Le Infezioni in Medicina, n. 3, 166-175, 2011

Articoli originali

Original articles

Socio-economic modelling of rotavirus vaccination in Castilla y León, Spain

Modello socio-economico della vaccinazione anti-rotavirus nella regione di Castilla y León, Spagna

Alberto Pérez-Rubio[1], Francisco Javier Luquero[2], Jose María Eiros Bouza[3], Jose Javier Castrodeza Sanz[1], Maria del Rosario Bachiller Luque[4], Raúl Ortiz de Lejarazu[3], Antonio Sánchez Porto[5]

[1]Regional Office for Public Health in Castilla y León, Spain;
[2]Department of Preventive Medicine, Hospital Clínico Universitario of Valladolid, Spain;
[3]Department of Microbiology, Hospital Clínico Universitario of Valladolid, Spain;
[4]Department of Pediatrics, Hospital Clínico Universitario of Valladolid, Spain;
[5]Department of Microbiology, Hospital of La Línea, Cádiz, Spain

INTRODUCTION

Rotavirus is one of the main causes of acute gastroenteritis in infants and young children [1]. In the first five years of life, approximately 70% of children will become ill from rotavirus diarrhoea [2]. Furthermore, rotavirus is the leading cause of hospitalization and death from acute gastroenteritis among infants and young children worldwide [3].

It has been estimated that 3.6 million episodes of RVGE (rotavirus gastroenteritis) occur annually among the 23.6 million children under five years of age in Europe [4]. Although deaths due to RVGE are uncommon in industrialized regions, such as Spain, thanks to adequate medical care, the burden of RVGE is substantial because of the elevated number of associated hospitalisations [5, 6]. In addition, some studies have reported the costs due to outpatient visits for RVGE and the indirect costs faced by families and society [7-9]. Safe and effective live oral vaccines against rotavirus have been developed in recent years [10]. Two rotavirus vaccines (Rotarix® and Rotateq®) have recently completed clinical trials and are being considered for routine infant immunization in several countries [11, 12].

The present study analyzes the cost-effectiveness and profitability of systematic vaccination against rotavirus in a European region, and estimates the economic impact of a regional rotavirus immunization program.

METHODS

This study examines the impact of a rotavirus immunization programme in Castilla y León (Spain) measured as the decrease in the disease burden and the associated costs during the first five years of life when most rotavirus diarrhoea cases occur [13]. We evaluated the cost-effectiveness and the cost-benefit of an immunization programme using a model that followed an imaginary cohort of 100,000 children in Castilla y León from birth to five years of age. This economic evaluation was analyzed from two perspectives:

1) that of the healthcare payer, Castilla y León Sanitary System (SACYL), which covers medical costs associated with rotavirus diarrhoea and the cost of the immunisation programme;
2) that of society, which also includes non-medical costs, including lost caregiver workdays.

We assumed that doses were administered to all infants in Castilla y León at 2, 4 and 6 months of age for RotaTeq®, and 2 and 4 months of age for Rotarix®, to match the manufacturers' recommendations and the childhood immunization schedule in Castilla y León [11, 12]. A decision tree was used to calculate total costs. We also estimated the number of adverse outcomes (rotavirus diarrhoea treated at home, physician and emergency department visits and hospitalizations).

The net cost of the programme was estimated

as the cost of vaccination less the saving to the health service as a result of outcomes prevented by vaccination. The value of caregivers' work loss prevented by reducing the number of rotavirus disease episodes was also estimated. Benefits were measured as the estimated number of QALYs saved in both patients and their carers as a result of the immunization programme. Medical costs of rotavirus cases occur over a five-year period according to the specific incidence estimates for each outcome. Costs and benefits were discounted at 5%.

Decision analysis model

We compared rotavirus disease outcomes with and without an immunization programme by using a decision-tree model (Figure 1). We analyzed the decision tree to determine the costs of the two options: vaccination at current levels of coverage for diphtheria and tetanus toxoids and pertussis (DTP) and the current situation of no immunisation programme. The vaccine price, coverage, efficacy, disease burden, medical costs, non-medical costs and other data used in the decision tree are presented in Table 1.

Burden of rotavirus infections

We consider the following health care outcomes attributable to rotavirus: inpatient hospitalizations, visits to emergency departments, consultations with a general practitioner or a paediatrician (GP) and ill children at home. These outcomes were estimated for children of Castilla y León from a retrospective observational study developed in the Hospital Clínico Universitario of Valladolid (HCUV) [5]. This study shows an annual hospitalization incidence rate attributable to rotavirus of 480 hospitalizations per 100,000 children under five years. It was assumed that no deaths due to rotavirus would occur in Castilla y León [5]. The visits to the emergency ward were estimated as three times higher than the number of hospitalizations [14].

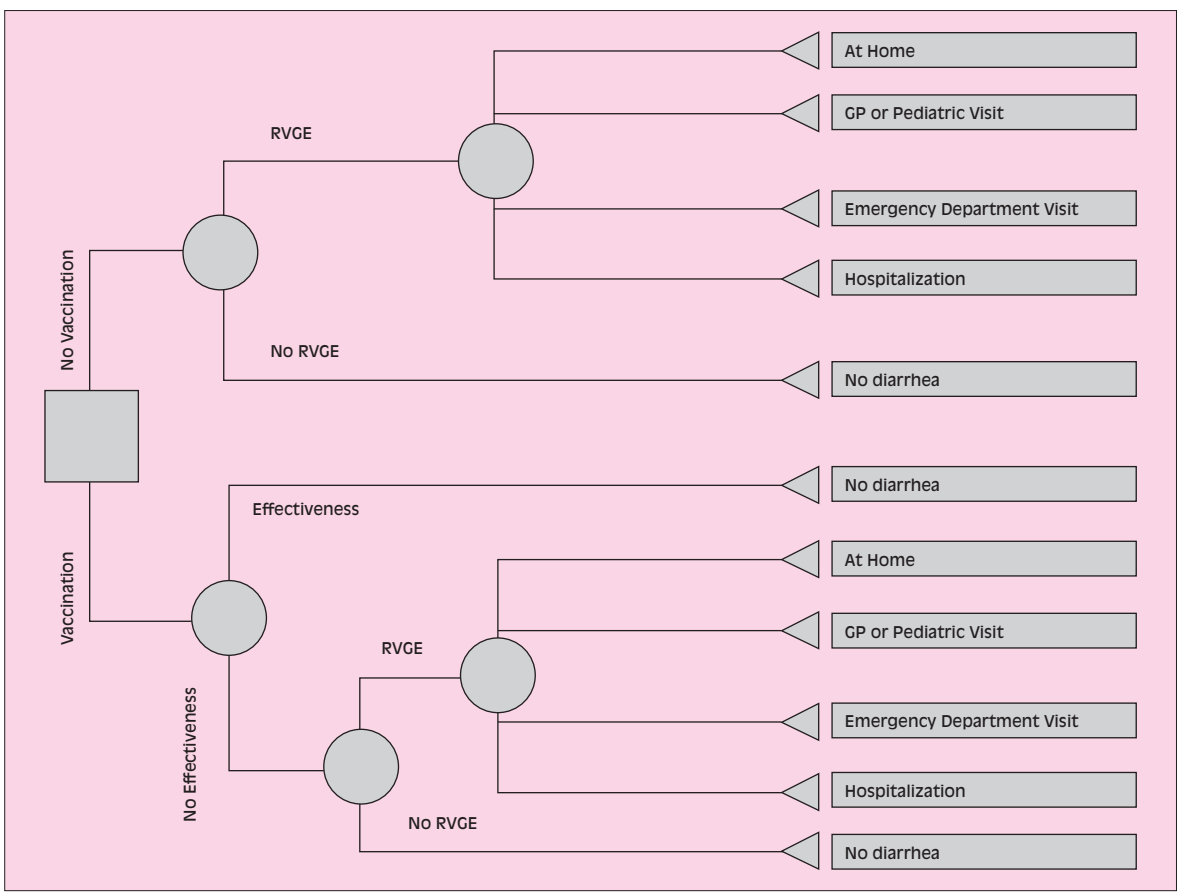

Figure 1 - Decision tree for rotavirus immunization in Castilla y León. The current practice with no vaccination is compared with a vaccination program in which rotavirus vaccine is included in a regional childhood immunization program. RVGE: Rotavirus gastroenteritis.

Vaccine characteristics

Vaccine efficacy was estimated from published phase III clinical trial data for RotaTeq® and Rotarix® [11, 12]. We assumed that the vaccine was fully effective from the first dose, and that there was no decrease due to waning protection within the ages considered [15]. The vaccine coverage rate was assumed 100% based on coverage data of DTP, which is given to children in Castilla y León at 2, 4 and 6 months of age, matching with the rotavirus vaccine programme [16].

Rotateq® is currently sold at a price of € 69.50 per dose and Rotarix® at € 93.66 per dose [17]. For administration costs, we assumed € 3 per dose, given that it takes a practised nurse about 10 minutes to deliver a dose (Soikos® database). It was assumed that the vaccine would be delivered concomitantly with other vaccines in the childhood vaccine schedule, so there is no additional cost of recruiting children for vaccination.

Table 1 - Point estimates for the parameter values used in the model.

Outcome	*Base case*	*Reference*
Annual incidence (per 1000 children under 5 years)		
Children at home	142.4	[5]
GP consultation	38.5	[5]
Emergency department visits	14.4	[5]
Hospital admission	4.8	[5]
Deaths	0	
QALY loss per episode of rotavirus		
To child	0.00220	[17] [20]
To each caregiver	0.00184	[17] [20]
Cost (€)		
Hospital admission	340	*
Emergency department visits	170	*
GP consultation	42.59	*
Dose of vaccine (RotaTeq®)	69.50	[19]
Dose of vaccine (Rotarix®)	93.66	[19]
Administration of vaccine dose	3	
	Work loss	
Media payroll annual	19,314,07	**
Media payroll per day	80,475	**
Vaccine efficacy (%)		
Non-severe (RotaTeq®)	66.9	[4] [17]
Severe (RotaTeq®)	94.0	[4] [17]
Any (Rotarix®)	85.2	[3] [17]
Vaccine coverage (%)		
All doses	100%	[18]
Others		
Discount rate	5%	
Average admission length	6.3 days	[5]

*Source: Primary and Specialized Healthcare Techniques Management of the Regional Healthcare Management of Castilla y León, hospital analytical accounting units of the province of Valladolid. **Source: National Statistics Institute. Salary structure survey 2002. Average annual earnings per worker in Castilla y León.

Impact on quality of life

Data for the impact on quality of life assessment were obtained from a Canadian survey administered by GPs to caregivers of children visiting GP clinics for rotavirus gastroenteritis [18]. The daily QALY loss reported for both affected children and their caregivers was calculated over three visits made over a two-week period. Figures used were those estimated from administering the HUI-2 questionnaire to caregivers to evaluate their children's QALY loss, and the EQ-5D questionnaire to evaluate their own QALY loss. In the base case, QALY losses for a child and two caregivers were applied for each episode of rotavirus gastroenteritis that occurred.

Cost estimates

The medical costs (direct costs) included in the study - cost of hospitalization, emergency department visits and GP or paediatric visits - were obtained by direct consultation of various sources: the Technical Management of Specialized and Primary Healthcare of the Regional Health Service Management for Castilla y León and the analytical accounting units of the hospitals of the province of Valladolid. The average hospital stay for a child with rotavirus diarrhoea was assumed to be 6.3 days [5].

In order to calculate the non-medical costs (indirect costs), we used the mean daily salary of the population of Castilla y León, estimated by the National Institute of Statistics through the salary structure survey. The percentage of families in which a parent or other relative took time off work because of a diseased child was estimated at 50%. The average number of workdays lost per episode was 4.2 days for a dis-

eased child at home, 4.4 days for a child that visited their GP or emergency department and 4.6 days if the child was hospitalised [19]. Savings in extra diapers and travel costs, when a child was sick, were not included.

Sensitivity analysis

To reduce the uncertainties that arise in such studies, we carried out a sensitivity analysis to give the results greater robustness and make them more reliable.

The price of the vaccines was analyzed and their effect was represented on all the results of the vaccination programme, the cost/utility index, cost/benefit index, cost per episode prevented and cost per hospitalization prevented, in order to obtain the profitable price of the vaccines.

RESULTS

The study was modelled using a decision tree with its branches and probabilities (Figure 1). In the "vaccination" strategy branch, the vaccine's lack of efficacy, it is assumed that the illness will behave in a like manner to the "no vaccination" strategy.

The global costs and the cases of rotavirus diarrhoea that occur in each strategy are shown in Table 2, using RotaTeq® vaccine, and in Table 3, using Rotarix® vaccine.

Table 2 - Discounted costs and benefits (in €) of vaccinating a cohort of infants with RotaTeq® under base-case assumptions

	No vaccine	*Vaccine*	*Difference*
Burden of disease			
Hospitalizations	1.609.78	96.59	1.513.19
Emergency department visits	4.836.07	290.16	4.545.90
GP consultations	12.925.37	775.52	12.149.84
Children at home	47.983.49	20.680.88	27.302.60
Total rotavirus diarrhoea	67354.69	21843.15	45511.54
QALYs lost			
Total QALYs lost	350.29	113.60	236.69
Costs (€)			
Medical costs			
Hospitalizations	3.049.761.94	182.985.72	2.866.776.22
Emergency department visits	727.146.53	43.628.79	683.517.74
GP consultations	486.890.37	29.213.42	457.676.95
Total costs	3.974.552.91	255.827.93	3.718.724.98
Vaccine	0	20.850.000	-20.850.000
Vaccine administration	0	900.000	-900.000
Total costs		21.750.000	-21.750.000
Non-medical costs	**10.217.004.31**	**3.273.908.74**	**6.943.095.57**
Total medical costs	**3.974.552.91**	**22.005.827.93**	**-18.031.275.02**
Total medical+non-medical costs	**13.991.557.22**	**25.279.736.67**	**-11.288.179.45**
SACYL Perspective			
Cost/QALY gained			**74 958.99**
Cost/episode prevented			**389.84**
Cost/hospitalization prevented			**11 724.91**
Cost/benefit			**0.18**
Social perspective			
Cost/QALY gained			**45 624.83**
Cost/episode prevented			**237.28**
Cost/hospitalization prevented			**7 136.53**
Cost/benefit			**0.50**

Base case

A rotavirus immunization programme is projected to prevent 45% of cases with RotaTeq® and 57% with Rotarix®.

Rotavirus gastroenteritis is predicted to account for about 1,610 hospitalizations, 4,836 visits to emergency departments, 12,925 visits to paediatricians and 47,983 episodes treated at home in the first five years of life of a cohort of 100,000 infants of Castilla y León.

The annual cost of rotavirus diarrhoea is estimated to be about € 4 million to the health system, 75% of which is accounted for by hospitalizations, and € 14 million to society in the first five years of life.

Given the Rotateq® vaccine price (€ 69.50 per dose), a rotavirus immunization programme would cost € 21,750,000 and would save € 3,718,724.98 in direct medical costs (Table 2). With the Rotarix® vaccine price (€ 93.66 per dose), a rotavirus immunization programme would cost € 19,332,000 and would save € 3,343,510.68 in direct medical costs (Table 3).

A programme using RotaTeq® would cost about € 74,959 per QALY gained (Table 2) whereas the program using Rotarix® would cost about € 52,603 per QALY gained (Table 3).

The cost per case prevented is about € 389.84 for RotaTeq® vaccine and € 11,724.21 for hospitalization prevented.

For Rotarix® vaccine the cost is about € 121.88 and € 5,099.67, respectively.

Table 3 - Discounted costs and benefits (in €) of vaccinating a cohort of infants with Rotarix® under base-case assumptions

	No vaccine	*Vaccine*	*Difference*
Burden of disease			
Hospitalizations	1.609.78	238.25	1.371.53
Emergency department visits	4.836.07	715.78	4.120.33
GP Consultations	12.925.37	1.912.95	11012.41
Children at home	47.983.49	7.101.56	40.881.93
Total rotavirus diarrhoea	67.354.70	9.968.49	57.386.20
QALYs lost			
Total QALYs lost	350.29	51.84	298.45
Costs (€)			
Medical costs			
Hospitalizations	3.049.761.94	451.364.77	2.598.396.23
Emergency department visits	727.146.53	107.617.69	619.528.84
GP consultations	486.890.37	72.059.78	414.830.59
Total costs	3.974.552.91	631.042.23	3.343.510.68
Vaccine	0	18.732.000	-18.732.000
Vaccine administration	0	600.000	-1.050.000
Total costs		19.332.000	-19.332.000
Non-medical costs	**10.217.004.31**	**1.512.116.64**	**8.704.887.67**
Total medical costs	**3.974.552.91**	**19.963.042.23**	**-15.988.489.32**
Total medical+non-medical costs	**13.991.557.22**	**21.475.158.87**	**-7.483.601.65**
SACYL Perspective			
Cost/QALY gained			**52.603.33**
Cost/episode prevented			**273.57**
Cost/hospitalization prevented			**11.446.52**
Cost/benefit			**0.19**
Social perspective			
Cost/QALY gained			**23.435.93**
Cost/episode prevented			**121.88**
Cost/hospitalization prevented			**5.099.67**
Cost/benefit			**0.64**

Cost to society

The value of work lost by carers of patients with rotavirus is estimated to be about € 10 m over the first five years of life of the cohort (discounted at the standard rate).

An immunization programme with RotaTeq® would prevent almost € 7 m, compared to almost € 9 m with Rotarix®.

Including work loss in the analysis gives a cost utility ratio of € 45,624 for RotaTeq® and € 23,435 for Rotarix® (Tables 2 and 3).

Sensitivity analysis

Figures 2 and 3 show the variations in the different indexes when the price of the vaccines is changed. For RotaTeq® a vaccination programme becomes profitable (net benefits) at about € 35 per dose and Rotarix® at about € 60 from society's perspective. For a health service payer (e.g. SACYL) the vaccines have cost-utility about € 60 for Rotarix® and € 35 for RotaTeq®, in which the cost per QALY is less than € 30,000. The cost per case prevented and hos-

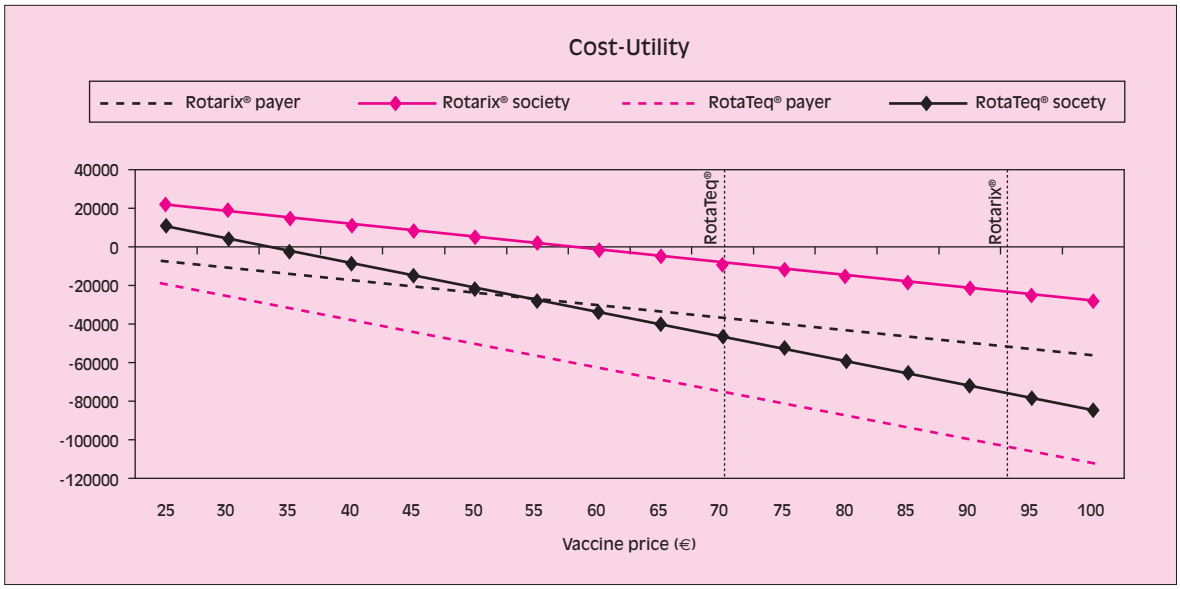

Figure 2 - Cost-utility of a rotavirus immunization programme for a range of vaccine prices. The shaded area represented is non-cost-effectiveness of the vaccination programme. The positive values are saved costs.

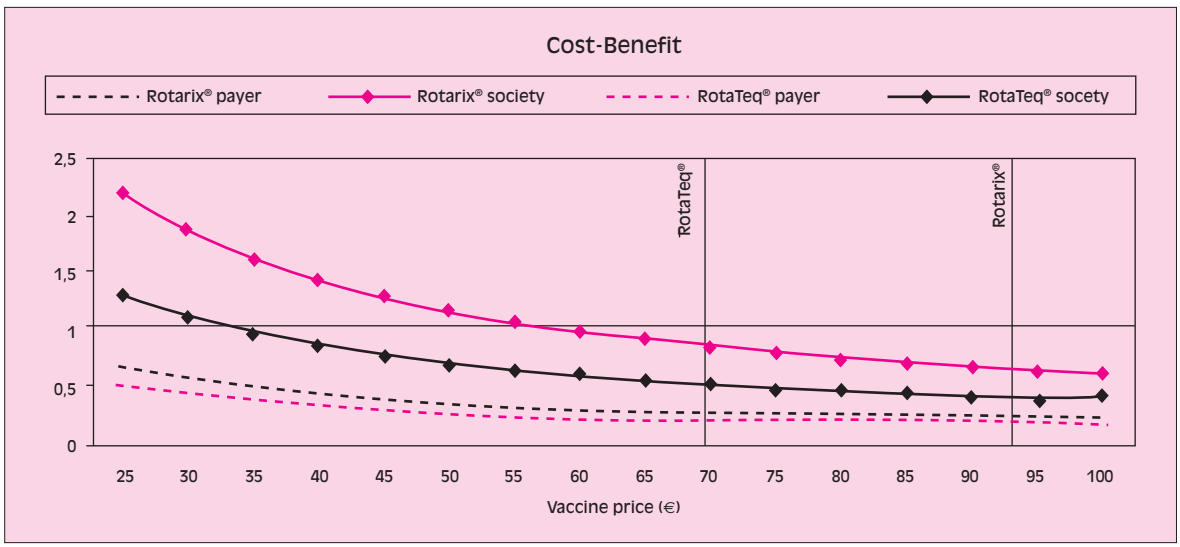

Figure 3 - Cost-benefit of a rotavirus immunization program for a range of vaccine prices.

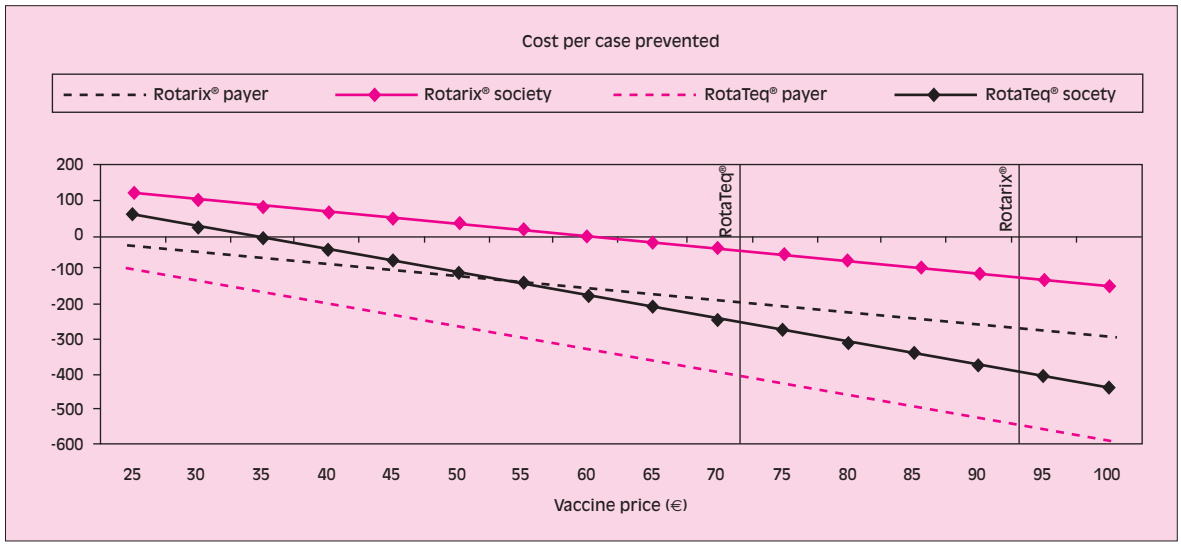

Figure 4 - Cost per case prevented examined in a sensitivity analysis over a range of vaccine prices. The positive values are saved costs.

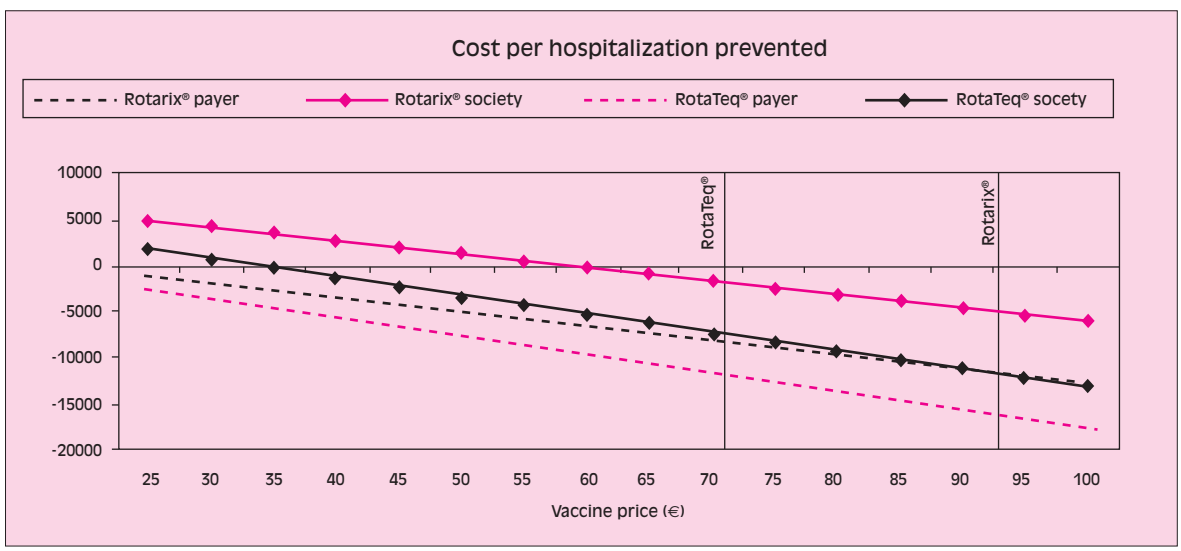

Figure 5 - Cost per hospitalization prevented examined in a sensitivity analysis over a range of vaccine prices. The positive values are saved costs.

pitalization prevented over a range of vaccine prices has been analyzed (Figures 4 and 5).

DISCUSSION

This study presents, as far as we know, the first cost-utility analysis of rotavirus vaccination in Spain. Few studies have analysed the cost-effectiveness of vaccination and the effect on quality of life of preventing episodes of rotavirus. Furthermore, we performed a cost-benefit analysis of a vaccination programme in a Spanish region. This analysis comes at an appropriate time because of the recent commercialisation of preventive vaccine against rotavirus and the high disease burden due to these viruses.

According to our results, a regional rotavirus immunization programme would not be cost-effective nor would it yield net benefits with current vaccine prices. Our analysis indicates that routine rotavirus vaccination can have a substantial short-term morbidity burden due

to infection. However, it would only be cost-effective if the vaccine price were extremely competitive.

The study shows that Rotarix® has more cost-utility than Rotateq®, and its utilization could be established from society's perspective, because the cost per QALY gained is less than € 30,000, consistent with other studies [20]. If we analyze the cost per prevented case, the vaccination programme with Rotateq® is more expensive than with Rotarix®.

This difference decreases when we compare hospitalizations prevented. Thus, Rotarix® seems, under base case assumptions, to be more cost-effective and profitable than Rotateq®. Other studies have presented the same conclusion, although Jit et al. found that the results for each vaccine should not be regarded as comparable because there was still uncertainty regarding the vaccine's price and because the case definitions used in efficacy trials for each vaccine were different [15]. In our study we sought to solve part of this limitation by using the current prices of these vaccines.

We estimate the full cost of the rotavirus disease in Castilla y León to be € 14 million, of which € 4 million would be attributable to medical costs. Hospitalizations are the main contributor to medical costs, while salary loss of the caregiver because of mild disease is the main contributor to social costs.

The indirect costs are closely related to the patient´s dependence. Rotavirus infection mainly affects children under two years old, who are totally dependent on their families; it entails an increase in the above-mentioned costs [6, 21-24]. Our figures show that the average cost (direct and indirect) per paediatric RVGE episode was € 207.73.

In the United Kingdom, Largelly et al. estimated the average total cost to be as high as £ 169 (approximately € 249 per child <5 years of age with RVGE) [25]. However, the mean direct medical cost funded by the Regional Healthcare payer per hospitalised child with RGVE was estimated to be € 1,895.44, more than the € 1,417 estimated by the REVEAL study [19]. This difference can be explained by the lower cost of hospitalisation assumed in the REVEAL study.

The current study has a number of limitations in the estimates used in the analysis as well as considerations of increased treatment with oral rehydration therapy, the unassessed cost of adverse events and other costs not included such as extra diapers and other non-medical costs. Effectiveness could be greater than efficacy since children continue to receive missed doses after six months and the potential of herd immunity [26]. Rotavirus transmission within families was not considered, yet it leads to an additional burden on health care services and society.

Our base case assumptions on the parameter values were chosen to be favourable to the vaccines. For instance, we assumed maximum protection from the first dose and no waning of immunity in the first five years of life.

A further important issue that could modify the results is deaths attributable to rotavirus diarrhoea.

This parameter was not included in the analysis since no deaths due to rotavirus infection are estimated for Castilla y León.

However, elsewhere, especially in developing countries, the attributable deaths could modify the ratios [27]. Moreover, we did not evaluate hospitalized children with nosocomial rotavirus gastroenteritis, which can be as high as 21% and contribute to the lengthening of hospital stays and cost increases [5, 22].

Our analysis suggests a number of important features in considering the introduction of a rotavirus vaccine. Hospitalization costs, vaccine efficacy and vaccine price are the main determinants of a cost-effectiveness equation. We only modified the price of the vaccine, keeping constant the rest of the features to calculate the break-even price per dose.

Thus, for RotaTeq® the price for a profitable vaccination programme would be about € 35 per dose, and for Rotarix® about € 60 from society's perspective.

If it is assumed that the vaccine has cost-utility when the cost per QALY gained is less than € 30,000, Rotarix® would have cost-utility under € 60 and RotaTeq® under € 35 from the Health Service payer's perspective.

The analysis presented in this study may be considered a useful support for decision making, and should be carried out prior to implementing a vaccination programme. A more in-depth analysis of direct and indirect costs would clarify some of the limitations mentioned above.

Thus, it would be very beneficial for healthcare administrations and industry to work together in this kind of analysis in order to develop a realistic needs assessment and suitable prioritisation in public health decisions.

In conclusion, systematic rotavirus vaccination

in Castilla y León is not cost-effective. Nonetheless, much of the rotavirus disease burden could be avoided with this vaccine. The high price of the vaccine limits the efficiency of this programme. A more competitive price could reduce this gap and bring the rotavirus vaccine closer to a cost-utility preventive measure.

Key words: rotavirus infection, vaccination, cost-effectiveness, cost-benefit.

SUMMARY

Rotavirus is one of the main causes of acute gastroenteritis in infants and young children. Furthermore, rotavirus is the leading cause of hospitalization and death from acute gastroenteritis among infants and young children worldwide. Although death due to rotavirus is rare in industrialized regions such as Spain, the rotavirus disease burden and its economic impact is severe. This study aims to assess systematic vaccination against rotavirus economically and socially in a Spanish region.
Economic cost-effectiveness and cost-benefit assessment through a choice tree was designed. We estimated health provider costs, economic costs and quality-adjusted life years (QALYs) lost due to rotavirus infections. The study includes a fictitious cohort of 100,000 children from Castilla y León who were also administered the rotavirus vaccine together with diphtheria and tetanus toxoids and pertussis (DTP) . The study adopted a society and health care system perspective. A sensitivity analysis was developed to assess the uncertainty of some variables. According to the estimated incidence rate for children in Castilla y León, rotavirus immunization is projected to prevent 45% of cases with RotaTeq® and 57% with Rotarix®. The respective cost per QALY is about € 75,000 and 50,000 from the perspective of the health care system. Routine infant vaccination in Castilla y León using either rotavirus vaccine is not profitable from the payer's perspective and is not cost-effective under basic case assumptions unless the vaccine is available at a lower cost.

RIASSUNTO

I rotavirus costituiscono una delle principali cause di gastroenterite acuta nel neonato e nel bambino. In tutto il mondo, i rotavirus sono la prima causa di ospedalizzazione e mortalità correlate a gastroenterite acuta nei neonati e nei bambini. Nonostante la mortalità attribuibile a rotavirus sia rara in regioni industrializzate quale la Spagna, il carico della malattia da rotavirus, e il conseguente impatto economico, sono rilevanti. Il presente studio è stato condotto nell'intento di valutare da un punto di vista economico e sociale la vaccinazione sistematica anti-rotavirus in una regione spagnola.
La valutazione economica di costo-efficacia e costo-beneficio è stata realizzata attraverso la elaborazione di un albero decisionale. Abbiamo valutato i costi a carico del sistema sanitario, e i "qualità-adjusted life years" (QALY) persi a seguito delle infezioni da rotavirus.
Lo studio ha considerato una coorte fittizia di 100.000 bambini nella regione di Castilla y León ai quali il vaccino anti-rotavirus è stato somministrato unitamente a quello anti-tetano/pertosse/difterite.
Lo studio è stato condotto tenendo conto della prospettiva della società e del sistema sanitario. Al fine di determinare l'incertezza di talune variabili, è stata sviluppata un'analisi di sensibilità.
In accordo al tasso di incidenza stimato per i bambini in Castilla y León, una immunizzazione anti-rotavirus dovrebbe prevenire il 45% dei casi con il vaccino RotaTeq® e il 57% con il Rotarix®. Il costo del QALY è pari a circa 75.000 e 50.000 €, secondo la prospettiva del sistema sanitario. Che si utilizzi l'uno o l'altro dei due vaccini anti-rotavirus, la vaccinazione infantile di routine a Castilla y León non è vantaggiosa dalla prospettiva del pagante e non è costo-efficace, a meno che il vaccino sia disponibile a un costo inferiore.

REFERENCES

[1] Crotti D., D'Annibale M.L., Fonzo G., Medori M.C., Ubaldi M. Enteric infections in the Perugia area: laboratory diagnosis, clinical aspects and epidemiology during 2001. *Infez. Med.* 10, 2, 81-87, 2002.
[2]Palumbo E., Malorgio C., Siani A., Bonora G. Diarrhoea in children: aetiology and clinical aspects. *Infez. Med.* 18, 2, 95-99, 2009.
[3] Parashar U.D., Hummelma E.G., Bresee J.S., et al. Global illness and deaths caused by rotavirus disease in children. *Emerg. Infect. Dis.* 9, 565-572, 2003.
[4] Soriano-Gabarró M., Mrukowicz J., Vesikari T., et al. Burden of rotavirus disease in European Union

countries. *Pediatr. Infect. Dis. J.* 25 (S1), 7-11, 2006.
[5] Luquero F.J., Eiros J.M., Pérez-Rubio A., et al. Gastroenteritis by rotavirus in Spanish children. Analysis of the disease burden. *Eur. J. Pediatr.* 167, 5, 549-555, 2008.
[6] Gil A., Carrasco P., Jimenez R., et al. Burden of hospitalization attributable to rotavirus infection in children in Spain, period 1999-2000. *Vaccine* 22, 2221-2225, 2004.
[7] Roberts J.A., Cumberland P., Sockett P.N., et al. The study of infectious intestinal disease in England: socio-economic impact. *Epidemiol. Infect.* 130, 1-11, 2003.
[8] Fontana M., Zuin G., Pancheri P., et al. SIGEP Working Group on Intestinal Infections. Costs associated with outpatient diarrhoea in infants and toddlers: a nationwide study of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP). *Dig. Liver Dis.* 36, 523-527, 2004.
[9] Floret D., Lina B., Pinchinat S., et al. Epidemiology and burden of rotavirus diarrhoea in day care centers in Lyon, France. *Eur. J. Pediatr.* 165, 905-906, 2006.
[10] Glass R.I., Bresee J.S., Turcios R., et al. Rotavirus vaccines: targeting the developing world. *J. Infect. Dis.* 192 (S1), 160-166, 2005.
[11]Vesikari T., Matson D.O., Dennehy P., et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N. Engl. J. Med.* 354 (1), 23-33, 2006.
[12] Ruiz-Palacios G.M., Pérez-Schael I., Velázquez F.R., et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N. Engl. J. Med.* 354 (1), 11-22, 2006.
[13] Parashar U.D., Holman R.C., Clarke M.J. et al. Hospitalizations associated with otavirus diarrhoea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. *J. Infect. Dis.* 177, 13-17, 1997.
[14] Tucker A., Haddix A., Bresee J, et al. Cost-effectiveness analysis of rotavirus immunization program for the united states. *JAMA* 279 (17), 1371-1376, 1998.
[15] Jit M., Edmunds W.J. Evaluating rotavirus vaccination in England and Wales Part II. The potential cost-effectiveness of vaccination. *Vaccine* 25, 3971-3979, 2007.
[16] Díez M.T., Rodríguez M.J. Coberturas de vacunación sistemática infantil en Castilla y León año 2003. *Bol. Epidemiol. Castilla León* 20, 2004.
[7] Consejo General de Colegios Oficiales de Farmaceúticos. Base de datos del medicamento. Disponibile *online* all'indirizzo: http://www.portalfarma.com/Home.nsf/Home?OpenForm Last visit: march 2011.
[18] Sénecal M., Brisson M., Lebed M.H., et al. Burden of rotavirus a associated gastroenteritis in Canadian families: a prospective community based study. *Can. J. Infect. Dis. Med. Microbiol.* 17, 6, 383, 2006.
[19] Giaquinto C., Van Damme P., Huet F., et al. Costs of community-acquires pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL study. *J. Infect. Dis.* 195 (S1), 37-44, 2007.
[20] Goosens L.M., Standaert B., Hartwig N. The cost-utility of rotavirus vaccination with Rotarix (RIX4414) in the Netherlands. *Vaccine* 26 (8), 1118-1127, 2008.
[21] Gil A., Bayas J., Anegón M., Carrasco P, González A, Ameal AI. Admisiones hospitalarias atribuibles a infección por rotavirus en Cataluña (período 1999-2000). *Vacunas* 6, 123-127, 2005.
[22] Gleizes O., Desselberger U., Tatochenko V., et al. Nosocomial rotavirus infection in European contries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. *Pediatr. Infect. Dis. J.* 25, S12-S21, 2006.
[23] Leung A.K., Kellner J.D., Davies H.D. Rotavirus gastroenteritis. *Adv Ther.* 22, 476-487, 2005.
[24] Sagnelli E., Coppola N., Liorre G. Infectious diarrhoeas. *Infez. Med.* 6, 1, 8-17, 1998.
[25] Lorgelly P.K., Joshi D., Iturriza-Gómara M., et al. Infantile gastroenteritis in the community: a cost of illness study. *Epidemiol. Infect.* 136, 1, 34-43, 2008.
[26] Meeting of the Immunization Strategic Advisory Group of Experts, April 2009-conclusions and recommendations. *Wkly Epidemiol. Rec.* 5, 84, 23, 220-236, 2009.
[27] Richardson V., Hernandez-Pichardo J., Quintanar-Solares M., et al. Effect of rotavirus vaccination on death from childhood diarrhoea in Mexico. *N. Engl. J. Med.* 362, 299-305, 2010.