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Potential impact and cost-effectiveness analysis of rotavirus vaccination of children in Israel

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Background: Rotavirus is a common cause of acute gastroenteritis in children under 5 years of age. Two effective vaccines against rotavirus gastroenteritis were recently licensed in many countries throughout the world. The study aimed to investigate the cost effectiveness of vaccinating an Israeli birth cohort of 143 500 children. **Methods:** The cost-effectiveness analysis was determined using a decision analytical model, based on evidence-based estimates of the medical burden of rotavirus gastroenteritis in Israel. **Results:** According to our model, a routine rotavirus immunization program using Rotarix® and RotaTeq® would prevent 17 801 and 13 288 office visits and 645 and 535 hospitalizations every year, respectively. When direct healthcare costs and societal costs are taken into account, the incremental cost-effectiveness ratio per gained QALY for Rotarix® and RotaTeq® are $10 995 and $30 674, respectively. **Conclusion:** Rotavirus vaccination can be considered a cost-effective intervention in Israel, depending on the precise vaccine price.

Keywords: rotavirus, cost effectiveness, immunization.

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Introduction

Diarrheal diseases are a leading cause of mortality and morbidity worldwide, with up to 5 million deaths annually.[1] Although, the burden of the disease is much lower in developed countries, it is still significant. In the US, more than 200 000 children ≤5 years are hospitalized with acute gastroenteritis (GE) each year, and nearly 500 die from its complications.[2] Gastrointestinal infections in children have a wide range of impacts on their families and society, including increased medical expenditure, lost productivity to caregivers, pain and suffering. The most common cause of severe acute GE in young children worldwide is rotavirus (RV). It is estimated that each year 600 000 children die of RVGE,[3] 2 million are hospitalized and 25 million require a physician visit.[4]

In 1998, a tetravalent rhesus-human reassortant rotavirus vaccine [Rotashield1 (RRV-TV)] (Wyeth Laboratories Inc., Marietta, PA, USA) was approved for use in the US. However, a year later it was withdrawn due to reports of its possible association with intussusception. Subsequent research has resulted in the development of two new vaccines, Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq® (Merck & Co., Inc., West Point, PA, USA). To date RotaTeq® has been approved for use in the US, Canada, and other countries, including Israel. Rotarix has received approval from the European Commission and other countries, including Israel.

According to the recommendations of the Rotavirus Vaccine Program (RVP),[5] new studies should be well targeted to meet countries' information needs to allow policy-makers understand the burden of the disease and the potential effects of adding the new rotavirus vaccine to an already busy vaccination schedule. The objective of the current study is therefore to perform a cost-effectiveness analysis of introducing Rotarix® or RotaTeq® into the national immunization program in Israel.

Methods

The decision model

We compared rotavirus disease outcomes with and without immunization program by using a decision-tree model with the TreeAge Pro 2007 software (TreeAge Software Inc., Williamstown, MA). A decision analysis using the Markov Decision Model[6] was constructed to compare rotavirus vaccination strategy with no vaccination. According to the model, RVGE illness may be severe enough to seek medical care or only take a mild form, which can be cared for at home. If the illness is severe, then the outcomes may vary from an office visit to the primary physician (or pediatrician) to hospitalization, while at its most severe form rotavirus infection may cause death. A vaccination program results in similar pathways and outcomes, but is affected by the assumed RV vaccine efficacy.

Assessment of RV GE disease burden

To estimate the national disease and economic burden of RVGE, we developed an epidemiological model to calculate numbers of cases in the community, consultations with family practitioners, hospitalizations and deaths due to RV infections that would occur without and with vaccination for the 2007 birth cohort in Israel throughout the first 5 years of life. Rotavirus-specific diarrhea events were derived from an epidemiological study of GE in a large health maintenance organization (HMO) in Israel, a survey of childhood hospitalizations in six hospitals and from the published medical literature.

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Hospitalization due to RVGE

Data were obtained from our recent survey at pediatric wards in six hospitals throughout Israel[7] that identified 1719 children hospitalized with microbiologically-proven RVGE during the period between 1 April 2004 and 31 March 2006. The length of hospital stay was extracted from medical records of each child. Our findings were used to assess the incidence of hospitalization due to RVGE and the case-fatality rate of RVGE. We assumed that 1% of hospitalized children have nosocomial RVGE, based on a recent prospective study of nosocomial RVGE in Israel (Ashkenazi, Personal Communication).

RVGE in the community

Since the use of laboratory confirmed rotavirus hospitalizations cases is known to greatly underestimate the true disease burden,[8,9] we obtained data on all cases diagnosed as acute GE among children ≤5 years in a 1.7-milliom member HMO in Israel (Maccabi Healthcare Services, MHS). We used MHS' computerized medical records on GE diagnoses and clinical microbiology laboratories to identify all pediatric GE events spanning 2004–06. For GE cases without recognizable etiological agent, we used previously published estimates from Israel and other developed countries to assess the proportion of RVGE among diarrhea cases in children <5 years of age. Using these data, we calculated the mean number of GP visits per GE episode and the rate of visits to ER among community GE cases.

Adjusting for quality of life

The health burden of RVGE was estimated in terms of quality-adjusted life years (QALY) We used previously published estimates of the mean QALY loss per RVGE episode (0.0022 ± 0.000264) based on a Canadian survey administered by GPs to caregivers of children visiting GP clinics for RVGE.[10] In the base case, QALY losses for two caregivers were also applied for each episode of rotavirus gastroenteritis that occurred.[10] Model cost and effectiveness estimates were discounted at a rate of 3% per annum, as recommended and by the World Health Organization[11] and by the Public Health Service Panel on Cost-Effectiveness in Medicine.[12]

Cost estimates

We performed an economic study to determine the medical and societal costs of disease in order to estimate the economic burden and project the cost effectiveness of vaccination.

Direct healthcare costs

The economic burden of RVGE to the healthcare system was estimated by combining the number of each type of potential event (i.e. visits to physician, hospitalizations and deaths) with information on the costs associated with the event. Unit costs of the hospitalization day were obtained from national price lists and hospital invoices for reimbursement, and cost estimates which were previously published in cost-effectiveness analyses in Israel (table 1). As Rotarix® has been licensed in Israel only recently, no information exists as to its cost. Therefore, we used a 93% ratio of RotaTeq® cost, according to a previous report.[10] Cost of nurses' time required for the preparation and administration of two doses of RotaRix or three doses of RotaTeq was based on estimates

from previous economic analysis in Israel[14] and Ministry of Health.

Non-medical and indirect costs

To calculate the societal costs, we used the human capital method, considering that the value of the days lost due to disease or premature death was equivalent to the value of lost productivity. These costs were defined as income lost by parents or caregivers due to this illness and were calculated by the number of days lost from paid work. We have assumed that, in the absence of other forms of child care, the patient's mother will have to forego earnings, stay at home and care for a period of 3 days[17] in all illness outcomes, including when the child has only a mild disease. For hospitalized children, the model assumes that the mother foregoes earnings for the period that the child is in hospital and also for an additional 3 days.[17] To assess the cost of lost earnings, the average income in Israel was multiplied by 76.8% to correct for the lower wage of working women in Israel compared with working men.[20] We also assumed that only 64.8% of all women aged 25–55 years are employed.[20] For a child who dies, we have assumed that each of parents may forego earnings in terms of taking five (assuming that Friday and Saturday are not working days) working days to grieve for their loss. All costs and savings and are presented at July 2007 price levels after conversion to $US at the prevailing exchange rate of 4.30 Israeli shekels to the US dollar.

Vaccine characteristics

RotaTeq® is a live pentavalent reassortant vaccine containing bovine rotavirus and surface proteins of human serotypes G1, G2, G3, G4 and P1A.[18] It is an oral vaccine, which requires three doses between ages 2 and 8 months. RotaRix® (RIX4414) is a human-attenuated G1(P8) oral rotavirus vaccine administered in two doses between ages 6 and 24 weeks.[21] Vaccine efficacy for prevention of both mild and severe rotavirus hospitalizations was based upon results of published reports.[10,18,22] For RotaTeq®, the assumed efficacy against severe cases requiring hospitalization and mild cases presented to GP were 92% (range 80–98%) and,[10,17,18] and 73% (range 55–80%), respectively. The assumed effectiveness of Rotarix® against mild and severe cases was 85% (range 71–92%).[10] Since the vaccine is expected to be included in the current immunization schedule to coincide with the administration of the first two doses of diphtheria–tetanus toxoids–pertussis vaccine (DTP), we used the DTP vaccine coverage rate (94%) in Israel as a proxy for rotavirus vaccination coverage.[14] We did not account for herd immunity due to lack of information from post-marking studies and complexity of analysis.

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from the healthcare system and societal perspectives. We calculated the incremental cost-effectiveness ratio (ICER) expressed as the cost per QALY added. Starting from the base case scenario, we performed one-way sensitivity analyses to examine the range of values for several key variables to reflect uncertainties in our estimates.

Results

Epidemiological model

During our retrospective follow-up of children under 5 years in MHS (912 663 person-years), there were 233 522

Table 1 Values of parameters used in the cost-effectiveness model of rotavirus vaccination

	Base case (sensitivity analysis)	References
Epidemiological model parameters		
Birth cohort (2007)	143 500	[13]
Compliance with rotavirus vaccination (%)	94	[14]
Community clinic GE due to RV (%)	27	[3,15]
RVGE cases requiring a GP visit (%)	25% (15–35%)	[16]
Hospitalization rate (%)	3	[7]
RVGE case fatality (percentage of hospitalized cases)	0.06	[7]
Nosocomial RV infection (percentage of hosp. patients)	1	See text
Vaccine effectiveness, mild cases (RotaTeq®)	73% (55–80%)	[10,17,18]
Vaccine effectiveness, severe cases (RotaTeq®)	92% (80–98%)	[10,17,18]
Vaccine effectiveness (Rotarix®)	85% (71–92%)	[10]
Vaccination-related costs		
Vaccine wholesale price per recipient (RotaTeq®)	$120–$243	MHS wholesale price list
Vaccine wholesale price per recipient (Rotarix®)	$227	MHS wholesale price list
Vaccine wastage (%)	0.5	[10]
Vaccine transportation (%)	2	[14]
Nurses time for vaccination (RotaTeq®)	$1.4	[14]
Nurses time for vaccination (Rotarix®)	$1.0	Based on $16.5/h (MOH)
Secretarial employment costs (RotaTeq®)	$1.01	[14]
Secretarial employment costs (Rotarix®)	$0.7	Based on $12.1/h (MOH)
Health education per potential recipient	$0.5	[14]
Total cost of vaccination (RotaTeq®)/recipient	$252 ($150–$200)	
Total cost of vaccination (Rotarix®)/recipient	$234 ($150–$200)	
Direct healthcare costs		
Physician consultation costs		
Physician consultation time (hours)	0.25	[14]
GP employment costs (per hour)	$28	[14]
Overheads and extra costs (%)	20	Assumed
Medications prescribed	$1.07	[17]
Hospitalization costs		
Per-diem child hospital costs $ (per day)	270	75% of per-diem cost [19]
Per-diem pediatric ICU $ (per day)	451	[19]
Indirect medical costs		
Burial cost	$990	[14]
Average annual income	$20 472	[20]
Average daily income (women, 25–54 year)	$41.2	[20] See text
Lost due to premature death	$242 622	[20] See text
Other		
Discount rate (per year)	3% (0–6%)	[11]
QALY loss per RVGE episode	$0.0022 (16.8–27.5 \times 10^{-4})$	[10]
QALY loss to each caregiver	$0.00184 (9.1–27.5 \times 10^{-4})$	[10]

GP, general practitioner, RVGE, rotavirus gastroenteritis; ICU, intensive care unit; QALY, quality-adjusted life year; MOH, Ministry of Health; MHS, Maccabi Healthcare Services.

consultations with physicians for GE. The highest annual incidence rate was calculated for children aged 12–24 months (43.9%; 95% CI 43.7–44.1%), declining with increasing age to 12.6% (95% CI: 12.4–12.7%) among children aged 48–60 months. Figure 1 describes the risk of rotavirus infection assuming that rotavirus accounts for 27% of all GE cases[3,15] and that 25% of all rotavirus cases require a physician consultation.[16] According to this model, the annual rate of GP consultations for RVGE is 6.9%, ranging between 11.9% in children aged 12–24 months to 4.2% in children aged 48–60 months.

Our survey of pediatric wards found 1719 hospitalized RVGE cases who were admitted during a 2-year period, of whom 52, 37, 17 and 5% were aged <12, 12–24, 24–36 and 36–60 months, respectively.[3,15] The population served by the participating hospitals was 25% of the total Israeli population; therefore, we estimate that the annual number of children hospitalized for RVGE in Israel is 3816 accounting for 3.5% of all hospitalizations in pediatric wards,[13] and reflecting a RVGE hospitalization rate of 2.9%. This hospitalization rate concurs with previous estimates from developed countries.[16] The calculated age-specific hospitalization rates due to RVGE are given in figure 1. During the survey period there was one death due to severe acidosis and dehydration among the 1719

hospitalized cases, representing a case-fatality rate of 0.06% (95% CI 0.001–0.29%), similar to a risk of 0.07% which was reported in high-income European countries.[16]

Direct healthcare costs and societal costs of rotavirus

The average number of physician consultations per GE case in MHS were 1.65, 1.40 and 1.25 among children aged <24, 24–36 and 36–60 months, respectively. Thus, under the assumptions described in table 1, the total direct healthcare cost of rotavirus disease requiring physician consultation is $18, $15 and $14 for children aged <24, 24–36 and 36–60 months, respectively. According to our previous study, the average length of hospital stay of the RVGE cases was 4.3 and 3.8 days for patients aged <24 and 24–60 months, so that the calculated cost of hospitalizations were $1155 and $1021, respectively. The societal costs incurred by mild RVGE cases due to loss of caregiver's working days are $123.6 for mild cases, $301 for hospitalized children under 24 months and $280 for older hospitalized children.

The results of our epidemiologic model indicate that inclusion of Rotarix® in the routine childhood vaccination program in Israel would prevent 17 801 visits to physician,
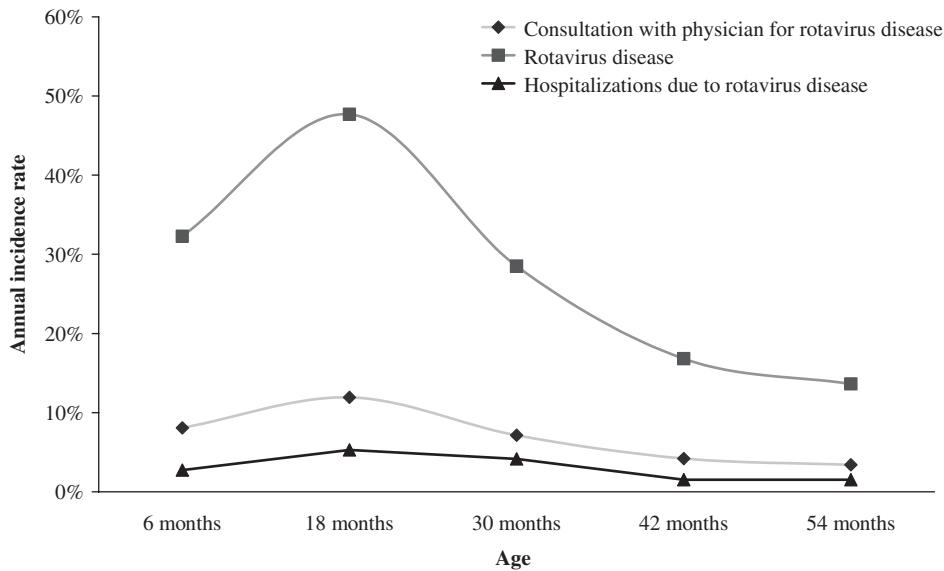
Figure 1 Assumed age-specific annual incidence of rotavirus disease, (Assuming that 25% of all cases consult with physicians[16]) physician consultations for rotavirus disease (Assuming that rotavirus accounts for 27% of all gastroenteritis cases are rotavirus[3,15]) and hospitalizations due to rotavirus, (Assuming hospitalization rate of 2.7, 5.3, 4.2 and 1.5% among rotavirus disease cases aged <12, 12–24, 24–36 and 36–60 months, respectively) based on an annual incidence of gastroenteritis in a large HMO in Israel during 2000–2006

Table 2 Cost-effectiveness analysis of routine vaccination program of infant birth cohort in Israel with a live pentavalent reassortant rotavirus vaccine (RotaTeq®) and monovalent rotavirus vaccine (Rotarix®)

Base case	Outpatient visits	Hospitalized patients	Deaths	Gained QALYs	Vaccination costs	All direct healthcare costs ($)	ICER ($/QALY)	Direct healthcare and societal cost ($)	ICER ($/QALY)
RotaTeq®									
No vaccination	26 174	789	0.055		–	24 075 626		36 239 232	
Vaccination	12 886	144	0.010	352	32 858 170	41 987 038	50 848	47 044 380	30 674
Rotarix®									
No vaccination	26 174	789	0.055		–	24 075 626		36 239 232	
Vaccination	8373	254	0.019	437	30 511 158	37 796 451	31 396	41 044 415	10 995

compared with 13 288 visits for RotaTeq®. According to our base case estimates, the incremental healthcare cost of the rotavirus vaccines are $13.7 and $17.9 million for Rotarix® and RotaTeq®, respectively. When direct healthcare costs and societal costs are taken into account, the ICER per gained QALY are $10 995 and $30 674, respectively (table 2).

Univariate sensitivity analyses shows that our base case estimates are particularly sensitive to the assumed proportion of RVGE among diarrhea cases in children, the efficacy of RV vaccine against mild cases of RVGE, and the cost of the vaccine (table 3). From the societal perspective, the break-even cost of RV vaccine per vaccine recipient is approximately $192 and $165 for Rotarix® and RotaTeq®, respectively.

Discussion

Our epidemiologic study shows that RVGE is common among children <5 years of age in Israel and therefore is a considerable burden on pediatric departments. In accordance with a recently published cost-effectiveness analysis in the US,[22] we estimate that a rotavirus immunization program using either Rotarix or RotaTeq® would prevent more than two-thirds of all serious rotavirus disease and more than half of GP consultations for rotavirus disease. Our cost-effectiveness analysis suggests also that at the current vaccine's cost, Rotarix® appears to be more cost effective than RotaTeq®,

due to its high efficacy with only two doses. The cost per gained QALY for both vaccines in the base model is <$31 000, which is almost universally considered as cost effective.[23,24] Similar to the results of a recently published analysis from Hong-Kong,[25] rotavirus vaccination program costing less than US$150 per child would most likely save costs from the societal perspective. It should be emphasized that vaccine costs will probably be reduced when a nationwide rotavirus vaccination is started (in 2001, the purchase price of HAVRIX® 720 for MHS declined from $17.0 to $6.7 following the inclusion of hepatitis A vaccine to the national immunization program in Israel).

Inherent to all model analyses, our model also has some limitations. For instance, we did not collect data on potential benefits. Such unquantified potential benefits include cost of transportation to seek medical care, cost of extra diapers and costs of over-the-counter medications. We also did not account for RVGE in children older than 5 years and in adults. Also, we might have underestimated the average value of a lost workday by assuming that all care providers are women, who have lower salaries than men.[20] In contrast, our model did not include several parameters that are not favorable to the vaccine, such as mild side effects incurred by the vaccine (an excess of 2 or 3% in the rates of diarrhea and vomiting in the 7-day period after any dose[11]) or waning immunity in first 5 years of life.

Table 3 One-way sensitivity analyses

	RotaTeq®			Rotarix®		
	Incr. cost ($)[a]	Gained QALY	ICER ($ per QALY)	Incr. cost ($)[a]	Gained QALYs	ICER ($ per QALY)
RVGE cases requiring a GP visit (%)						
15	16 842 452	247	68 208	11 239 422	323	34 837
35	7 660 016	408	18 765	1 481 422	497	2 980
Vaccine effectiveness, RotaTeq® (mild cases) (%)						
55	16 664 741	243	68 700	–	–	
80	8 254 622	401	20 606	–	–	
Vaccine effectiveness, RotaTeq® (severe cases) (%)						
80	11 306 781	349	32 356	–	–	
98	10 554 210	354	29 843	–	–	
Vaccine effectiveness, Rotarix® (%)						
71	–	–		16 906 524	235	72 006
92	–	–		1 574 439	492	3 203
Discount rate (%)						
0	8 721 916	387	22 553	2 360 073	480	4 912
6	12 630 440	322	39 202	6 946 491	399	17 402
Societal cost of mild rotavirus ($)						
100	12 135 250	352	34 450	6 476 987	437	14 821
200	6 402 066	352	18 175	–	–	(Dominated)
Loss of QALY from mild rotavirus (patient)						
0.00168	10 805 148	322	33 511	4 805 184	400	12 027
0.00272	10 805 148	382	28 281	4 805 184	474	10 127
Loss of QALY from symptomatic rotavirus (caregiver)						
0.00091	10 805 148	187	57 892	4 805 184	231	20 769
0.00275	10 805 148	297	36 417	4 805 184	368	13 059
Vaccine cost (per vaccine recipient) ($)						
150	–	–	(Dominated)			(Dominated)
200	4 859 871	352	13 797	1 072 103	437	2 453

a: Direct healthcare costs and societal costs

In addition to cost effectiveness alone, affordability and sustainability are key concepts that must be examined with regard to new vaccination policies.[5] This is particularly true in countries with a national healthcare insurance like Israel, where the public resources allocated for new technologies are limited. With current prices, the approximate annual direct cost of administrating the rotavirus vaccine in Israel is between $34 and $36 million. This is considerably higher compared with most other routine vaccines in the childhood immunization schedule and it may sharply increase the government expenditure for vaccination. However, the introduction of previous vaccines at a similarly high cost in the past (e.g. hepatitis A vaccine) has been successful and effective in reducing morbidity.[26,27]

Rotavirus is often an unrecognized cause of disease, thus a major key element of our model is estimating the proportion of GE attributable to RV. Our base model assumes that ~27% of GP consultations for gastroenteritis in children ≤5 years can be attributable to rotavirus. This was based on studies which used laboratory investigations of all or a fraction of GE cases[3,15] and thus may not reflect the true burden of rotavirus, as the laboratory tests are <100% sensitive. However, a very similar rate (25%) was calculated by a recently published regression-based analysis that was not affected by a lack of sensitivity.[28]

The cost effectiveness of RV vaccination program differs substantially across perspectives reflecting the fact that RVGE is a significant burden on caregivers. Our results indicate that the ICER of the vaccination program is particularly sensitive to the societal cost of RVGE. Therefore, the favorable ICER of RVGE could be negated in societies with low labor force participation rates, where caregivers do not have to take time off employment to take care for their ill child. The results of the current analysis were also sensitive to efficacy of the RV vaccine. However, in large cohorts of young children,[18,21] both vaccines have been shown to be safe and effective against any G1-G4 RVGE, the most prevalent rotavirus serotypes also in Israel.[29]

Although the cost per gained QALY approach is subject to significant uncertainty due to the use of proxy respondents to assess the loss of QALY in children suffering from RVGE and the diverse severity of rotavirus disease, it provides an important measure for decision makers.[30] Thus, we were limited to the only available empirically-derived assessment of the impact of RVGE on quality of life (and its 95% CI for sensitivity analysis). However, this QALY agrees with the estimates of the United States Institute of Medicine,[31] which were based on experts opinion.

In conclusion, although the present estimate of the expected reduction in the direct and societal costs of RVGE disease are smaller compared with the ones calculated in previous analyses of childhood vaccination programs in Israel, such as hepatitis A (91 million US$[32]) and Varicella (24 million US$[14]), our assessment underscores the potential benefits of universal immunization against RVGE in reducing both morbidity among children and loss of working days among caregivers. The present study suggests that under the base model assumptions, a routine RV nationwide vaccination strategy is expected to be cost effective from the societal perspective at a total cost of vaccination of $234 per child and vaccination coverage of 94%. At a cost of less than $150 per child, the rotavirus vaccines are net-saving.

Acknowledgements

Conflicts of interest: None declared.

Key points

- This is the first cost-effectiveness evaluation study of a national vaccination against RVGE in Israel, where rotavirus gastroenteritis accounts for 27% of all GE cases in children <5 years.
- The results of the epidemiologic model indicate that inclusion of Rotarix® in the routine childhood vaccination program in Israel would prevent 17 801 visits to physician a year, compared with 13 288 visits for RotaTeq®. According to the base case estimates, the incremental healthcare cost of the rotavirus vaccines are $13.7 and $17.9 and million for Rotarix® and RotaTeq®, respectively. When direct healthcare costs and societal costs are taken into account, the ICER per gained QALY are $10 995 and $30 674, respectively.
- The study underscores the potential benefits of universal immunization against RVGE and suggests that a routine RV nationwide vaccination strategy is expected to be net-saving from the societal perspectives at a cost of less than $150 per child.

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