 10,000 in Australia [6]. Within these industrialized countries, for every 10 children admitted to hospital with rotavirus gastroenteritis, between 6 and 20 are treated and discharged from the Emergency Department (ED) [7,8] and 50 to 100 are managed solely in primary health care [3,7,8]. Furthermore, in countries with temperate climates, rotavirus epidemics every winter and spring coincide with peak respiratory virus activity, placing further pressure on health-care facilities, including hospitals where elective surgery may be canceled and overcrowding increases the risk of nosocomial infections [9]. The annual health and society-related costs in the United States from rotavirus gastroenteritis is estimated at $US1 billion dollars [10], in the European Union, the cost is €550 million [11] and, in Australia, direct medical costs are estimated at $26 million [7].

Although improvements in sanitation, personal hygiene, food, and water quality have resulted in substantial health benefits, rates of rotavirus disease remain substantially the same in both industrialized and developing countries [1,10]. Consequently, rotavirus vaccines are seen as the only public health intervention capable of controlling rotavirus disease. Two licensed oral vaccines have recently shown 85% to 96% efficacy against severe rotavirus gastroenteritis leading to hospitalization or ED attendance in trials conducted in Europe and the Americas [12,13]. One vaccine contains RIX4414, a single live attenuated human P1A [8] G1 strain (Rotarix; GlaxoSmithKline, Rixensart, Belgium). The other is a live naturally attenuated pentavalent bovine-human reassortant vaccine containing the four most common human G serotypes (G1-G4) and the most common human P serotype (P1A [8]) worldwide (pentavalent rotavirus vaccine [PRV] or RotaTeq; Merck and Co, Whitehorse Station, NJ). Although the two vaccines differ in their strain composition, both seem to provide protection against a variety of strains, including those not included in the vaccine. Moreover, the vaccines are well tolerated and do not appear to be associated with intussusception, a rare complication found previously in recipients of RotaShield, the first ever licensed rotavirus vaccine [12–14]. Rotavirus vaccines are now licensed in more than 100 countries and they have been incorporated into the national childhood immunization programs of 10 countries from Europe and Latin America, the United States, and Australia.

Address correspondence to: Richard J. Milne, School of Population Health, Tamaki Campus, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail: richard.milne@hoa.co.nz

10.1111/j.1524-4733.2009.00534.x
As other countries decide upon introducing rotavirus vaccines into their immunization programs, many will undertake an economic evaluation of these vaccines. This is because of large differences in hospitalization incidence rates and costs between countries, including even neighboring regions [1,8,15]. Such variations may result from differences in primary care access, referral patterns, disease management, hospital admission policies, unit costs, and accuracy of diagnostic coding practices.

Because the annual cost of rotavirus gastroenteritis in New Zealand and the impact of immunization are unknown, the present study estimates the current burden of rotavirus gastroenteritis in New Zealand and the annual health benefits, budget impact, and cost-effectiveness of including PRV in the national childhood immunization schedule. A catch-up program was not included as there are insufficient safety and efficacy data in infants older than 32 weeks of age to allow authorities to make such a recommendation.

The primary measures of cost-effectiveness are the cost per life-year gained and the cost per quality-adjusted life-year (QALY) gained in year 5 of a 5-year universal vaccination program for successive birth cohorts. At this stage, incidence rates will have stabilized at a new level because there are few cases of serious rotavirus gastroenteritis in children older than 5 years of age [16]. Secondary measures are the cost per case averted and the cost per hospital admission averted. The analysis takes into account consecutively the societal, health-care (Government plus patient) and Government (Ministry of Health and Pharmaceutical Management Agency [PHARMAC]) perspectives.

**Methods**

**Disease Burden**

National public hospital discharge data from the New Zealand Health Information Service (NZHIS) between July 1, 2003 and June 30, 2006 were reviewed to identify children less than 3 years of age with a primary diagnosis of acute gastroenteritis as categorized by the International Classification of Diseases, 10th revision, Australian modification (ICD-10-AM), codes A00-A09 and K52.9 for infectious diarrhea of known and unknown origins. There were 10,382 admissions including 391 readmissions (3.8%) within 7 days. The latter were excluded from incidence calculations, but included in cost burden estimates, because these readmissions will most likely have resulted from ongoing complications from the original illness or nosocomial acquisition of another enteric agent while in the hospital. Mortality from acute gastroenteritis in the period 2002 to 2003 was also obtained from NZHIS [17].

Incidence rates for rotavirus gastroenteritis in children less than 3 years of age were estimated by applying age and season-adjusted proportions of rotavirus [18] to national hospitalization rates for acute gastroenteritis. As rotavirus proportions were unavailable for New Zealand children more than 3 years of age, the proportion of severe rotavirus gastroenteritis at 4 and 5 years of age was estimated as the seasonally adjusted mean of that at 2 and 3 years of age, which was stable at 0.45. Because only 14% of admissions for all cases of gastroenteritis in New Zealand children less than 5 years of age occur after 3 years of age, this parameter has a relatively minor impact on the outcome of the analysis (see Results). We also assumed conservatively that the incidence of rotavirus gastroenteritis is zero beyond 5 years of age. The longest and largest study of hospitalized children with gastroenteritis was reported from Melbourne, Australia [19]. In this 13-year study, 97% of rotavirus hospital admissions were in children less than 5 years of age. Cases of acute rotavirus gastroenteritis over the period 2009 to 2019 were then estimated for children less than 5 years of age, based on the birth rate in the period July 2007 to June 2008 (64,140) assumed to be stable for 10 years and adjusted for all-cause mortality as the cohort matures [17].

**Immunization**

Immunization with PRV reduces rotavirus disease, resulting in either an ED presentation or hospital admission by 94% and 96%, respectively, but this degree of efficacy is not achieved until 2 weeks after the final dose is taken at 5 months of age [12]. Nevertheless, the NZHIS national public hospital discharge data showed that, on average, 80% of gastroenteritis admissions during infancy occurred in the second 6 months of life when 85% of children would be fully immunized with PRV if it were taken on schedule at the coverage rate for the recently discontinued oral polio vaccine [20]. Therefore, the two halves of the first year were analyzed separately, with adjustment in the first half of the year for the amount of time during which infants are vaccinated with one, two, or three doses according to the New Zealand immunization schedule.

Because fecal samples are collected infrequently from ED cases that are not admitted to the hospital, and because there is no national database of ED presentations, the incidence of ED presentations of rotavirus gastroenteritis was estimated from rotavirus hospitalizations by applying the ratio of “ED presentations” to “hospitalizations” for intestinal infectious diseases (ICD10 A00 to A09 and K52.9) at Middlemore Hospital in South Auckland (2.05). This ratio is very similar to that for rotavirus gastroenteritis in Australia (2.22) [7] and England and Wales (2.08) [21]. This ratio was varied by ±30% in sensitivity analyses.

Similarly, because the incidence of primary health-care cases of rotavirus gastroenteritis is not available, this was estimated from the mean of the ratio of rotavirus gastroenteritis primary health-care consultations to hospitalizations from British [21] and Australian [7] studies adjusted for referrals to hospital, assuming that 70% of hospital cases are referred by a general practitioner (GP) [22]. The British and Australian ratios (4.2 and 9.3, respectively) were used as limits in sensitivity analysis. The large phase III randomized clinical trial of PRV also reported that “nonurgent” consultations in the placebo group outnumbered admissions sevenfold [12]. The percentage of hospital cases referred by GPs was also varied in sensitivity analysis.

**Budget Impact of PRV Immunization Program**

When a novel vaccine is introduced into the childhood immunization schedule, it remains there for at least 5 years and generally longer. Government decision-makers need to know the budget impact during its introduction and its cost-effectiveness after an introductory period of time has passed, taking into account all associated costs and health benefits. We therefore developed a spreadsheet static equilibrium economic model to show the benefits, costs, budget impact, and cost-effectiveness of vaccinating successive New Zealand birth cohorts for 5 years, commencing in 2010. In the first year, the impact of immunization is limited to the birth cohort, then by year 5, protection extends to most children less than 5 years of age as the cohort ages, assuming that PRV maintains its effectiveness.

Adverse events are not included in the model because combined safety data from 71,799 subjects recruited into the 3 phase III trials showed PRV to be safe and well tolerated [23]. In particular, there is no increased risk of intussusception or clustering of cases after immunization [14,24]. Costs and health benefits were evaluated over a 10-year time horizon. This period was chosen because the incidence rate for severe gastroenteritis is
much lower in children 5 years of age and over and, consequently, the impact of 5 years of vaccination of successive birth cohorts is almost complete after 10 years. Work loss by the caregiver was estimated from UK data in the large randomized clinical trial, Rotavirus Gastroenteritis Epidemiology and Viral Types in Europe Accounting for Losses in Public Health and Society (REVEAL) [22].

Cost-effectiveness

The cost-effectiveness of infant immunization was obtained in year 5 of the program, when the number of cases averted each year is expected to have stabilized. Traditional measures of cost-effectiveness, such as the cost per QALY gained [25], allow comparisons across different health-care programs but are difficult to capture reliably in young children because gastroenteritis, although common and on occasions severe, is a transient illness with low mortality in industrialized countries. Also, the cost per QALY relies heavily on estimates of case fatality and quality of life (health state utility), which are somewhat uncertain. Therefore, secondary economic outcomes were also utilized.

Deaths from acute gastroenteritis are rare in New Zealand children, being no more than one to two per year [26]. In New Zealand, the ratio of admission rates to mortality (a measure of case fatality) for children less than 5 years of age with gastroenteritis in the period 1990 to 2006 (admissions) and 1990 to 2004 (deaths) was 0.00048 [27], which is similar to that for rotavirus gastroenteritis in France (0.000534) [28] and Australia (0.00040) [29] but higher than in England and Wales (0.000020) [30]. We utilized the age-specific case fatality for gastroenteritis in New Zealand [27] and varied it by ±50% in sensitivity analyses. The disutility associated with an episode of gastroenteritis in a child and their caregiver was taken from a recent Canadian study [31]. Based on UK consultation patterns for gastroenteritis, this translates to a QALY loss of 0.00220 per episode for a child and 0.00184 for a caregiver [32]. This parameter was also varied by ±50% in sensitivity analyses. The impact of including disutility for two caregivers was also estimated in a sensitivity analysis for comparison with other studies [29,32].

Life-years gained by universal infant immunization were estimated as deaths averted multiplied by life expectancy from New Zealand life tables (Statistics NZ), discounted to present value at 3.5% per annum. The QALYs gained by universal immunization were obtained by adding the discounted life-years gained to the utility gained by child and caregiver(s) by averting rotavirus admissions, ED presentations, and GP cases. Secondary outcomes were the cost required to avert one GP consultation or hospital admission for rotavirus gastroenteritis in year 5 of the program.

Vaccine Administration and Coverage

If PRV is introduced into the national immunization schedule, it will be made available to each birth cohort where it can be safely administered with other vaccines at 6 weeks, 3 months, and 5 months of age [10,24,33]. Uptake of the first, second, and third doses of PRV is assumed to be the same as that reported by the latest national immunization coverage survey based on uptake of the recently discontinued oral polio vaccine in three doses at the same ages (91%, 89%, and 85%, respectively [20,33]). We assumed that coverage at these levels would be achieved on schedule by each successive birth cohort for 5 years.

Vaccine Efficacy

The phase III PRV efficacy trial reported that rotavirus gastroenteritis of any severity and severe rotavirus disease were reduced by 74% and 98%, respectively [12]. Nonurgent medical visits were reduced by 86%, ED consultations by 93.7%, and hospitalizations for rotavirus gastroenteritis by 95.8%. We assumed protective efficacy of 83%, 81%, and 95% for reducing hospitalizations and ED visits after doses 1, 2, and 3, respectively [24], and proportionally lower efficacy for reducing GP consultations (75%, 73%, and 86%, respectively). Vaccine effectiveness in the first year of life was adjusted for the expected coverage by age, in months.

The Finnish Extension Study involving 20,736 subjects enrolled in the pivotal phase III trial reported that protective efficacy against severe rotavirus disease requiring ED presentation or hospital admission remained at 94% (95% confidence interval [CI] 91, 96) for up to 3.1 years after receiving the third dose, by which time there was a marked reduction in rotavirus cases seeking hospital-based care [34]. In the base-case analysis, we assumed that PRV protective efficacy remains stable for 5 years. In a sensitivity analysis, we investigated the impact of a 5% annual decline in protection in years 3 to 5. It is not necessary to make assumptions about vaccine efficacy beyond 5 years because of the low incident rate for rotavirus gastroenteritis after 5 years of age [19].

Direct Medical Costs

For societal and health-care perspectives, our analysis utilized the mean cost (weighted by the annual numbers of acute gastroenteritis admissions in the corresponding hospitals) of consecutive hospitalizations for children less than 5 years of age with a principal diagnosis of rotavirus gastroenteritis (ICD10 A080) at four of New Zealand’s largest hospitals (Middlemore, Waikato, Wellington, and Christchurch), all of which utilized patient-level costing systems. The weighted mean hospitalization cost across these four centers for 350 admissions (including one admission to an intensive care unit) was $1889 (95% CI $1709, $1990). Mean hospitalization costs to the Government were calculated using diagnosis-related group (DRG) cost weights for 2398 consecutive cases of rotavirus gastroenteritis (ICD10 A080) in the period July 2003 to June 2006 (NZHIS) multiplied by the national price for 2006/2007 ($3151).

Often, children with gastroenteritis presenting to the ED are not admitted to the hospital and few of these have their feaces collected, so the causative agent is usually unknown. We estimated the unit cost from 208 consecutive nonhospitalized ED presentations for children aged less than 5 years with a principal diagnosis of confirmed rotavirus gastroenteritis at Middlemore Hospital (n = 139) and Waikato Hospital (n = 69), weighted by the annual numbers of acute gastroenteritis cases in this age group presenting to the corresponding facility. Costs included ED and pediatric staff and overheads. The weighted mean cost of such presentations was $585 (95% CI $550, $620). Corresponding information was unavailable from other hospitals. Nevertheless, for comparison, Wellington Hospital’s average price was $486 for ED triage level 3 (attendance within 30 minutes, which is the routine triage level for children with acute gastroenteritis). Children who were discharged directly from the ED are prescribed one box containing 10 sachets of oral rehydration solution (pharmaceutical subsidy $2.86 [35]; no copayment).

In the community, PRV is usually administered by practice nurses and it effectively replaces an oral polio vaccine that was withdrawn recently and replaced by an inactivated injectable polio vaccine [33]. Most primary care practices are now capitated. Because PRV is administered during the routine scheduled immunization visits and, as an oral gel, requires minimal additional handling, there is unlikely to be additional cost or
Government reimbursement. For GP consultations other than immunization, the notional charge to the Government at the time of writing is $39.70 per visit for children less than 6 years of age, which includes a practice nurse subsidy [36]. Primary health organizations are discouraged from charging copayments for children less than 6 years of age. Because information was not available and costs are relatively minor, we excluded costs of additional diapers, pharmaceuticals, and laboratory tests, if any.

**Nonmedical Costs by Informal Caregivers**

The marginal cost of travel to the hospital's ED was estimated at $4.00 based on one 20-km return trip at $0.20 per kilometer. For cases that were admitted to the hospital, this cost was doubled because at least two trips are required. GP cases are likely to incur only minor transportation costs, which were set to zero.

**Indirect Costs by Informal Caregivers**

The median age for women giving birth in 2005 was 30 years (Statistics NZ). Based on the median income for female wage and salary earners 30 to 34 years of age of $33,000 per year (Statistics NZ) and 70% workforce participation [37] we estimate the median pretax cost of work loss as $59.36 per person per day, adjusting for weekends and holidays. Because there is no information about work loss associated with caring for children with gastroenteritis in New Zealand, we applied this figure to a study from the Northwest of England showing that 91% of caregivers took a mean of 4.0 days off work during a hospitalization for rotavirus gastroenteritis; 54% of caregivers who were treated in the ED took 2.9 days off work; and 20% of caregivers of children treated by a GP took 7.5 days off work [22]. A study from the United States showed a median of 2 days work loss for caregivers of children with rotavirus gastroenteritis treated at outpatient centers [38]. The loss of income was varied by ±30% in sensitivity analyses.

Because oral PRV would be administered alongside other scheduled infant vaccines, we assumed that no additional time would be lost from immunization. Home care cases that do not come to medical attention were excluded from the analysis because no information is available on costs or incidence rates. This is conservative, because home care cases will contribute to loss of quality of life, caregiver income, and nonmedical costs such as transportation, oral rehydration solutions, additional diapers, and child care changes [39].

**Discount Rate**

For cost-effectiveness analyses in year 5, a 3.5% annual discount rate was applied to future life-years, as this is the rate used by the national Pharmaceutical Management Agency [40]. There are no future costs. The discount rate varied in sensitivity analyses from 0% to 5%. Discounting was not applied to the budget impact analysis because it is intended as a year-by-year projection to guide budgetary planning, not a "net present value" analysis.

Table 1 shows the input parameters for the economic model, and their sources. Ranges for sensitivity analyses of potentially influential variables were set using 95% CIs where available (e.g., efficacy, incidence rate for admissions, cost of an admission) or conservative, plausible limits.

**Results**

**Disease Burden**

The rotavirus health-care disease burden for New Zealand is shown in Table 2 where the estimated cases and incidence rates for rotavirus-associated hospitalization, ED presentations that were not admitted to hospital and cases that were managed solely by GPs for children less than 5 years of age for the 2009 calendar year are presented. Most cases of gastroenteritis occur during winter and spring and in the current study, 83% of cases were captured in this period.

In the baseline year (2009), an estimated 1506 children less than 5 years of age (incidence rate 476 per 100,000, 95% CI: 451, 502) will be admitted to hospital with rotavirus gastroenteritis. There will be an estimated 3086 ED presentations for rotavirus gastroenteritis that are not hospitalized and 10,120 cases managed solely by GPs plus an unknown number of cases that do not reach medical attention. For children less than 3 years of age, the hospital admission rate is 661 (95% CI: 623, 700) per 100,000 (not shown), which is comparable to previous estimates of rotavirus hospitalization rates for New Zealand children in this age group [18]. This agreement illustrates some external validity in methodology.

By the age of 5 years, one in five children will have consulted a medical practitioner for rotavirus gastroenteritis and one in 43 will have been hospitalized. Based on our assumptions, about one-quarter of children less than 5 years of age who consult a GP for acute rotavirus gastroenteritis are referred to hospital and one-third of these are admitted to hospital. The remainder are treated and discharged.

Table 3 illustrates the annual cost of rotavirus gastroenteritis in New Zealand from a societal perspective, excluding cases that do not present to the health-care system ($7.07 million). Two-thirds of the cost is incurred by hospital cases, including ED, and one-quarter is the indirect cost from loss of caregiver income. The estimated annual cost per child under 5 years of age is $22.17.

**Impact of PRV on Disease Burden**

Figure 1 shows the modeled annual health benefits of introducing PRV into the national childhood immunization schedule for a period of 5 years. Immunization of successive birth cohorts against rotavirus becomes increasingly effective as more children develop vaccine-induced protective immunity. The benefits stabilize after year 5 of the program, and then decline if PRV were to be withdrawn (as shown). It should be noted that some patients incur costs at each level of the health-care system (GP, ED, and hospitalization).

In year 5 of the inclusion of PRV in the national child immunization schedule, 1191 hospitalizations, 2442 ED presentations that are not admitted to hospital, and 9762 GP consultations would be averted (Table 4). It would require 49 children to have up to three doses of PRV to prevent one hospitalization, and six children vaccinated to prevent one GP consultation. Because rotavirus gastroenteritis is seldom fatal, it would require vaccination of more than one birth cohort to prevent one death.

**Cost of Rotavirus Gastroenteritis**

**Budget impact of PRV immunization.** Figure 2 demonstrates how the annual burden of illness would change from baseline if PRV were to be introduced into the immunization schedule for 5 years, assuming that 85% coverage (3 doses) is achieved immediately. The burden of rotavirus illness from a societal perspective reduces from $7.07 million to $1.58 million in year 5 of the program, and would gradually increase again if PRV were to be withdrawn. By year 5, immunization would offset $5.5 million (78%) of the cost of rotavirus illness in that year. Including the cost of immunization, the overall cost of illness almost doubles in
year 1, when only children in the birth cohort develop vaccine-induced immunity (Fig. 2). Nevertheless, in subsequent years successively more children are protected, which reduces the annual cost of illness. The budget impact per child would remain stable beyond year 5 if PRV remained on the schedule because the incidence rate is very low after this age and the benefits of immunization therefore are almost fully achieved. In practice, coverage is likely to build up over several years, which will reduce the annual costs and benefits in parallel but have little impact on cost-effectiveness ratios.

If PRV were incorporated into the national childhood immunization schedule, the major cost drivers would be the acquisition cost of the vaccine and the number of hospitalizations averted due to introduction of the universal immunization program. If the annual cost of the program remained constant (assuming constant coverage), the annual cost of rotavirus disease would decline as progressively more children were immunized and it would continue to fall for as long as the protective effectiveness of the vaccine is maintained. Nevertheless, any decrease after 5 years would be small as the incidence of rotavirus gastroenteritis in children over 5 years of age is relatively low.

In the fifth year of immunization, the incremental cost to society is $2.99 (Table 5). The break-even acquisition vaccine unit costs in year 5 are $32.39, $24.40, and $21.82 per dose.
from societal, health-care, and government perspectives, respectively. This cost is highest when a societal perspective is taken because caregiver loss of income and transportation costs is taken into account.

Cost-Effectiveness of PRV Immunization
The cost-effectiveness can be expressed in terms of future costs and cases averted, either hospital admissions or overall. If PRV were included in the childhood immunization schedule for 5 years, health benefits would cumulate for at least 10 years, provided that protection was maintained for 5 years (Fig. 1). In year 5, in the base-case analysis from a societal perspective, the societal cost is $2509 to avert one hospitalization and $305 to avert one GP consultation. Because gastroenteritis is seldom fatal in New Zealand, the cost per death prevented is high.

Because decisions may entail comparing expenditure on other programs with different time frames, in accordance with international practice, future life-years are discounted to the baseline year [25,41]. The cost per life-year gained in year 5 is high ($143,097) because rotavirus illness is seldom fatal in New Zealand (Table 6); however, the cost per QALY gained is modest.

Table 2
Estimated annual cases in 2009 and incidence rates for rotavirus gastroenteritis in New Zealand children under 5 years of age

<table>
<thead>
<tr>
<th>Cases per year</th>
<th>Hospitalizations</th>
<th>ED</th>
<th>GP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>466</td>
<td>956</td>
<td>3,135</td>
<td>4,557</td>
</tr>
<tr>
<td>1–2</td>
<td>549</td>
<td>1,125</td>
<td>2,690</td>
<td>5,364</td>
</tr>
<tr>
<td>2–3</td>
<td>253</td>
<td>519</td>
<td>1,703</td>
<td>2,476</td>
</tr>
<tr>
<td>3–4</td>
<td>143</td>
<td>292</td>
<td>958</td>
<td>1,393</td>
</tr>
<tr>
<td>4–5</td>
<td>94</td>
<td>193</td>
<td>634</td>
<td>922</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>1,506</td>
<td>3,086</td>
<td>10,120</td>
<td>14,712</td>
</tr>
<tr>
<td>5 years risk</td>
<td>1.43</td>
<td>1.21</td>
<td>1.7</td>
<td>1.5</td>
</tr>
</tbody>
</table>

| Based on the acute incident gastroenteritis hospitalizations for July 2003 to June 2006 (NZ Health Information Services) and proportions of rotavirus by age and season.
| Estimated from the ratio of ED presentations (not admitted) to hospitalizations for acute gastroenteritis at Middlemore Hospital (2.05).
| Estimated from the mean of the ratios of GP consultations to hospitalizations in the United Kingdom and Australia (7.21) adjusted for referrals.
| Some totals do not equal the sum of the stated components because of rounding errors.
| ED, Emergency Department; GP, general practitioner; ORT, oral rehydration therapy (Enerlyte).

Table 3
Estimated cost to New Zealand society in 2009 of rotavirus gastroenteritis for children less than 5 years of age, without a program of rotavirus immunization

<table>
<thead>
<tr>
<th>Cost to New Zealand ($M)</th>
<th>Cost per child under 5 years ($)</th>
<th>Cost distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>2.89</td>
<td>9.07</td>
</tr>
<tr>
<td>ED visits, not hospitalized</td>
<td>1.81</td>
<td>5.66</td>
</tr>
<tr>
<td>Caregiver income</td>
<td>1.80</td>
<td>5.64</td>
</tr>
<tr>
<td>GP visits, Government reimbursement</td>
<td>0.53</td>
<td>1.66</td>
</tr>
<tr>
<td>Transportation to hospital</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Subsidy on ORT</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Total</td>
<td>7.07</td>
<td>22.17</td>
</tr>
</tbody>
</table>

*Includes visits managed solely by GPs plus referred cases; patient copayment is zero for preschool children.
ED, Emergency Department; GP, general practitioner; ORT, oral rehydration therapy (Enerlyte).

Table 4
Estimated rotavirus cases in year 5 of inclusion of pentavalent rotavirus vaccine (PRV) in the childhood immunization schedule compared with exclusion

<table>
<thead>
<tr>
<th>No PRV</th>
<th>PRV</th>
<th>Events averted</th>
<th>NNV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>1,506</td>
<td>314</td>
<td>1,191</td>
</tr>
<tr>
<td>ED presentations</td>
<td>3,086</td>
<td>644</td>
<td>2,442</td>
</tr>
<tr>
<td>GP consultations</td>
<td>13,335</td>
<td>3,543</td>
<td>9,792</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.0</td>
<td>0.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Assumes 84.6% uptake (three doses); no discounting.
Includes 2343 cases referred by a GP to hospital.
ED, Emergency Department; GP, general practitioner; NNV, number of children needing to be vaccinated each year to prevent a single health-care encounter of the type specified.
at $46,092 (US$26,774). The cost-effectiveness ratios are lower (more favorable) from a societal perspective than a health-care or government perspective because of the influence of caregiver work loss. These ratios will improve slightly (i.e., decrease) in subsequent years as the birth cohorts mature, provided protection is maintained. Nevertheless, any improvement is probably modest because the incidence of severe rotavirus gastroenteritis is very low in school-age children.

Uncertainty

The cost per QAL Y varies from base case over the range –36% to +39% with realistic changes in input variables, assuming utility loss for just one caregiver. The strongest determinants of variability are: the rates of hospital admissions, GP consultations, and ED presentations; caregiver income loss per case; vaccine unit price; efficacy; case fatality; and the transient loss of quality of life by the child and caregiver (Fig. 3). It is relatively robust to uncertainty in other parameters including immunization coverage and costs other than vaccine acquisition. When the disutility of a second caregiver is taken into consideration, the cost per QAL Y is reduced by 45%.

Ideally, probabilistic sensitivity analysis could be used to examine the impact of stochastic uncertainty. Nevertheless, because neither CIs nor distributions are available for many of the key parameters, the findings could be misleading. In particular, the findings are sensitive to the transient disutility due to rotavirus, which has been reported in only one study to our knowledge, and case fatality, which is imprecise because deaths from rotavirus gastroenteritis are rare in New Zealand. Nevertheless, when the eight key parameters listed above are set at their extreme values simultaneously (see Table 1), the incremental cost-utility ratio (ICUR) ranges from –$9,755 (dominant) to +$251,542, indicating that research is required to determine some of the variables more precisely.

Discussion

This study demonstrates that incorporating PRV into New Zealand’s immunization schedule for 5 years confers cumulative health benefits, accompanied by up to 80% decline in the cost of rotavirus illness as progressively more children are immunized. If PRV were to remain on the schedule beyond year 5, annual

### Table 5  Estimated budget impact in year 5 of an immunization program with a pentavalent rotavirus vaccine (PRV)*

<table>
<thead>
<tr>
<th></th>
<th>No PRV ($M)</th>
<th>PRV ($M)</th>
<th>Incr. cost ($M)</th>
<th>Break-even PRV price per dose ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost to society</td>
<td>7.07</td>
<td>10.06</td>
<td>2.99</td>
<td>32.39</td>
</tr>
<tr>
<td>Cost to health care†</td>
<td>5.27</td>
<td>9.62</td>
<td>4.35</td>
<td>24.40</td>
</tr>
<tr>
<td>Cost to government‡</td>
<td>4.72</td>
<td>9.50</td>
<td>4.78</td>
<td>21.82</td>
</tr>
</tbody>
</table>

*All costs are undiscounted because they are incurred in the same year.
†Ministry of Health, PHARMAC, and direct caregiver costs including hospitalizations, ED visits, GP visits, and the standard subsidy for oral rehydration therapy.
‡Ministry of Health and PHARMAC only.

### Table 6  Cost-effectiveness in year 5 of including a pentavalent rotavirus vaccine in the childhood immunization schedule

<table>
<thead>
<tr>
<th></th>
<th>Cost per admission averted</th>
<th>Cost per case averted</th>
<th>Cost per death averted</th>
<th>Cost per life-year gained*</th>
<th>Cost per QAL gained*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost to society</td>
<td>$2,509</td>
<td>$305</td>
<td>$3,756,803</td>
<td>$143,097</td>
<td>$46,092</td>
</tr>
<tr>
<td>Cost to health care†</td>
<td>$3,648</td>
<td>$444</td>
<td>$5,461,436</td>
<td>$208,027</td>
<td>$67,007</td>
</tr>
<tr>
<td>Cost to Government‡</td>
<td>$4,015</td>
<td>$488</td>
<td>$6,011,114</td>
<td>$228,964</td>
<td>$73,751</td>
</tr>
</tbody>
</table>

*Annual discount rate 3.5%.
†Ministry of Health, PHARMAC, and direct caregiver costs including hospitalizations, ED visits, GP visits, and the standard subsidy for oral rehydration therapy.
‡Ministry of Health and PHARMAC only.
QAL Y, quality-adjusted life-year.

Figure 3  Univariate sensitivity analyses on the cost-effectiveness (cost per quality-adjusted life-year) of including a pentavalent rotavirus vaccine in the national immunization schedule (societal perspective). Parameters that varied the cost-effectiveness ratio within ±15% are excluded. Parameter ranges can be found in Table 1. CI, confidence interval; ED, Emergency Department; GP, general practitioner.
benefits and costs would remain relatively stable for as long as protective immunity is maintained. Inclusion of PRV on the childhood immunization schedule would confer important clinical benefits and is moderately cost-effective by year 5.

The estimated overall annual incidence of rotavirus gastroenteritis resulting in health-care attendance in New Zealand children under 5 years of age of 4655 per 100,000 is similar to that in Europe [8]. The New Zealand rotavirus hospitalization rate per 100,000 for this age group of 476 (95% CI: 451, 502) approximates that of Germany (500), Italy (520), Finland (520), Spain (650), and the United Kingdom (290–520) but is lower than that recorded in Australia (750–870) [6–8,42–44]. Recently, the incidence rate for rotavirus-related hospitalization in New Zealand was reported as 637 (95% CI: 619, 696) per 100,000 in children under 3 years of age during 1998 to 2000 [18], which is similar to the rate of 661 (95% CI: 623, 700) per 100,000 for this age group in the present study based on a more recent time period. Based on our findings, one in five New Zealand children will consult a GP or visit a hospital for rotavirus gastroenteritis by the age of 5 years and one in 43 will be admitted to hospital. In comparison, by the age of 5 years, the cumulative risk of hospitalization from rotavirus gastroenteritis among children in the United States is 1 in 60 [4], 1 in 54 in Europe [5], 1 in 44 in the United Kingdom [21], and 1 in 27 in Australia [6].

The annual cost of rotavirus gastroenteritis from a societal perspective in 2009, excluding home care cases not seeking medical advice, is estimated at $7.07 million, or $22.17 per child younger than 5 years of age. An Australian study [7], which also excluded home care cases, estimated the annual cost of rotavirus disease in children under 5 years of age as $A26 million at 1998 prices, which corresponds to $NZ27.5 million when adjusted for population differences, price inflation, and purchasing power parity. This level of agreement provides some external validation of our findings, although there are differences in both incidence rates and study methodologies. In the Australian study, the admission rate was based on a limited number of centers, whereas in the current study, it was estimated from national hospitalization rates. In addition to incidence rates, there are differences between the two countries in primary care access, referral patterns, disease management, hospitalization policies, and unit costs. In contrast to New Zealand, the societal cost of rotavirus gastroenteritis for children younger than 5 years of age in four European countries (Belgium, France, The Netherlands, and the United Kingdom) is about twofold higher at €23 per child and is similar across all four countries [11]. The difference is partly accounted for by proportionally higher indirect costs (caregiver income) for women in Europe compared with New Zealand.

In a recent US study of 548 children hospitalized with rotavirus gastroenteritis [39], the mean length of stay was 2.2 days, which is comparable to the New Zealand data (1.9 days) [18] and the mean lost income per family was $US448.77. Although they cannot be applied directly to New Zealand, costs attributable to caregiver work loss account for most (80%) of the indirect costs in the United States, amounting to a mean of 40 hours work loss per child hospitalized with rotavirus illness. This figure accounts for caregivers who were working full time or part time or who were not employed. About half this cost occurred during hospitalization. In our study, indirect costs based on assumptions about work loss taken from Britain [32] contributed just 25% of the total cost.

The cost-effectiveness of including PRV in the immunization schedule is sensitive to the rotavirus incidence rate and the unit price of PRV as expected. It is also sensitive to caregiver loss of income and the transient decline in the quality of life experienced by the child. Specific New Zealand research is needed on the incidence of GP and ED cases and the income loss and disutility associated with caring for children with rotavirus disease. The incremental societal cost of immunization in our study is probably overestimated and the break-even price may be underestimated because the model does not take into account nosocomial infections, emerging evidence of herd immunity contributing to vaccine effectiveness, or loss of income due to home care cases [45–47].

Our findings may be compared to other studies, some of which have been reviewed recently [48]. Carlin and colleagues in Australia concluded that the net cost per hospitalization avoided was $A394 from a societal perspective and $A1023 from a health-care perspective [49]. These figures are much lower than ours, partly because the Australian study assumed a vaccine unit price of $A30 compared to $NZ50 in our base-case analysis.

A more recent study in Hong Kong, like ours, simulated successive vaccination of all newborns each year for 5 years and assumed no fatalities. It concluded that, from a Government perspective, PRV would be cost-saving in this setting if it costs less than $US40–92 to immunize a child fully [50]. This may be compared with $NZ24.40 per dose (about $US40 per three-dose immunization series) from a Government perspective in our study. In a US study, at a vaccine price of $US62.50 per dose, vaccination would cost $US138 per case avoided and $US3024 per serious case avoided from a societal perspective. Based on a very low case fatality, the cost was almost $US200,000 per life-year saved [51]. Nevertheless, because of inconsistent methodologies and vaccine prices across studies, it is difficult to draw firm conclusions about our findings in relation to those of other studies. The cost-effectiveness of routine immunization with PRV is likely to be much better in developing countries with relatively high mortality from rotavirus infection than in industrialized countries, including New Zealand.

Recent modeling studies on the cost-effectiveness of rotavirus vaccination have provided a wide range of conclusions depending on the country setting, the type of economic model and the input assumptions and parameters. We estimated cost-effectiveness ratios for year 5 of an immunization program for successive birth cohorts in a static equilibrium model. This contrasts with the more traditional Markov model used by other researchers, which follows a single birth cohort for a defined period of years or a lifetime [28,29,32,50,52]. In Australia, PRV was found cost-saving from a societal perspective when the disutility of a child and two caregivers (based on the same Canadian study as we used [31]) was included [29]. When only one caregiver was included, the cost per QALY from a health-care perspective was higher than that in our study ($A67,681 vs. $NZ44,092) at a slightly higher unit acquisition cost ($A60 vs. $NZ50) and coverage (90% vs. 85%). A study from England and Wales concluded that PRV would not be cost-effective to the health-care provider [32]. This study had similar hospital admission rates but a somewhat higher unit vaccine price (£2.5 vs. £18.65), which would increase the cost per QALY; however, it also included disutility for two caregivers, which will reduce it.

The main health benefit of rotavirus immunization in New Zealand and other developed countries is avoidance of the transient morbidity associated with episodes of severe gastroenteritis, and the main limitation of our study and others is the scanty information about the disutility associated with rotavirus infection. We and others [29,32] utilized the findings of a recent Canadian study which estimated the disutility of gastroenteritis presenting to a GP at 8% for a child and 7% for a caregiver using standard, well-validated methodologies [31]. Given the sensitiv-
ity of the cost per QALY (ICUR) to this parameter, further research is needed in a range of settings. In developing countries, case fatality ratios will have a much greater influence on the ICUR.

Another important limitation is that, because local data are lacking, incidence rates for GP consultations were estimated from the ratio of GP cases to hospitalizations from recent studies in Britain and Australia. This ratio differs more than twofold between Australia [7] and Britain [21], and it also varies widely across continental Europe [8]. As local data are unavailable, we utilized UK data on caregiver work loss because this is culturally more appropriate to New Zealand than continental European countries in which work loss was estimated [22]. The sensitivity analysis (Fig. 3) and comparison of the ICUR from the societal perspective (where work loss is included) with the health-care perspective (where it is excluded) show that this parameter is moderately important. We also assumed immediate uptake of the immunization program, which is unrealistic. Gradual uptake over say 5 years would reduce the rate at which costs are incurred and health benefits are achieved in parallel, but would have little influence on the cost-effectiveness ratios, which are insensitive to coverage.

In most respects, our analysis is conservative. Transmission of vaccine strains and resulting potential herd immunity could also be important, as rotavirus is transmitted by infants and children within families, day care and health-care settings [53–55]. Preliminary data from the United States show that 2 years after the introduction of PRV into the immunization schedule, the reduction in severe rotavirus disease appears to approximate that seen in the phase III efficacy trials despite immunization rates being lower than for other vaccines because of time limit constraints upon vaccine administration [46,47,56,57]. Moreover, there have also been reductions in rotavirus disease in older and unimmunized age groups [46,47]. Because of lack of information, our analysis excluded follow-up telephone calls with GPs, laboratory tests ordered by some GPs, community laboratory tests, complementary therapies, extra diapers, special foods, and over-the-counter and complementary medications. Community pharmaceuticals such as antibiotics and antidiarrheals were excluded from the analysis; however, although these can cost almost as much as GP consultations [58], they would not add substantially to the total cost of illness in New Zealand preschool children because GP consultations comprise only 7.5% of the total cost (Table 3).

Cases of rotavirus gastroenteritis that are not brought to medical attention were excluded because the incidence rate, resource consumption, disutility and work loss, and the proportions of acute gastroenteritis cases that are due to rotavirus are unknown. Two recent population-based studies have estimated the incidence of home care cases as three- to fourfold higher than medical consultations [5,59]. The cost-effectiveness ratios for PRV would be improved by including home caregiver disutility, loss of income, over-the-counter medications such as antipyretics and oral rehydration therapy, and additional diapers.

Our study did not consider the impact of PRV upon nosocomial rotavirus gastroenteritis because there are no reliable New Zealand data available. Nevertheless, the burden of nosocomial rotavirus disease is likely to be seriously underestimated. It has been suggested that as many as 25% of rotavirus-coded cases collected from hospital discharge data might be due to health-care associated rotavirus infections [45]. We excluded these cases by counting only those with a primary diagnosis of acute gastroenteritis, even though such infections could add as much as 50% to the annual hospital cost of rotavirus diarrhea by prolonging hospital stay [60]. In addition, during such outbreaks, students and hospital staff can become ill and unable to perform their duties. Control of rotavirus infection in a hospital setting has been shown to be extremely difficult despite good hygiene practices, but a vaccine could reduce this burden considerably. Importantly, PRV immunization will greatly attenuate winter/spring epidemics of rotavirus disease, which place an additional burden on both primary and hospital health-care services by coinciding with annual peaks in respiratory virus activity.

There are no formal benchmarks for New Zealand’s willingness to pay for novel vaccines. A cost per QALY of $46,092 ($US26,774), although modest by international standards [61] and lower than the value that informed a previous funding decision for meningococcal type B vaccination during an epidemic in New Zealand, is higher than that informing most historic funding decisions for general pharmaceuticals [62]. Ultimately, some value judgment is required concerning society’s willingness to pay to reduce the high incidence of distressing severe gastroenteritis in preschool children, compared with other health-care funding priorities, most of which have never been subjected to detailed economic analysis.

Source of financial support: Merck & Co., Inc. partially funded this study but had no role in the study design, in the analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

References


B предложенной текстовой строке содержит информацию о ротавирусной вакцине, ее эффективности и экономической эффективности. В тексте упоминаются различные источники и исследования, касающиеся ротавирусной инфекции и ее влияния на общество.

В частности, говорится о том, что ротавирусная вакцина является эффективной меры контроля за распространением этого заболевания, особенно в детском возрасте. Также отмечается, что вакцинация может сократить число госпитализаций и смертей от ротавирусных инфекций.

В тексте упоминаются исследования, проводившиеся в различных странах, таких как Австралия, Новая Зеландия, США, и демонстрируются результаты, указывающие на эффективность вакцинации.

Таким образом, представленная информация подчеркивает важность вакцинации против ротавируса для предотвращения распространения заболевания и уменьшения негативных последствий его воздействия на общество.


