Exploring new ways of measuring the economic value of vaccination with an application to the prevention of rotaviral disease

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2 THE CONVENTIONAL WAY OF PERFORMING THE HEALTH ECONOMIC ANALYSIS OF ROTAVIRUS VACCINE

As mentioned in the introduction, the economic assessment of new vaccines has followed the same pathway as the one designed for therapeutic drugs. I applied the technique on rotavirus vaccination following this classic approach. By doing so I was able to present the basic economic value of this vaccine. It allows learning what is appropriate and what can be discovered in addition (see next chapter).

2.1 ROTAVIRUS DISEASE BURDEN

In the absence of getting access to very detailed information at country level about the disease burden caused by rotavirus diarrhoea in children which should include cost estimates, I investigated the problem using a modelling approach for 4 different countries in Europe: two big countries (United Kingdom (UK) and France) and two smaller ones (the Netherlands and Belgium). The comparison between the countries is interesting as France and Belgium have a more open health care system where people may have direct access to emergency rooms. This is different for the Netherlands and the UK where stricter control of patients moving to the next health care level is organised through gate-keeping rules set by primary health care physicians. As a result in France and Belgium the disease burden shifts to the health care delivery system in terms of a higher number of hospitalisations and emergency room services, and eventually, a higher medical cost. In the UK and the Netherlands more burden remains at the level of the parents (i.e. the non-professional care-givers) where the indirect cost is higher. It is estimated that the overall cost including direct and indirect cost does not vary that much between the countries and is estimated at around €23.00/yr per child at risk [9].

THE FINANCIAL BURDEN OF ROTAVIRUS DISEASE IN FOUR COUNTRIES OF THE EUROPEAN UNION

PIDJ, 2008, 27: S20-S27

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ABSTRACT

Background: Rotavirus disease is associated with a substantial financial burden. Rotavirus gastroenteritis in children under 5 results in considerable medical resource utilization and burden for parents and society.

Methods: For this study a modelling approach was employed to assess the financial burden of rotavirus disease in 4 European Union countries (Belgium, France, the Netherlands, and the United Kingdom). Both direct medical costs to health authorities and indirect costs borne by society, parents and employers are calculated.

Results: The Purchasing-Power-Parity (PPP)-adjusted direct cost expressed as a cost per exposure year, per child under five, is highest in France (€ 12.26) and Belgium (€ 11.80) compared with the Netherlands (€ 8.13) and the UK (€ 7.67). The PPP-adjusted indirect cost is estimated to be highest in the UK (€ 15.47) and the Netherlands (€ 15.33) compared with France (€ 11.31) and Belgium (€ 10.24). The sum of the direct medical and indirect costs of rotavirus disease management is estimated to be € 23.11 ± € 0.70/yr per child under 5 years for all 4 countries.

Conclusions: In countries where more emphasis is placed on first-line intervention (UK, the Netherlands), direct costs were lower than in countries where access to second-line healthcare support was more open (Belgium, France). The data suggest that the greater burden of financial responsibility of managing rotavirus disease in children is borne by society (higher in the UK and the Netherlands than in France and Belgium). In Europe investment in rotavirus disease management is substantial, therefore medical and economic benefits of a vaccination strategy should be considered to reduce the medical and financial burden associated with acute rotavirus gastroenteritis.

INTRODUCTION

Rotavirus disease is associated with a substantial financial burden. The virus is a major cause of acute gastroenteritis (AGE) in infants and children under the age of 5 years worldwide [1-4]. Each year in industrialized countries, rotavirus AGE is responsible for an estimated 223,000 hospitalizations, 1.8 million outpatient visits, and 7.1 million episodes of home care [2]. Thus, rotavirus AGE results in considerable medical resource utilization and substantial costs to national health care payers, families of patients and employers [5]. In Europe, these costs have only been studied in a limited way and in a few countries [6].

Total cost evaluation of a disease has a significant added value if positioned in the right context. This context is normally the evaluation of the total disease burden which, in addition to costs, includes the clinical consequences at population level (epidemiology) and the Quality of Life (QoL) impact. This complete set of information is essential for the economic evaluation of new treatment options emerging in the market and as such it may be requested from health care authorities as part of the assessment for their policies.

The impact of new interventions on clinical outcomes and on QoL is most often measured and reported through randomized clinical trials. Total cost impact in contrast is generally more complex to assess and may be estimated using modelling techniques. This presents some specific challenges; one such is to include the appropriate cost items in the analysis to reflect the cost perspective under consideration such as that of the patient, the health care provider, the third party payer, or the society. Furthermore, it is impossible to report an overall cost across different countries because cost burden is country-specific. For instance, a treatment resource may be used more often if it is relatively inexpensive, therefore the treatment uptake will influence the disease outcome and total management cost of the disease. Price differences between countries may therefore influence the total cost picture.

In terms of managing diarrhoea in infants and children caused by rotavirus infection, resource use and cost per case are well documented since the disease itself and the different treatment options are well defined [1;3]. The remaining unknowns are the exact frequency of the disease per year, its distribution across various age groups and the proportion of the population following the different treatment patterns available.

There are several methods for capturing epidemiological and financial information relating to a disease. The most accurate is the application of prospective, observational cohort studies with duration of at least one year. An alternative method is the modelling approach that mimics the country-specific disease distribution per year plus the country-specific treatment options. Modelling allows the prediction of values missing in real life, such as the total number of diarrhoea events and associated emergency visits [7;8].

In the present study, we used the modelling approach to assess the financial burden of rotavirus disease in four countries of the EU: Belgium, France, the Netherlands and the UK. We compared the cost of rotavirus disease in terms of direct medical and indirect costs and explored new ways of reporting the results.

METHODS

Country Selection

A decision tree model has been selected to investigate the financial burden caused by rotavirus disease in EU countries. We selected countries for which sufficient reliable back-ground data are available or easily accessible: Belgium, France, the Netherlands and the UK. This selection enabled us to make a comparison between two relatively small and two larger EU countries.

Model selection

We constructed a Markov cohort model [9] developed in TreeAge software (http://www.treeage.com/) (Figure 1). This model reflects the change in disease occurrence adjusted by subject age. The model also includes the different treatment patterns for rotavirus disease, and can be adjusted to the pattern specific to each country. For example, the Netherlands and the UK have an organized medical telephone service where the caller can obtain treatment advice; this is a form of paid support which is not available in other countries. The model is calibrated to the overall disease frequency estimates by country per year over the different age groups and time periods.

Model assumptions

Model assumptions specific to the disease or country include the following:
1) From the underlying disease pattern for rotavirus disease [9-11], a Weibull distribution [12] of probability of infection over the first 70 months of life was constructed with the following parameters: shape coefficient 1.5 and scale coefficient 24.2 (see Figure 2). These parameter values were confirmed by a multi-centre prospective study of the burden of rotavirus acute gastroenteritis in Europe, the REVEAL study [13].

Figure 1 General cohort model structure for rotavirus diarrhea to estimate cost of illness by country

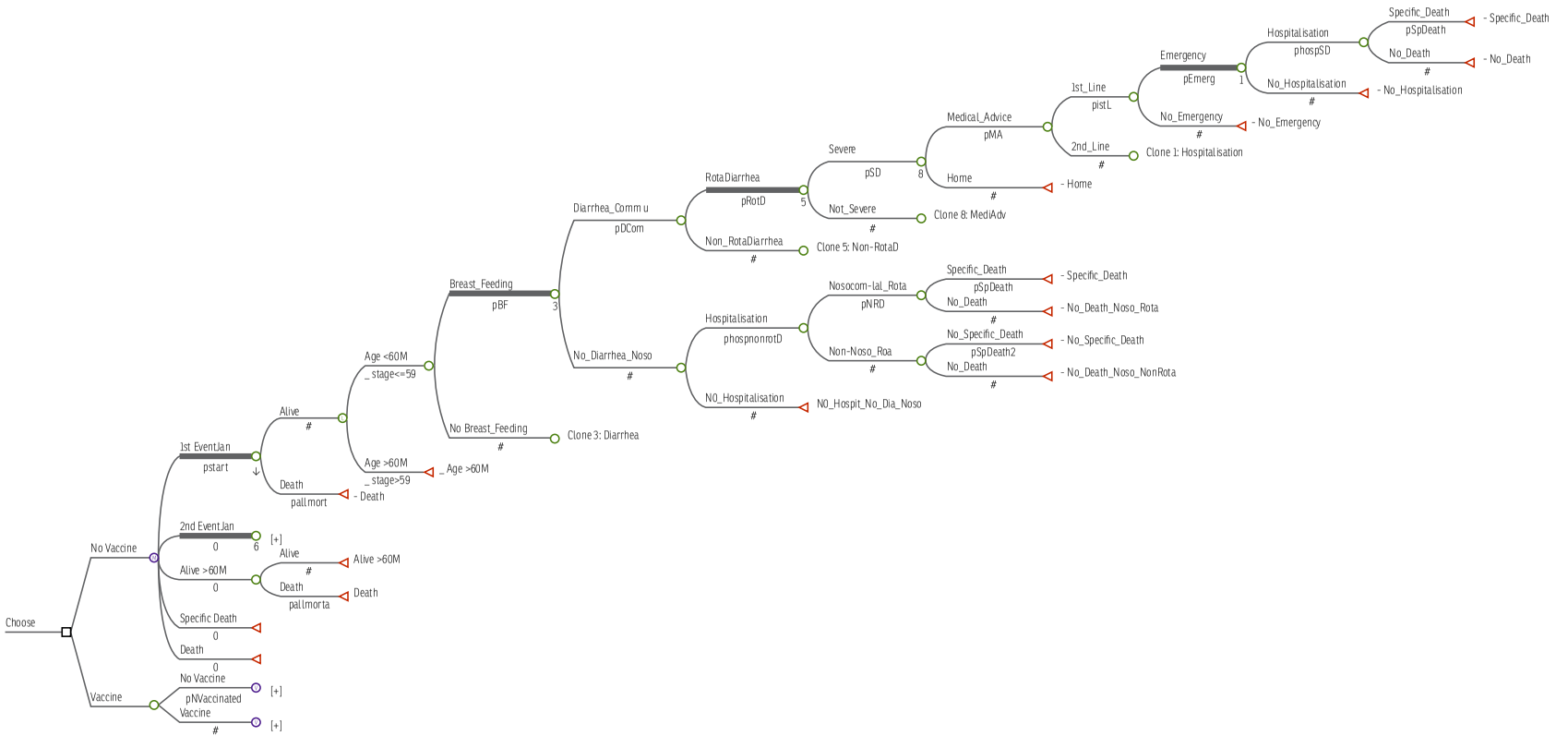
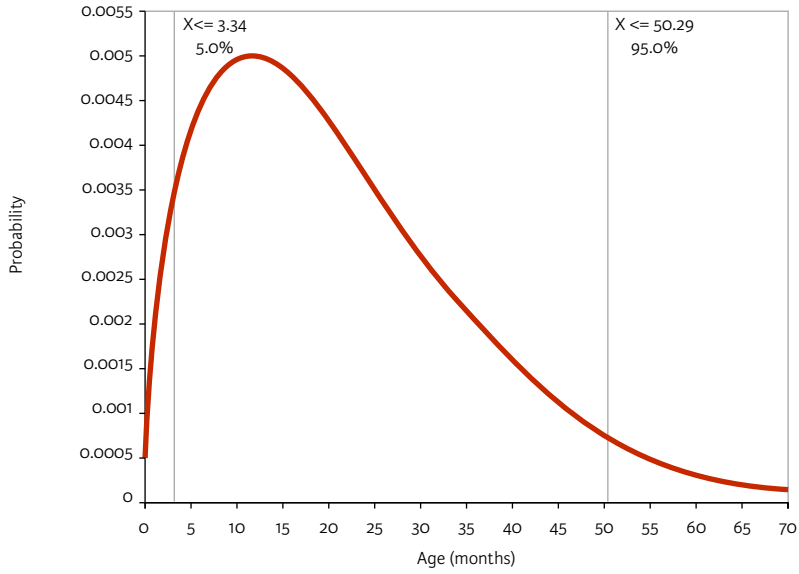


Figure 2 Weibull distribution simulating rotavirus disease frequency as a function of age (months)



2) Overall frequency data on rotavirus diarrhoea events in children under 5 years old are absent. Only data on children seeking medical advice are available. Unless specified, we assumed conservatively that overall a minimum of 40% of the subjects of one birth cohort would suffer from rotavirus diarrhoea before 5 years of age and that medical advice would be sought for a maximum of one in two sick children. The values are comparative estimates based upon studies conducted in France [9]. They are submitted to sensitivity analysis (see below).

3) Full breastfeeding confers protection against viral diarrhoea events [14;15]. We assumed that at least 50% of infants are breast-fed at birth with an exponential decrease thereafter (beta-scale coefficient = 2).

4) Only severely ill children for whom medical advice is sought will be sent to hospital. The severity scale used here is based on a Vesikari score of 11 or more out of 20 points [16].

5) Nosocomial infections occur in a maximum of one-third of young children hospitalized for causes other than community acquired rotavirus diarrhoea, and they are age-dependent [17].

Cost data

Two cost perspectives are considered in this analysis. One is the authority in a country funding the medical costs; the other is the society which includes all the other costs related directly or indirectly to the management of the disease under study. Unit cost data by country for direct medical costs reimbursed or paid by the health authorities in a country are collected from national databases. However, one

Table 1 Unit costs for different items in the treatment of diarrhea per country (expressed in € 2006)[1]

Unadjusted	**Netherlands**			**France**			**Belgium**			**UK**		
Medical visit (GP or Paediatrician)	GP: Home visit:	21€ [25] 41€ [25]	70% 30%	GP: Ped: Home visit:	20€ [26] 22.87€ [26] 30€ [26]	67% 17% 16%	GP: Ped:	16.71€ [27] 19.58€ [27]	50% 50%	GP:	<1y >1y	43.21€[28] 40.79€ [28]
Drug therapy	12€			10€ [29]			N/A			7.51€		
Medical calls	10€ [25]			N/A			N/A			22.50€ [28]		
Emergency visit	N/A			22.87€ [26]			424€ [27]			85.50€ [28]		
Total hospitalization cost (community acquired)	1 844€ [25;30]			1 556 € [31]			1 696€ [27]			918€ [28]		
Total hospitalization cost (nosocomial infection)	1 712€ [32-34]			2 485€ [35]			848€ [27]			1 070€ [36]		
PPP-adjusted	**Netherlands**			**France**			**Belgium**			**UK**		
Rate adjustment	0.923			0.930			0.865			0.963		
Medical Visits (GP or Paediatrician)	GP: Home visit:	19.38€ 37.84€	70% 30%	GP: Ped: Home visit:	18.6€ 21.27€ 27.9€	67% 17% 16%	GP: Ped:	14.45€ 16.94€	50% 50%	GP:	<1y >1y	41.61€ 39.28€
Drug therapy	11.07€			9.3€			N/A			7.23€		
Medical calls	9.23€			N/A			N/A			21.66€		
Emergency visit	N/A			21.27€			366.76€			82.33€		
Total hospitalization cost community acquired infection)	1 702€			1 447€			1 467€			884€		
Total hospitalization cost (nosocomial infection)	1 580€			2 311€			733.52€			1 030€		

[1] References are indicated in parentheses

PPP, Purchasing Power Parity

N/A, Not applicable

Table 2 Maternity, parental and sick child related leave arrangements per country

Country	Maternity Leave	Parental Leave	Sick Child-Related Leave	Ref
Netherlands	16 weeks or 112 days, starting 4 to 6 weeks before childbirth	3 months FT or 6 months PT until the child's 8th birthday	10 days a year	[37-39]
France	16 weeks or 112 days (6 weeks before and 10 weeks after birth) 26 weeks for the third child and subsequent births (8 weeks before and 18 weeks after birth)	1 year Renewed twice per family until the child is 3 years old	3 days a year 5 days a year if the child is under 12 months of age or if parent is caring for at least 3 children under the age of 16	[37-40]
Belgium	15 weeks	3 months FT or 6 months PT per parent per child until the child is 6 years old	10 days a year	[38;39;41]
UK	26 weeks or 182 days, starting at the 11th week before delivery Note: as of April 1st 2007, flat-rate allowance can be paid up to 39 weeks for eligible mothers	13 weeks per parent per child before the child is 6 years old Maximum 4 weeks a year	To be arranged with the employer	[37-39;42]

FT, Full time

PT, Part time

Other sources used:

1) EURES – the European Job Mobility Portal (The European Commission): http://ec.europa.eu/eures/main.jsp?acro=lw&lang=en&catId=490&parentId=0

2) The EMIRE database (European foundation for the improvement of living and working conditions): http://www.eurofound.europa.eu/emire/emire.html

should be aware that reimbursement costs vary slightly within short time periods in a country and one should therefore check for regular updates of those cost values. Table 1 presents the unit costs for a medical (first-line), emergency, and hospital visit, plus the unit costs for treatment. To perform cross-country comparisons, we adjusted the unit cost values with the Purchasing Power Parity (PPP) health care exchange rates per country provided by the OECD [18]. No discount rate was applied on the cost figures as the analysis reports costs per child per year.

Indirect costs were estimated by considering the loss of productivity of the parents of children with rotavirus diarrhoea using the human capital approach [19]. The data for out-of-pocket costs such as additional nappies, co-payment for drugs and medical visits, transport and parking costs are not readily available or are difficult to assess at the country level, therefore they were not included in this analysis.

To obtain an accurate assessment of lost productivity at country level, we analyzed the legislation of social security regarding maternity, parental and sick child-related leave for paid jobs in each country (Table 2). The period of legislated,

Table 3 Proportions of women in the workforce (aged 15-39 years) and average hourly wages per country[1]

Country	Proportion of women in the workforce (%)	Average hourly wage (€)
Netherlands	75	12.20
France	54	12.20
Belgium	55	11.55
UK	66	14.58

[1] Source: Structure of Earnings Survey (SES) 2002 and Labour Force Survey (EU-LFS) 2002 from the Statistical Office of the European Communities (Eurostat). http://ec.europa.eu/eurostat

paid maternity leave is included in the analysis. This period does not allow for accounting an indirect cost during maternity leave. Due to the lack of detailed data on parental and sick child-related leave these issues are too complex to be considered and accounted for in this model. Therefore we estimate a minimum and maximum value of indirect cost due to the impact of rotavirus diarrhoea for each country in the following way: the model generates the number of days of sick child-related leave (due to the child's diarrhoea) for one year (post-maternity leave). This value was multiplied by the reported proportion of employed women in the age-range of 15 to 39 years and the average payment per working hour per women per country. Data on women in the workforce were obtained from the official European statistics database for each country (Table 3). These calculations are considered to yield the maximum estimate of indirect cost by country. The minimum estimate assumed that only half the women in the workforce have a paid job during the first and subsequent years post-partum. Many mothers choose part-time work during that period or benefit from parental leave as authorized in their country. The true value of the indirect cost estimate should fall between the estimates of maximum and minimum values. Lastly, we investigated which group (authorities, employers, and/or employees) paid the most in terms of indirect costs by country.

Sensitivity Analysis

Multiple probabilistic sensitivity analysis is performed on direct medical costs with TreeAge software on two aspects of the input data using distribution estimates: proportion of children with rotavirus AGE and unit cost data (Table 4).

Statistical Analysis

The overall results are reported as absolute costs in Euros (€), per child under 5 years of age and per country. In the multiple probabilistic sensitivity analysis the model is run in second-order Monte-Carlo simulation [12] with 1,000 iterations for each country and reports a cost distribution per country per child under 5 years of age.

RESULTS

The observed values and modelled annual estimates of the total number of rotavirus-related AGE events in children <5 years of age in each country are shown in Table 5. The model accurately reproduces the known values such as the number of medical visits and the hospitalizations for each country. In addition, the model

Table 4 Normal distribution values (mean and standard deviation (SD)) for the probabilistic sensitivity analysis on direct medical cost estimate per country

Cost item	Netherlands		France		Belgium		UK	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cost 1st line	35.93 €	8.98 €	30.70 €	7.68 €	15.45 €	3.86 €	39.75 €	9.94 €
Cost 2nd line			32.87 €	8.22 €	366.76 €	91.69 €	89.56 €	22.39 €
Medical calls	9.23 €	2.31 €	N/A		N/A		21.66 €	5.42 €
Cost of hospitalization visit (community acquired infection)	1 702 €	426 €	1 556 €	389 €	1 467 €	367 €	884 €	221 €
Cost of hospitalization visit (nosocomial infection)	1 580 €	395 €	2 485 €	621 €	734 €	183 €	1 030 €	258 €
Probability of severe diarrhoea	0.53	0.13	0.53	0.13	0.53	0.13	0.53	0.13
Probability of seeking medical advice after severe event	0.50	0.13	0.69	0.07	0.50	0.13	0.50	0.13
Probability of emergency visit after 1st line	N/A		0.51	0.13	0.40	0.13	0.40	0.13

N/A Not applicable

1st line: visit to GP, Paediatrician, home care

2nd line: visit to emergency service

is able to generate estimates for some variables such as rotavirus diarrhoea events and severe rotavirus diarrhoea events that are not available at country level.

Numerical values assembled in Table 5 are then used to estimate the total direct medical costs per year and the direct cost per child under the age of 5 years (Table 6). These costs are presented unadjusted and PPP-adjusted and are tabulated as major cost items for each country per year. The unadjusted cost per child per year varied from € 7.97 to € 13.64, and the PPP-adjusted cost from € 7.67 to € 12.26.

Table 7 shows the estimated PPP-adjusted indirect costs with minimum and maximum values, overall and per child per year. The range of the indirect cost per child per year is estimated at € 10.22 - € 20.44 in the Netherlands, € 7.54 - € 15.07 in France, € 6.83 - € 13.65 in Belgium, and € 10.31 – € 20.63 in the UK.

The calculation of the grand total of direct medical and indirect costs related to rotavirus AGE is reported in Table 8. The sums of both, the direct medical and the indirect costs, reveal that the calculated cost per child of the annual birth cohort and per country is around € 23.11 ± 0.70 (± 3%). In other words, all four countries spend very similar amounts per child per year for the total management of rotavirus AGE.

Table 5 Estimated number of rotavirus related AGE events per year in four EU countries[1]

	Netherlands		France		Belgium		UK	
Birth cohort	187,910 [43]		740,000 [9]		113, 609 [27]		715,900 [44]	
Total number children estimated <5y	935,735		3,684,978		565,739		3,564,967	
Observed (O)/ Model based (M)	O	M	O	M	O	M	O	M
Rotavirus diarrhoea events		73,461 (39.1%)	300,000 (40.5%) [9]	300,083 (40.6%)		44,897 (39.5%)		259,113 (36.2%)
Severe rotavirus diarrhoea		34,762 (18.5%)		141,985 (19.2%)		21,245 (18.7%)		122,648 (17.1%)
No medical advice		49,125 (26.1%)		162,061 (21.9%)		22,884 (20.1%)		147,074 (20.5%)
Seeking medical advice	24,343 (13%) [45]	24,336 (13%)	138,000 (18.6%) [9]	138,021 (18.7%)	22,003 (19,4%) [27]	22,013 (19.4%)	112,000 (15.6%) [28]	112,059 (15.7%)
Medical calls	22,147 (11.7%)	22,145 (11.7%)						36,999 (5.1%)
1st line medical visits	24,343 (13%)	24,336 (13%)	124,200 (16.8%)	124,278 (16.8%)	22,000 (19.4%) [27]	21,994 (19.4%)	112,000 (15.6%) [28]	112,059 (15.7%)
Emergency visits			45,000 (6.1%) [9]	44,973 (6.1%)	5,338 (4,7%) [27]	5,356 (4.7%)	37,496 (5.2%) [28]	37,513 (5.2%)
Hospitalizations (community acquired)	2,940 (1.56%) [45]	2,936 (1.56%)	18,000 (2.43%) [9]	17,943 (2.42%)	2,502 (2.2%) [27]	2,504 (2.2%)	14,300 (2%) [28]	14,363 (2.01%)
Hospitalizations (nosocomial)	808 (0.43%) [45]	813 (0.43%)	6,000 (0.81%) [9]	6,000 (0.81%)	958 (0.84%) [27]	951 (0.84%)	5,897 (0.82%) [46]	5,860 (0.82%)

O, Observed, M, model based.

[1] References are indicated in parentheses

Table 6 Absolute direct medical cost per country, per year & per child (<5y) (unadjusted and PPP-adjusted), and relative proportion of total costs expressed in %

Unadjusted	**Netherlands**		**France**		**Belgium**		**UK**	
Medical visits (1st line)	€ 1,433,212	17%	€ 4,267,179	9%	€ 400,776	5%	€ 5,464,516	19%
Emergency visits			€ 1,478,255	3%	€ 2,262,792	29%	€ 3,489,312	12%
Hospitalizations (community acquired infection)	€ 5,414,899	66%	€ 27,919,885	57%	€ 4,246,249	55%	€ 13,185,070	47%
Hospitalizations (nosocomial infection)	€ 1,391,849	17%	€ 14,909,653	31%	€ 806,801	11%	€ 6,270,006	22%
Total cost	€ 8,239,960	100%	€ 48,574,972	100%	€ 7,716,618	100%	€ 28,408,904	100%
Cost per child per year	€ 8.81		€ 13.18		€ 13.64		€ 7.97	
PPP-adjusted	**Netherlands**		**France**		**Belgium**		**UK**	
Medical visits (1st line)	€ 1,322,855	17%	€ 3,968,476	9%	€ 346,671	5%	€ 5,262,329	19%
Emergency visits			€ 1,374,777	3%	€ 1,957,315	29%	€ 3,360,207	12%
Hospitalizations (community acquired infection)	€ 4,997,952	66%	€ 25,965,493	57%	€ 3,673,005	55%	€ 12,697,222	47%
Hospitalizations (nosocomial infection)	€ 1,284,677	17%	€ 13,865,977	31%	€ 697,883	11%	€ 6,038,016	22%
Total cost	€ 7,605,483	100%	€ 45,174,724	100%	€ 6,674,875	100%	€ 27,357,775	100%
Cost per child per year	€ 8.13		€ 12.26		€ 11.80		€ 7.67	

PPP, Purchasing Power Parity

Figure 3 Probabilistic sensitivity analysis of PPP-adjusted direct medical cost per child, per country, per year

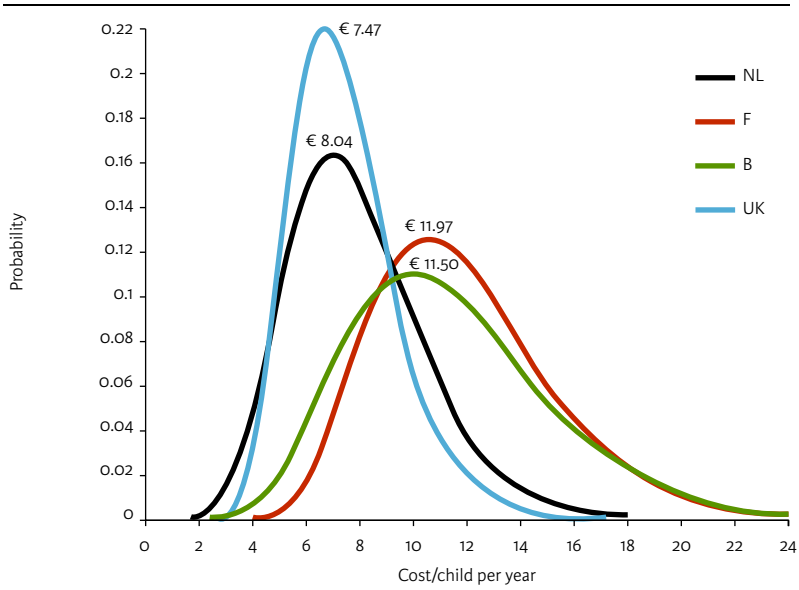


Table 7 PPP-adjusted maximum and minimum indirect costs of rotavirus diarrhea per year in each country

	Netherlands	France	Belgium	UK
Maximum indirect costs	€ 19,204,365	€ 55,786,314	€ 7,756.358	€ 73,838,944
Minimum indirect costs	€ 9,602,182	€ 27,893,157	€ 3,878,179	€ 36,919,472
Maximum per child per year[1]	€ 20.44	€ 15.07	€ 13.65	€ 20.63
Minimum per child per year[1]	€ 10.22	€ 7.54	€ 6.83	€ 10.31
Average per child per year	€ 15.33	€ 11.31	€ 10.24	€ 15.47

[1] Taking into account the size of the birth cohort, Table 5

Table 8 PPP-adjusted total costs of rotavirus diarrhea per year in each country

	Netherlands	France	Belgium	UK
Direct costs	€ 7,605,483	€ 45,174,724	€ 6,674,875	€ 27,357,775
(% of total)	35%	52%	53%	33%
Average Indirect costs	€ 14,403,000	€ 41,840,000	€ 5,817,000	€ 55,379,000
(% of total)	65%	48%	47%	67%
Total costs	€ 22,008,483	€ 87,014,724	€ 12,491,875	€ 82,736,775
Exposure population	935,735	3,684,978	565,739	3,564,967
Total costs per child per year	€ 23.52	€ 23.61	€ 22.08	€ 23.21

Arithmetic mean ± S.D. of total costs per child per year: € 23.11 ± € 0.70 (± 3%)

Figure 3 shows the results from the multiple probabilistic sensitivity analysis of PPP-adjusted direct medical costs per child, per country, and per year. The graph shows the cost range over which the direct medical cost might vary in each country. Countries spending more money in direct medical costs have a higher average value with a higher standard deviation or a wider spread in their costs figures. The average

values in the Figure deviate slightly from the reported cost figures in Table 6 because the results in the graph are skewed following Monte-Carlo simulation.

DISCUSSION

Contrary to what one might expect, estimating the total management cost of a disease at country level is not a straightforward exercise. Although the epidemiology of rotavirus disease, its distribution as a function of age and its annual peak during the winter period may be similar across the different countries, its management and its related costs vary considerably. The use of available healthcare resources depends upon the specific structure of each country's healthcare system. In the UK and the Netherlands, more emphasis is placed on first-line intervention, limiting the use of the more costly second-line healthcare support systems such as emergency services and hospitals. By contrast, Belgium and France provide open access to second-line interventions sooner during the disease process, incurring a higher average direct cost per child for the treatment of rotavirus disease. Consequently, the average direct medical costs per child per year vary by an approximate cost difference of € 4.6 between the most and the least expensive countries.

The probabilistic sensitivity analysis suggests that healthcare systems such as those in the Netherlands and the UK may manage rotavirus disease more efficiently compared with the systems in France and Belgium as they do not seem to have comparatively more diarrhoea cases or specific deaths, yet their average global medical management costs per child are lower. This is also reflected in the curves of Figure 3 where France and Belgium have much larger standard deviations around average costs than the Netherlands and the UK.

In all four countries, 70 to 80% of the total direct medical costs are due to hospitalization including community acquired and nosocomial infections. The indirect costs are, however, highest in the Netherlands and the UK, contrary to what is observed for the direct medical costs. The surprising result is that the total costs of AGE are very similar in all 4 countries studied, with the difference between the most and the least expensive country being marginal (€ 1.53). This result demonstrates that a direct medical cost analysis alone would only have revealed part of the total relevant costs. One can conclude that the more emphasis is placed on first-line treatment and parental care of sick children, the higher the indirect costs are for society, as the comparison between the UK and the Netherlands on one hand and France and Belgium on the other demonstrates.

The strength of our comparative analysis is that it follows a standard approach for every country and uses the same basic model with the underlying distribution of the disease as a function of age. It allows for a better comparison across countries. Another advantage is that we are able to estimate an average investment per child per year per country. It is known that for every child born in one of the four countries studied, the health authorities will invest on average between € 7.67 and € 12.26 in direct medical costs against rotavirus disease per year and between € 10.2 and € 15.5 in indirect costs per year. The total costs (direct and indirect) are very similar for all 4 countries at € 23.11 ± 0.7 (± 3%).

Table 9 Distribution of indirect costs by country

	Netherlands	France	Belgium	UK
Maternity leave	Compulsory health insurance	Compulsory social insurance	Compulsory social insurance	
	Financed by contributions from employers, employees, state	Financed by contributions from employers, employees, taxes	Financed by contributions from employers, employees, state	Financed by contributions from employers, employees, taxes
Parental leave	Unpaid	As above	As above	Unpaid
Sick child - related leave	Employer	Unpaid	Unpaid	Employer

Sources:
Netherlands: Ministry of Health, Welfare and Sport: Health Insurance in the Netherlands. The new health insurance system from 2006
Other countries: European Commission: Mutual information system on social protection (MISSOC) http://ec.europa.eu/employment_social/soc-prot/missoc98/english/f_main.htm

The limitations of our analysis should also be considered. The cost per unit for each service offered and the total number of rotavirus disease events has been difficult to quantify with sufficient accuracy. The use of modelling implies that assumptions and uncertainties are introduced into the evaluation. Thus, our modelling approach may be open to criticism regarding the way some data are analyzed and interpreted, particularly with respect to the missing data. Serious disease events may lead to hospitalization whereas mild and moderate events are more often treated at home or in outpatient settings. In that respect, the model introduces limits on the units it generates: the number of emergency visits and hospitalizations should always be lower than the number of serious rotavirus-related AGE events. The sum of subjects staying at home, not seeking medical advice, together with those seeking advice should be equal to the total number of children with rotavirus diarrhoea. Using sensitivity analysis, we tested these uncertainties to observe their combined importance as shown in Figure 3.

Our approach is appropriate or even conservative when the results presented here are compared with recent investigations in Belgium and France [20;21]. For instance, the direct medical and grand total cost for rotavirus disease estimated by Bilcke et al. [20] for Belgium amount to € 7.4 million and € 19.6 million, respectively. Our results of € 7.7 million for direct medical and € 14.5 million (unadjusted cost figures in Tables 6 and 8, respectively) for the grand total were in line for the direct medical, but underestimated for the indirect cost as expected. For France, Huet et al. [21] report total direct costs of € 63 million to the National Healthcare Payer rising to € 177 million from the societal perspective compared with € 48.5 million and € 87.1 million, respectively, here. This can in part be explained by the inclusion of out-of-pocket costs by Huet et al. Another important difference is that Huet reports a much higher percentage of children with rotavirus AGE seeking medical care compared with this publication. Lorgelly et al. [22] reported the total cost per child from a societal perspective in the UK as £86.33. During the at risk period of 5-years this would equate to approximately € 26 per year, compared with the unadjusted total cost per child per year of € 24 presented in this analysis.

Finally, the Netherlands will in general report a lower indirect cost than presented here as they are using the friction cost method [23] to estimate this type of societal cost, which could be half the cost calculated when the human capital method is chosen [19]. Our estimate for indirect costs should be substantiated with additional data to be collected through information supplied by the parents. We expect to have details on this type of data soon. In the absence of accurate data, the cost estimate for parental and sick child-related leave yielded only a range. In this analysis, it was further assumed that only mothers took sick child-related leave.

In healthcare systems such as those of the Netherlands and the UK, much of the financial responsibility of caring for children with rotavirus disease falls on the parents. Indirect costs are often not included in health economic analyses but constitute a considerable burden for families and society. Thus, in countries where first-line management is most promoted, a vaccination policy to prevent rotavirus disease is likely to benefit individuals and employers more than the healthcare sector. Employers may see the benefit in offering a free-of-charge vaccination program to young children of their employees (Table 9). Further data are required before this approach is more thoroughly considered.

Rotavirus infection is a major cause of AGE in children under the age of 5 years [2]. Children with severe diarrheal disease are often hospitalized, contributing a significant cost to the healthcare expenditures in a country. In addition, rotavirus disease causes considerable burden for parents and families who must take time off work or other activities to care for their sick children. Studies in the UK and the US have shown that rotavirus vaccination is a cost-effective intervention and can improve the QoL of children and their parents affected by rotavirus AGE [22;24]

REFERENCES

[1] Parashar UD, Bresee JS, Gentsch JR, Glass RI. Rotavirus. Emerg Infect Dis 1998 Oct;4(4):561-70.
[2] Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003 May;9(5):565-72.
[3] Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006 Feb;12(2):304-6.
[4] Koopmans M, Brown D. Seasonality and diversity of Group A rotaviruses in Europe. Acta Paediatr Suppl 1999 Jan;88(426):14-9.
[5] Giaquinto C, Van DP, Huet F, Gothefors L, Van der WM. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. J Infect Dis 2007 May 1;195 Suppl 1:S36-S44.
[6] Van Damme P., Van der Wielen M., Ansaldi F, Desgrandchamps D, Domingo JD, Sanchez FG, et al. Rotavirus vaccines: considerations for successful implementation in Europe. Lancet Infect Dis 2006 Dec;6(12):805-12.
[7] Djuretic T, Ramsay M, Gay N, Wall P, Ryan M, Fleming D. An estimate of the proportion of diarrhoeal disease episodes seen by general practitioners attributable to rotavirus in children under 5 y of age in England and Wales. Acta Paediatr Suppl 1999 Jan;88(426):38-41.

[8] Ryan MJ, Ramsay M, Brown D, Gay NJ, Farrington CP, Wall PG. Hospital admissions attributable to rotavirus infection in England and Wales. J Infect Dis 1996 Sep;174 Suppl 1:S12-S18.
[9] Melliez H, Boelle PY, Baron S, Mouton Y, Yazdanpanah Y. [Morbidity and cost of rotavirus infections in France]. Med Mal Infect 2005 Oct;35(10):492-9.
[10] Brandt CD, Kim HW, Rodriguez WJ, Arrobio JO, Jeffries BC, Stallings EP, et al. Pediatric viral gastroenteritis during eight years of study. J Clin Microbiol 1983 Jul;18(1):71-8.
[11] Fourquet F, Desenclos JC, Maurage C, Baron S. [Acute gastro-enteritis in children in France: estimates of disease burden through national hospital discharge data]. Arch Pediatr 2003 Oct;10(10):861-8.
[12] Law A, Kelton W. Simulation Modeling and Analysis. 3 ed. McGraw Hill Higher Education; 2000.
[13] Giaquinto C, Van DP, Huet F, Gothefors L, Maxwell M, Todd P, et al. Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004-2005: the REVEAL study. J Infect Dis 2007 May 1;195 Suppl 1:S26-S35.
[14] Clemens J, Rao M, Ahmed F, Ward R, Huda S, Chakraborty J, et al. Breast-feeding and the risk of life-threatening rotavirus diarrhea: prevention or postponement? Pediatrics 1993 Nov;92(5):680-5.
[15] Newburg DS, Peterson JA, Ruiz-Palacios GM, Matson DO, Morrow AL, Shults J, et al. Role of human-milk lactadherin in protection against symptomatic rotavirus infection. Lancet 1998 Apr 18;351(9110):1160-4.
[16] Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 1990;22(3):259-67.
[17] Gleizes O, Desselberger U, Tatochenko V, Rodrigo C, Salman N, Mezner Z, et al. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. Pediatr Infect Dis J 2006 Jan;25(1 Suppl):S12-S21.
[18] OECD in Figures 2006-2007. www.oecd.org/infigures 2006 [cited 2007 Jul 6] (2006-2007 Edition)
[19] Le T, Gibson J, Oxley L. Cost- and income-based measures of human capital. Journal of Economic Surveys 2007;17(3):271-307.
[20] Bilcke J, Beutels P, De Smet F, Hanquet G, Van Ranst M, Van Damme P. Vaccination des nourrissons contre le rotavirus en Belgique. Analyse coût-efficacité. Centre fédéral d'expertise des soins de santé (KCE); 2007. KCE reports 54B.
[21] Huet F, Largeron N, Trichard M, Miadi-Fargier H, Jasso-Mosqueda G. Burden of paediatric rotavirus gastroenteritis and potential benefits of a universal rotavirus vaccination programme with RotaTeq(R) in France. Vaccine 2007;In Press, Uncorrected Proof.
[22] Lorgelly PK, Joshi D, Iturriza GM, Gray J, Mugford M. Exploring the cost effectiveness of an immunization programme for rotavirus gastroenteritis in the United Kingdom. Epidemiol Infect 2007 Mar 5;1-12.
[23] Brouwer WB, Koopmanschap MA. The friction-cost method : replacement for nothing and leisure for free? Pharmacoeconomics 2005;23(2):105-11.

[24] Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Cost-effectiveness and potential impact of rotavirus vaccination in the United States. Pediatrics 2007 Apr;119(4):684-97.
[25] Kemmeren JM ., Mangen M-JJ, van Duynhoven YTHP, Havelaar AH. Rotavirus, in Priority setting of foodborne pathogens. Disease burden and costs of selected enteric pathogens. Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment): Bilthoven; 2006. RIVM report 330080001/2006.
[26] Official medical tariff list (UCANSS). Ucanss 2006 2007 June 22 [cited 2007 Jul 1]Available from: URL: http://www.ucanss.fr/
[27] Fruytier AC, Van Schoor J, Standaert B. Vaccination with RIX4414 is cost-effective in a Belgian setting (Poster PIH3, presented at ISPOR 9th Annual Congress, Copenhagen (DK), October 29, 2006). Ref Type: Generic
[28] Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales: Part I. Estimating the burden of disease. Vaccine 2007 May 16;25(20):3962-70.
[29] Martinot A, Dumonceaux A, Grandbastien B, Hue V, Leclerc F. Reseau interhospitalier d'evaluation des pratigues medicales dans les affections courantes de l'enfant. [Evaluation of the ambulatory treatment of acute diarrhea in infants]. Arch Pediatr 1997 Sep;4(9):832-8.
[30] de Wit MA, Koopmans MP, van der Blij JF, van Duynhoven YT. Hospital admissions for rotavirus infection in the Netherlands. Clin Infect Dis 2000 Sep;31(3):698-704.
[31] National Costs Study 2005. Public hospitals 2005 [cited 2007 Oct 16] Available from: URL: www.atih.sante.fr
[32] Contactisolatie kinderen (Contact isolation children). Dutch Workingparty on Infection Prevention 2004 [cited 2007 Jul 6]Available from: URL: http://www.wip.nl/
[33] Oostenbrink J, Koopmanschap M, Rutten F. Handleiding voor kostenonderzoek - Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg [Guide to cost research - Methods and standard costs prices for economic evaluatons in healthcare]. College voor zorgverzekeringen (Health Care Insurance board): Amstelveen; 2004.
[34] Oostenbrink R, Moons KG, rksen-Lubsen AG, Grobbee DE, Moll HA. A diagnostic decision rule for management of children with meningeal signs. Eur J Epidemiol 2004;19(2):109-16.
[35] Sermet-Gaudelus I, de La RF, Salomon JL, Lachassine E, Leruez-Ville M, Baujat G, et al. [Rotavirus nosocomial infection in pediatric units. A multicentric observation study]. Pathol Biol (Paris) 2004 Feb;52(1):4-10.
[36] Harrington M, Butler K, Cafferkey M. Rotavirus infection in hospitalised children: incidence and impact on healthcare resources. Ir J Med Sci 2003 Jan;172(1):33-6.
[37] Directionate General of Human Rights. Parental Leave in Council of Europe Member States. 1-50. 2005. Strasbourg, Council of Europe. Ref Type: Generic

[38] European Foundation for the Improvement of Living and Working Conditions. Parental leave in European companies: establishment survey on working time 2004-2005. 1-57. 2007. Dublin, Ireland, European Foundation for the Improvement of Living and Working Conditions. Ref Type: Generic
[39] Moss P, O'Brien M. International review of leave policies and related research 2006. Department of Trade and Industry; 2006. [Series] Employment relations research series no. 57.
[40] Guide sécurité sociale de l'employeur. L'Union des Caisses Nationales de Sécurité Sociale 2006Available from: URL: http://www.ucanss.fr/services/textes_documents/gsse/accueil_gsse.htm
[41] Interruption de carrière dans le cadre du congé parental. NEO - National employment office 2007:1-9. Available from: URL: http://www.onem.fgov.be/D_opdracht_LBO/Regl/Werknemers/ouderschap/Ov_Cp/ContentFR.htm#TopOfPage
[42] Time off for dependants: A guide for employers and employees (UK). Department of Trade and Industry (UK) 2000:1-20. Available from: URL: http://www.berr.gov.uk/files/file11419.pdf
[43] Bevolking, geboorte. (Population, birth). Centraal Bureau voor de Statistiek, Voorburg/Heerlen 2007 [cited 2007 Jul 9]Available from: URL: www.statline.cbs.nl
[44] Mid-2005 population estimates. Office of National Statistics 2007Available from: URL: http://www.statistics.gov.uk/statbase/Expodata/Spreadsheets/D9387.xls
[45] Al MJ, Goossens L, Hövels AM, Michielsen CP, Standaert B. Cost-effectiveness of mass vaccination with a rotavirus vaccine in the Netherlands (Poster PIN19, presented at ISPOR 9th Annual Congress, Copenhagen (DK), October 30, 2006). Ref Type: Generic
[46] Martin A, Stantaert B. Cost effectiveness of infant vaccination with Rotarix in the UK. 25th Annual Meeting of the European Society for Paediatric Infectious Diseases, ESPID, Porto, Portugal 2007.

2.2 QALY-MEASUREMENT

When the first estimates on cost-effectiveness of rotavirus vaccination were reported around 1998 when RotaShield came on the market, there was no clear way to include QALYs for the different health states to which children could be exposed to during the management process of rotavirus disease. Different options were explored to get that type of information collected in one or another way.

One proposal was to collect the data through surrogate persons who are classified as most neutral to the situation but still having enough experience with the disease and its consequences to be able to evaluate correctly the situation.

A number of GPs and paediatricians in the UK were interviewed and they were exposed to series of scenarios from mild to severe diseases and that for two

different age-groups (<18 months and >=18 months). This way of working allows getting a good range of utility scores by different health states the disease can go through. This was reported in the following publication [10].

ESTIMATING UTILITY SCORES IN YOUNG CHILDREN WITH ACUTE ROTAVIRUS GASTROENTERITIS IN THE UK

JME, 2008, 11: 471-484.

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ABSTRACT

Objective: To estimate utility scores for different severities of acute rotavirus gastroenteritis in children aged <5 years in the UK.

Methods: UK general practitioners (n=25) and paediatricians (n=25) rated four different health state descriptions of acute rotavirus gastroenteritis using the EuroQol (EQ-5D) questionnaire for children aged <18 months and 18 months to 5 years. EQ-5D scores were modified to account for limited self-care and mobility, and converted into utility values using the standard algorithm using UK data.

Results: General practitioners rated the mean utility for primary care cases at 0.781 (SD 0.263) and 0.688 (SD 0.345) for the younger and older age groups, respectively. For hospitalised cases the corresponding scores were 0.425 (SD 0.243) and 0.200 (SD 0.386). Paediatricians rated the mean utility for hospitalised severe cases at 0.595 (SD 0.171) and 0.634 (SD 0.217) in the younger and older groups, respectively, and for hospitalised very severe cases at 0.256 (SD 0.251) and 0.077 (SD 0.340), respectively. In all cases, the utility differences between the health states were statistically significant (p<0.0001).

Conclusions: Acute rotavirus gastroenteritis substantially impairs quality of life in children aged <5 years as rated by health professionals. This study provides useful quantitative utility estimates for economic evaluations.

INTRODUCTION

Acute rotavirus gastroenteritis is a highly contagious viral disease that is most common during the winter and mainly affects infants and young children less than five years old. The main symptoms of acute rotavirus gastroenteritis are vomiting, fever and profuse watery diarrhoea, which may result in serious dehydration [1] [2]. It has been estimated that almost every child will be infected with the virus before the age of five years [3]. Over 600,000 children will die annually from rotavirus-related illness worldwide [4]. Most of the deaths (over 80%) occur in the developing world.

In industrialised countries death from acute rotavirus gastroenteritis is rare, but the disease burden is substantial. For example, rotavirus is responsible for 50% of

hospital admissions for acute gastroenteritis in children aged <5 years in Australia [5]. In the UK, the number of children aged <5 years hospitalised for acute rotavirus gastroenteritis is estimated to be as high as 17,000 a year, or 5.2 per 1000 [6]. Other developed countries report similar rates; 7.5 per 1000 in Australia, and 3 per 1000 in the European Union [7].

Many rotavirus infections are hospital-acquired. A study in a UK paediatric hospital estimated that rotavirus was responsible for 19% of healthcare-associated acute gastroenteritis [8], and across the European Union countries 21% of in-patient cases of rotavirus gastroenteritis were hospital-acquired [7]. Hospitalised cases of acute rotavirus gastroenteritis have been estimated to cost approximately 900–1800 Euros (€) per case in four European Union countries (Belgium, France, the Netherlands and the UK) [9]. Acute rotavirus gastroenteritis is also a substantial burden on primary care, accounting for up to 29% of the visits to general practitioners (GPs) for infectious intestinal disease in children aged <5 years, or over 150,000 GP visits per year in the UK [10].

There is no specific treatment for rotavirus infection [4;4], and the aim of clinical management in most cases is the prevention of dehydration [1]. However, oral rehydration therapy can be difficult to administer successfully in children with severe vomiting, which is common in acute rotavirus gastroenteritis [4], and rotavirus gastroenteritis occurs mainly in the winter, when health services are already under pressure. This makes vaccination an attractive option to prevent rotavirus-related illness and hospitalisations [11], with the potential to reduce considerably the associated morbidity and healthcare costs in both primary and secondary care.

A recent study in infants in their first two years of life in six European countries showed that the vaccine RIX4414 (Rotarix™[1]) was highly effective, reducing acute rotavirus gastroenteritis episodes of any severity by 87% [12]. RIX4414 is a monovalent vaccine derived from the most common human rotavirus strain, G1P [13]. It provides cross-protection against most other serotypes and is given in two oral doses. A second rotavirus vaccine, RotaTeq™[2], a pentavalent vaccine based on a bovine strain (WC3), has also demonstrated efficacy and is administered in three oral doses [14]. The research presented in the current paper is applicable to both vaccines. When deciding whether to introduce and fund mass rotavirus vaccination programmes, healthcare providers will require data on the cost-effectiveness of vaccination as well as on safety and efficacy. Cost-utility analysis, in which health benefits are expressed in quality-adjusted life-years (QALYs), is a widely accepted approach for assessing the cost-effectiveness of healthcare technologies [15], and is applied by bodies such as the UK National Institute for Health and Clinical Excellence (NICE). Calculation of the potential gain in QALYs from implementing a vaccination programme requires a health-related quality of life (HRQL) weighting or utility value for acute rotavirus gastroenteritis health states, on a scale between 0 (death) and 1 (full health).

1 Rotarix™ is a trade mark of the GlaxoSmithKline group of companies

2 RotaTeq™ is a trade mark of Merck & Co

Such utility values are presently lacking, because of the difficulty of obtaining those values from young children and/or their direct environment. A study in Canada presented as an abstract has estimated utility values for children with acute rotavirus gastroenteritis by proxy assessment using the Health Utilities Index Mark 2 (HUI2), but did not distinguish between different severities of illness [16]. A recently published study in Germany has estimated HRQL in young children with diarrhoea by proxy assessment using a visual analogue scale [17]. To our knowledge, no previous study has estimated utility scores for different severities of acute rotavirus gastroenteritis using a recognised HRQL instrument with a validated method for converting the scores into utility values.

The objective of the present study was to estimate utility values for various severities of acute rotavirus gastroenteritis in children aged <5 years in the UK. Results from the study have been presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 9th Annual European Congress in 2006 [18].

PATIENTS AND METHODS

Utility was rated by 25 general practitioners (GPs) and 25 paediatricians as proxy respondents, as infants and young children would be unable to complete a HRQL questionnaire. Physicians were selected instead of parents as they were considered more likely to be able to distinguish between different severities of acute rotavirus gastroenteritis. All respondents were working within the UK National Health Service (NHS) and had a minimum of 5 years and maximum of 25 years of experience. They were drawn from five geographical regions of the UK (Scotland, Wales, South-east England, Midlands and North/North-east England).

Currently there is no disease-specific HRQL questionnaire developed for diarrhoea in children and few specific instruments are designed to assess the generic HRQL in children aged <5 years [19;20]. HRQL in young children can be assessed using parents or physicians as proxy respondents [19]. Several tools are available for measuring HRQL and utility [21;22]. For the present study we decided to use the EuroQol (EQ5D) questionnaire [23], completed by healthcare professionals acting as patient proxies with the necessary clinical experience to rate the health state of children with acute gastroenteritis. The EQ5D was chosen because it is widely used, was designed to be applicable in multiple countries, and the rating scores derived from it can be converted to utility values using a standard country-specific algorithm [24]. The EQ5D rates quality of life in five dimensions or domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents were presented with health state descriptions, representing the clinical presentation of different severities of acute rotavirus gastroenteritis, and asked to rate each health state for infants aged <18 months and children aged 18 months to 5 years. Two age bands were used because most children aged 18 months or over are able to walk and so the mobility domain of the EQ5D is more relevant in this age group. Health state descriptions were checked by a GlaxoSmithKline physician (Dr Norman Begg) with both clinical and public health experience.

Table 1 Health state descriptions presented to respondents

General practitioners	
Primary care only	**Referred to hospital**
Acute gastroenteritis NOT severe enough to warrant referral for hospital admission Liquid diarrhoea (loose stools, non-bloody), 1–3 episodes/day Vomiting either not present or infrequent Fever may or may not be present Dehydration may be present BUT parents/carers are able to manage rehydration at home OR No signs of dehydration present and risk of dehydration is LOW	Acute gastroenteritis severe enough to warrant referral for hospital admission Liquid diarrhoea present (more than usual loose stools, non-bloody), 4 or more episodes/day Vomiting may or may not be present Fever may or may not be present Signs of dehydration are present AND parents/carers are unable to manage rehydration at home OR There is a high risk of dehydration (>4 vomits/day; >8 liquid stools/day; child aged <6 months)
Paediatricians	
Hospitalised, severe	**Hospitalised, very severe**
Acute rotavirus infection severe enough to warrant admission or at least short-term observation Vesikari score ≥10 Signs of 3–8% dehydration present OR high risk of dehydration Parents unable to manage rehydration	Acute rotavirus infection severe enough to warrant admission or at least short-term observation Vesikari score ≥10 Signs of ≥9% dehydration present

Vesikari score described in reference [2]

Table 2 Respondent characteristics

	GPs (n=25)	**Paediatricians (n=25)**
Number (%) in each region:		
Scotland	5 (20)	4 (16)
Wales	5 (20)	6 (24)
South-east England	5 (20)	6 (24)
Midlands	5 (20)	5 (20)
North/North-east England	5 (20)	4 (16)
Years of experience:		
Mean	15.8	9.3
SEM	0.95	1.07
Median	18.0	8.0
Number of cases of acute gastroenteritis seen each month:		
Mean	18.1	20.6
SEM	4.00	4.60
Median	12.0	12.0

GP = general practitioner; SEM = standard error of the mean

GPs do not routinely test for rotavirus infection and so were presented with two health state descriptions of acute infectious gastroenteritis, one describing a case severe enough to be referred to hospital, and the other describing a case that could be managed in primary care. The GPs were not asked to decide whether they would refer each case, the criterion of referral was explicit in the health

state descriptions presented (Table 1). The health state descriptions were based on the major symptoms of acute rotavirus gastroenteritis described in the clinical literature, including frequency of liquid diarrhoea, presence of fever and/or vomiting, the risk of dehydration and the ability of parents to manage rehydration at home [25;26] (Table 1). All GPs were presented with the same two health state descriptions.

Paediatricians were presented with two health state descriptions of acute rotavirus infection with a Vesikari score of at least 10, which indicates a clinical severity sufficient to be considered for admission to hospital. The two health states were differentiated by the severity of dehydration present (Table 1). All paediatricians were presented with the same two health state descriptions.

Respondents were asked to rate the health status of a child in each of the two age bands and each of the described health states in relation to the child's normal capability in full health. If they felt a domain was not applicable for a child of the given age band, they could mark the domain "not applicable". Where a respondent marked a domain "not applicable", this was assigned a default rating of 1, meaning "no impairment". In the main analysis, the self-care and mobility domains were assigned a rating score of 1 for children aged <18 months, and the domain of self-care a rating score of 1 in children aged 18 months to 5 years, regardless of whether respondents rated these domains. This modification was applied because children aged <5 years would normally have limited capacity for self-care and children aged <18 months would normally have limited mobility, so it may not be valid to attempt to rate the impact of acute rotavirus gastroenteritis on these domains. A secondary analysis considered the raw data scores, without these modifications, and both sets of data are presented here.

The raw and modified EQ5D scores were converted to weighted utility values using a published algorithm [24]. This assigns each EQ5D score a utility value based on a survey of a representative sample of the UK population using the time trade-off method.

Descriptive statistics were compiled, including mean, standard deviation, median and 95% confidence intervals (95% CI). Non-normality was tested using kurtosis and skewness and confirmed by the Kolmogorov-Smirnov test. Comparisons between different age groups were performed using the Wilcoxon Signed Rank test, as the data were not normally distributed. However, reporting focuses on mean values, as these are of more interest for economic evaluation than medians. P-values ≤0.05 determined statistically significant differences. Descriptive summary statistics were analysed using Microsoft Excel and the comparative statistics were analysed using Stata (StataCorp, Texas, US) version 9.

RESULTS

A total of 25 GPs and 25 paediatricians participated in the survey. Their distribution across the five geographic regions of the UK is shown in Table 2.

Table 3 General practitioner utility scores

	Age <18 months		Age 18 months – 5 years	
	Primary care only	**Referred to hospital**	**Primary care only**	**Referred to hospital**
EQ5D utility scores (modified)				
Mean	0.781	0.425	0.688	0.200
95% CI	0.678, 0.884	0.330, 0.520	0.553, 0.824	0.049, 0.352
SD	0.263	0.243	0.345	0.386
Median	0.796	0.362	0.760	0.128
Lower quartile	0.760	0.197	0.620	–0.117
Upper quartile	1.000	0.433	0.883	0.620
P-value for difference between health states	P<0.0001		P<0.0001	
EQ-5D utility scores (raw)				
Mean	0.601	0.102	0.634	0.032
95% CI	0.434, 0.768	–0.042, 0.246	0.473, 0.794	–0.131, 0.195
SD	0.426	0.367	0.409	0.417
Median	0.760	0.082	0.746	0.079
Lower quartile	0.436	–0.166	0.587	–0.331
Upper quartile	0.883	0.242	0.796	0.336

CI = confidence interval; SD = standard deviation

Modified = EQ-5D scores adjusted to show no impact in mobility and self-care domains in age group <18 months, and no impact in self-care domain in age group 18 months – 5 years

Raw = actual EQ5D score from respondents

Table 4 Paediatrician utility scores

	Age <18 months		Age 18 months – 5 years	
	Hospitalised severe	**Hospitalised very severe**	**Hospitalised severe**	**Hospitalised very severe**
EQ5D utility scores (modified)				
Mean	0.595	0.256	0.634	0.077
95% CI	0.528, 0.662	0.157, 0.354	0.549, 0.718	–0.057, 0.210
SD	0.171	0.251	0.217	0.340
Median	0.689	0.197	0.620	0.048
Lower quartile	0.433	0.099	0.620	–0.117
Upper quartile	0.689	0.433	0.991	0.293
P-value for difference between health states	P<0.0001		P<0.0001	
EQ5D utility scores (raw)				
Mean	0.208	–0.208	0.542	–0.093
95% CI	0.100, 0.315	–0.335, –0.080	0.445, 0.638	–0.242, 0.055
SD	0.275	0.325	0.246	0.379
Median	0.137	–0.331	0.516	–0.163
Lower quartile	0.079	–0.380	0.516	–0.331
Upper quartile	0.208	–0.095	0.621	0.079

CI = confidence interval; SD = standard deviation

Modified = EQ-5D scores adjusted to show no impact in mobility and self-care domains in age group <18 months, and no impact in self-care domain in age group 18 months – 5 years

Raw = actual EQ-5D score from respondents

The main (modified) utility scores derived from the EQ5D ratings provided by GPs are shown in Table 3, with the raw scores for comparison. The mean modified disutility score (1 – the utility score) for a child with acute gastroenteritis seen by the GP was –0.219 in the younger age group (aged <18 months), and –0.312 for children aged 18 months to 5 years, indicating substantial impairment of HRQL. In both age groups, the more clinically severe health state requiring referral to hospital was associated with a significantly ($p<0.0001$) lower utility score than less severe gastroenteritis that could be managed in primary care. The raw utility scores showed the same pattern as the modified scores in the main analysis.

Table 4 presents the modified and raw utility scores from the paediatricians' EQ5D ratings of acute rotavirus gastroenteritis admitted to hospital. The mean modified disutility scores were –0.405 for children aged <18 months and –0.366 for children aged 18 months to 5 years with severe rotavirus gastroenteritis needing hospitalisation. In the older age group hospitalised with very severe rotavirus gastroenteritis, the lower bound of the 95% confidence interval was below zero, indicating that this health state could have a utility value lower than death. Although the EQ5D questionnaire cannot be scored at less than zero, the process used to convert the EQ5D scores into utility values can produce negative values. As with the ratings provided by GPs, the difference in utility scores between the two severities of illness was statistically significant ($p<0.0001$). The raw data scores displayed the same pattern, with lower utility scores in the more clinically severe health states in both age groups (Table 4).

Figure 1 EQ-5D utility scores (mean and 95% CI) in age group <18 months

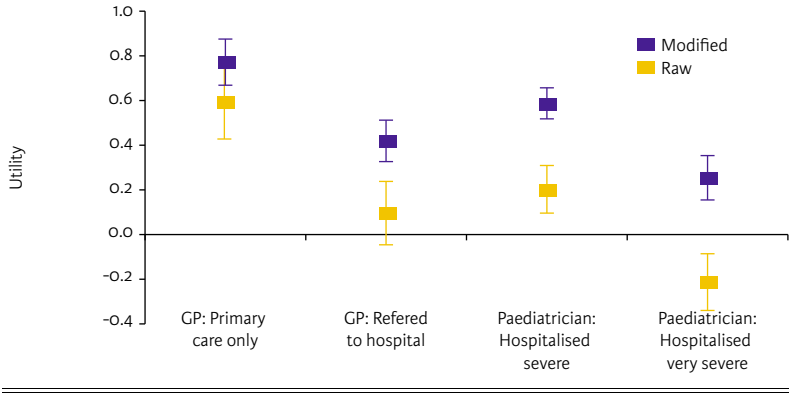


Figure 1 compares the raw and modified utility scores in the younger age group (aged <18 months) for all four health states. The utility score was highest (least impaired) in the health state requiring primary care only, and lowest (most impaired) in the health state representing hospitalisation for very severe rotavirus illness. The more severe of the health states rated by GPs (presenting in primary care and referred to hospital) and the less severe of the hospitalised health states rated by paediatricians both had intermediate utility scores, consistent with their intermediate clinical severity.

Figure 2 EQ-5D utility scores (mean and 95% CI) in age group 18 months – 5 years

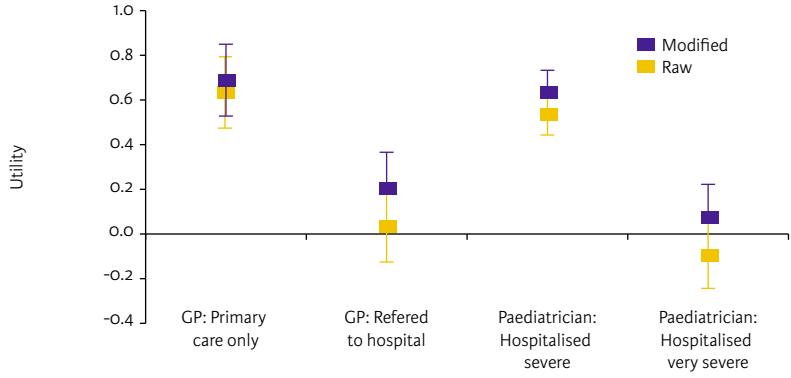


Figure 2 presents the raw and modified utility scores for the older age group (18 months to 5 years). Consistent with the results for the younger age group, these data also show the highest utility score in the health state requiring primary care only and the lowest score in the hospitalised very severe health state.

The differences between the modified and raw scores were consistently larger in the younger age group (Figure 1) than in the older age group (Figure 2). This is to be expected, as two domains were modified in the younger age group and only one was modified in the older age group. Figures 3 and 4 present the utility scores for the two age groups as box and whisker plots, showing median and interquartile ranges.

Figure 3 Box and whisker plot showing utility scores in age group <18 months. The mid-line indicates the median, the box covers the interquartile range (IQR) from the 25th to the 75th percentile, and the whiskers extend to the upper and lower adjacent values, defined as (x[75th percentile]) + 1.5 x IQR and (x[25th percentile]) + 1.5 x IQR, respectively. GP health state B = primary care only (not severe enough for hospital referral). GP health state A = referred to hospital (severe enough to warrant referral). Paediatrician health state A = hospitalised severe. Paediatrician health state B = hospitalised very severe

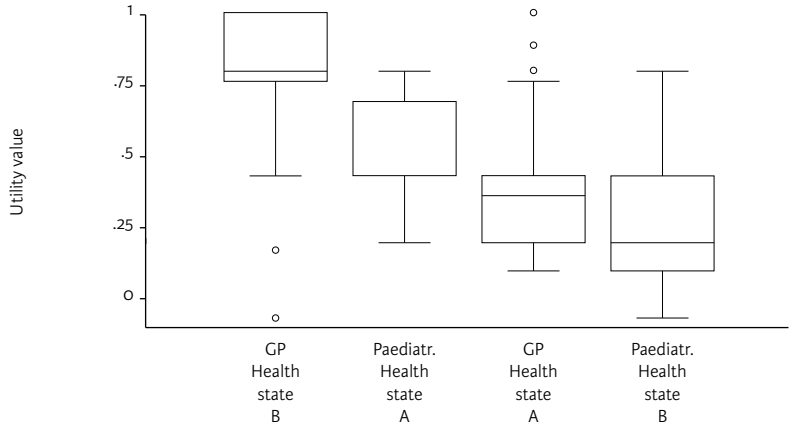
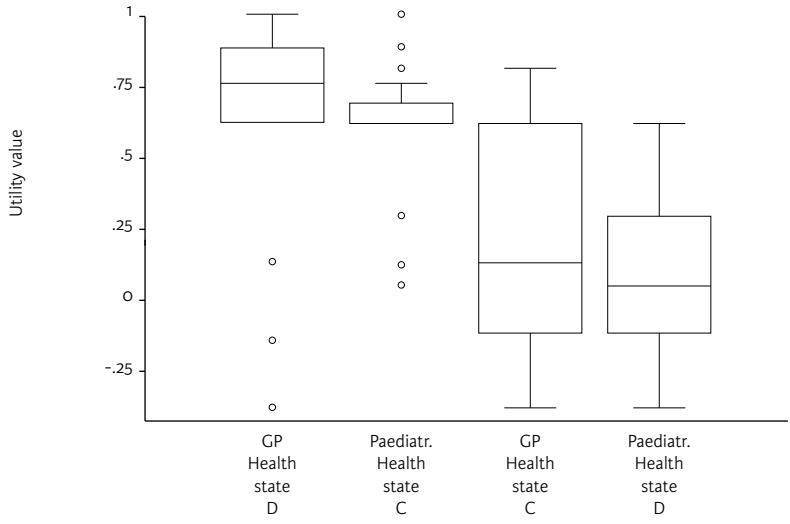


Figure 4 Box and whisker plot showing utility scores in age group 18 months – 5 years. The mid-line indicates the median, the box covers the interquartile range (IQR) from the 25th to the 75th percentile, and the whiskers extend to the upper and lower adjacent values, defined as (x [75th percentile]) + 1.5 x IQR and (x [25th percentile]) + 1.5 x IQR, respectively. GP health state D = primary care only (not severe enough for hospital referral). GP health state C = referred to hospital (severe enough to warrant referral). Paediatrician health state C = hospitalised severe. Paediatrician health state D = hospitalised very severe



DISCUSSION

This study estimated utility scores for different severities of acute rotavirus gastroenteritis in children aged <5 years in the UK, using GPs and paediatricians as proxy respondents. Each group of health professionals rated two health states of differing clinical severity for children in each of two age groups using the EQ-5D questionnaire. The EQ-5D scores were then converted into utility values using the standard algorithm as described by the EuroQoL group [24].

As expected, all four health states in both age groups were associated with impaired HRQL, as indicated by mean and median utility scores. This finding suggests that acute rotavirus gastroenteritis imposes a burden of decreased HRQL on patients, and consequently that prevention of infection could provide valuable gains in utility. There was some variation between respondents' scores, as would be expected (Tables 3 and 4). Exploration of the factors underlying such variations, such as potential differences in perception between regions or between rural and urban settings, could be an interesting subject for future study, but is beyond the scope of the present paper. Both GPs and paediatricians rated the more clinically severe health states as having significantly ($p<0.0001$) lower utility scores than the less severe health states, and this result held true across both age groups. Thus, it appears that the utility score derived from the EQ5D used in this study is able to differentiate between different severities of acute rotavirus gastroenteritis, and should therefore be able to provide useful estimates of utility for use in economic evaluations.

The results of the main analysis are further supported by the raw scores, which followed a similar pattern of lower utility in the more clinically severe health states. As expected, the numerical difference between the raw and modified scores was greater in the younger age group (aged <18 months), reflecting the fact that two of the five EQ5D domains (mobility and self-care) were modified in this age group, while in the older age group only the self-care domain was modified. It should be noted that the modifications to the score provide a conservative estimate of the utility impact, as no impairment was assumed in the modified domains, even if the respondents indicated that there was impairment. As a result, the raw utility scores were always lower than the modified scores across all age groups and all health states (Tables 3 and 4, Figures 1 and 2). Thus, this study may have underestimated the true impact of acute rotavirus gastroenteritis on HRQL. A further potential limitation of the study may be that it only considered the impact of acute rotavirus gastroenteritis on the HRQL of the patients, without attempting to capture the impact on parents or carers. This would also tend to underestimate the loss of utility attributable to rotavirus infection, as a recent cost-effectiveness study using utility estimates from a Canadian study [16] reported that the number of QALYs lost by carers was one of the three parameters with the greatest effect on the modelled results [27].

The EQ-5D was developed for use in adults and has not been validated in children aged <5 years. However, as reported in a recent review [28], no satisfactory generic HRQL instrument has yet been developed for use in this age group. The ability of the EQ-5D-derived utility scores to discriminate between the different severities of health states presented to the respondents in the present study suggests that it provides a reasonably reliable measure of utility. The study was conducted using proxy respondents because of the obvious difficulties in obtaining responses in this age group. This is consistent with current theory and practice, as the lower age-limit for self-reported instruments in children is generally 5–6 years [29], and a proxy respondent is the recommended approach [20]. Healthcare professionals were chosen for this study rather than parents because it was considered that they would be more likely to be able to distinguish between different clinical severities of acute rotavirus gastroenteritis.

There is a clear need for more data on the effect of rotavirus infection on utility scores for use in conducting economic evaluations of rotavirus vaccines [15]. A recent cost-effectiveness study of rotavirus vaccination in the UK suggested that health service funding of a rotavirus vaccine programme may be considered appropriate if there were a sufficient gain in quality of life for the parents and children involved, but was unable to estimate the potential gain because of the absence of utility data [30]. A separate analysis in the UK [27] estimated QALYs for both patients and parents by applying utility data derived from a Canadian study, although there was no differentiation according to disease severity.

The present study provides the first estimate of the impact of acute rotavirus gastroenteritis on HRQL in infants and young children that distinguishes between different severities of illness and utilises a recognised HRQL instrument (the EQ-

5D) with a validated method (25) for converting to utility scores. As such, it offers a valuable contribution to research on the potential cost-effectiveness of rotavirus vaccination programmes in Europe. Economic modelling studies applying these estimates are underway in several European countries, including the Netherlands [31], Belgium [32], Italy [33] and the UK [34]. These should provide new information to add to previous cost-effectiveness studies of rotavirus vaccination that have been based on the Canadian utility estimates that did not distinguish between different severities of rotavirus illness [27;35], or that have considered other outcome measures such as disability-adjusted life-years (DALYs) [36].

In conclusion, the present study provides quantitative utility estimates for young children with varying severities of acute rotavirus gastroenteritis, which should be useful in economic evaluations of rotavirus vaccines.

REFERENCES

[1] Eliason BC, Lewan RB. Gastroenteritis in children: principles of diagnosis and treatment 1. Am Fam Physician 1998 Nov 15;58(8):1769-76.
[2] Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 1990;22(3):259-67.
[3] Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003 May;9(5):565-72.
[4] Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006 Feb;12(2):304-6.
[5] Carlin JB, Chondros P, Masendycz P, Bugg H, Bishop RF, Barnes GL. Rotavirus infection and rates of hospitalisation for acute gastroenteritis in young children in Australia, 1993-1996. Med J Aust 1998 Sep 7;169(5):252-6.
[6] Ryan MJ, Ramsay M, Brown D, Gay NJ, Farrington CP, Wall PG. Hospital admissions attributable to rotavirus infection in England and Wales. J Infect Dis 1996 Sep;174 Suppl 1:S12-S18.
[7] The Pediatric ROTavirus European CommitTee (PROTECT). The paediatric burden of rotavirus disease in Europe. Epidemiol Infect 2006 Oct;134(5):908-16.
[8] Cunliffe NA, Allan C, Lowe SJ, Sopwith W, Booth AJ, Nakagomi O, et al. Healthcare-associated rotavirus gastroenteritis in a large paediatric hospital in the UK. J Hosp Infect 2007;67(3):240-4.
[9] Standaert B, Harlin O, Desselberger U. The financial burden of rotavirus disease in four countries of the European Union. Pediatr Infect Dis J 2008;27(1):S20-S27.
[10] Djuretic T, Ramsay M, Gay N, Wall P, Ryan M, Fleming D. An estimate of the proportion of diarrhoeal disease episodes seen by general practitioners attributable to rotavirus in children under 5 y of age in England and Wales. Acta Paediatr Suppl 1999;88(426):38-41.
[11] Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep 1999 Nov 5;48(43):1007.

[12] Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet 2007;370(9601):1757-63.
[13] Glass RI, Parashar UD. The promise of new rotavirus vaccines. N Engl J Med 2006 Jan 5;354(1):75-7.
[14] Vesikari T, Matson DO, Dennehy P, Van DP, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006 Jan 5;354(1):23-33.
[15] Rheingans RD, Heylen J, Giaquinto C. Economics of rotavirus gastroenteritis and vaccination in Europe: what makes sense? Pediatr Infect Dis J 2006 Jan;25(1 Suppl):S48-S55.
[16] Senecal M, Brisson M, Lebel M, Yaremko J, Wong R, Gallant L, et al. Burden of rotavirus-associated gastroenteritis in Canadian families: a prospective community based study (abstract P99). Canadian Journal of Infectious Disease and Medical Microbiology 2006;17(6):383.
[17] Huppertz HI, Forster J, Heininger U, Roos R, Neumann HU, Hammerschmidt T. The Parental Appraisal of the Morbidity of Diarrhea in Infants and Toddlers (PAMODI) Survey. Clin Pediatr (Phila) 2008;47(4):363-71.
[18] Martin A, Cottrell S. Estimating utility in rotavirus gastroenteritis in children under five in the UK (abstract PIH19). Value Health 2006;9(6):A258.
[19] Janse AJ, Sinnema G, Uiterwaal CS, Kimpen JL, Gemke RJ. Quality of life in chronic illness: perceptions of parents and paediatricians 1. Arch Dis Child 2005 May;90(5):486-91.
[20] Prosser LA, Hammitt JK, Keren R. Measuring health preferences for use in cost-utility and cost-benefit analyses of interventions in children: theoretical and methodological considerations. Pharmacoeconomics 2007;25(9):713-26.
[21] Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. Health Utilities Index 12. Pharmacoeconomics 1995 Jun;7(6):503-20.
[22] Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed ed. Oxford University Press: Oxford Medical Publications; 2005.
[23] Brooks R. EuroQol: the current state of play. Health Policy 1996 Jul;37(1):53-72.
[24] Dolan P. Modeling valuations for EuroQol health states. Med Care 1997 Nov;35(11):1095-108.
[25] Armon K, Stephenson T, MacFaul R, Eccleston P, Werneke U. An evidence and consensus based guideline for acute diarrhoea management. Arch Dis Child 2001 Aug;85(2):132-42.
[26] Polanco-Marin G, Gonzalez-Losa MR, Rodriguez-Angulo E, Manzano-Cabrera L, Camara-Mejia J, Puerto-Solis M. Clinical manifestations of the rotavirus infection and his relation with the electropherotypes and serotypes detected during 1998 and 1999 in Merida, Yucatan, Mexico. J Clin Virol 2003 Aug;27(3):242-6.
[27] Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. Vaccine 2007;25(20):3971-9.

[28] Grange A, Bekker H, Noyes J, Langley P. Adequacy of health-related quality of life measures in children under 5 years old: systematic review. J Adv Nurs 2007 Aug;59(3):197-220.
[29] Solans M, Pane S, Estrada MD, Serra-Sutton V, Berra S, Herdman M, et al. Health-Related Quality of Life Measurement in Children and Adolescents: A Systematic Review of Generic and Disease-Specific Instruments. Value Health 2007 Dec 17.
[30] Lorgelly PK, Joshi D, Iturriza GM, Gray J, Mugford M. Exploring the cost effectiveness of an immunization programme for rotavirus gastroenteritis in the United Kingdom. Epidemiol Infect 2008;136(1):44-55.
[31] Goossens LMA, Standaert B, Hartwig N, Hovels AM, Al MJ. The cost-utility of rotavirus vaccination with Rotarix(TM) (RIX4414) in the Netherlands 1487. Vaccine 2008 Feb 20;26(8):1118-27.
[32] Fruytier A, Van Schoor J, Standaert B. Vaccination with RIX4414 is cost-effective in a Belgian setting (abstract PIH3). Value Health 2006;9:A253.
[33] Standaert B, Marocco A, Assael B, Gabutti G, Guarino A, Lopalco P, et al. Analisi di costo-efficacia della vaccinazione universale in Italia con il vaccino Rix4414 contro i rotavirus. Pharmacoeconomics 2008;10(1):23-35.
[34] Martin A, Standaert B. Cost-effectiveness of infant vaccination with Rotarix(TM) in the UK (abstract 586). ESPID 25th Annual Meeting 2007.
[35] Newall AT, Beutels P, Macartney K, Wood J, Macintyre CR. The cost-effectiveness of rotavirus vaccination in Australia. Vaccine 2007 Dec 17;25(52):8851-60.
[36] Constenla D, O'Ryan M, Navarrete MS, Antil L, Rheingans RD. [Potential cost effectiveness of a rotavirus vaccine in Chile] 1. Rev Med Chil 2006 Jun;134(6):679-88.

2.3 COST-EFFECTIVENESS

Cost-effectiveness of rotavirus vaccination has been assessed using a cohort model that included many different features such as the importance of breast-feeding during the first months after birth, the enclosure of indirect cost specified at the moment of returning from maternity leave, the reduction of the so-called waning process of the vaccine over time, the adjustment of dose compliance and completion (1st and 2nd dose), and a fixed herd effect. The model –called Roxanne (Rotarix Analysis of Economics)- allowed the comparison of a 2 versus 3 dose program that is administrated at different time points or months.

The starting point for the model development was the model first published by Melliez et al. showing the importance of breast feeding to reduce the rotavirus disease burden presented in 2005 before the rotavirus vaccine was available in the market. I have built on that model concept and added the many additional features [11].

Interesting was the direct comparison between Melliez's model published in 2007 [12] on the cost-effectiveness analysis of rotavirus vaccination in France with what I did in 2008 [13]. The point I wanted to highlight in the publication was to demonstrate how the change of many different features in a same constructed model can shift the analysis from not-being cost-effective to become cost-effective. The difference was not only related to the data input but as well some structural differences between the two models such as the risk period of 3 years for Melliez et al versus 5 years in our model.

Roxanne model has been used and presented in many different forums and in many different countries. It has been part of many submissions at country level for getting reimbursement or participating in tenders. It was also part of an evaluation process organised by the WHO to compare the available rotavirus models worldwide in 2011. The model is accessible and has been made available to many health authorities worldwide [14]; [15]; [16]; [17].

One may be surprised to see that I didn't publish a cost-effectiveness analysis with a dynamic model that includes the herd effect of the vaccine. There are two reasons for that. One is that I developed a dynamic model in-house and came to the same results that were presented in the literature by Pitzer et al [18], Atkins et al [19;20], and Atchison et al [21]. There was nothing new to present that was already published. But I was more interested in what real life data should be able to give. Comparing those data with the results of the cohort model for which still today more people are familiar with, was a second motivation to analyse the problem that way instead of using a dynamic model. One issue I had with the dynamic compartmental model for rotavirus vaccination is how to disentangle correctly the different sources of infection and the different ways of getting the immune protection developed in function of age, forced by the vaccine on the one hand and by the exposure to the natural infection on the other hand. An important issue found is that after the age of 5 years the susceptible group became large again possibly leading to new infections but I was not sure if those new infections should lead to severe conditions that need medical attention or not. My suspicion was not because the rotavirus vaccination program was not able to eliminate the virus. So the wild type virus could still circulate in the community and may act as regular booster dose to enhance the immune response. This is further tackled with the impact studies in the next paragraph.

COST-EFFECTIVENESS ANALYSIS OF VACCINATION AGAINST ROTAVIRUS WITH RIX4414 IN FRANCE

Appl Health Econ & Health Policy, 2008: 6(4): 1-18.

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ABSTRACT

Background: It is estimated that annually 300,000 cases of rotavirus-induced gastroenteritis (RVGE) occur in children aged up to 5 years in France. RIX4414 (Rotarix™, GlaxoSmithKline), a two-dose vaccine against rotavirus infection, has been shown to be highly effective against severe RVGE.

Objective: This study evaluated the cost-effectiveness of general vaccination against rotavirus using RIX4414 in France.

Methods: A Markov model simulated RVGE events and the associated outcomes and costs in a birth cohort of children in France with a combined adjustment for age distribution with the seasonality of the infection.

Setting: Costs and outcomes were estimated from a limited societal perspective, including direct medical costs paid out-of-pocket or by third-party payers, as well as the proportion of direct medical costs reimbursed by the health authorities. Indirect costs were not included in the base case analysis.

Patients: Children up to the age of 5 years in France.

Intervention: General vaccination of infants against rotavirus infection using RIX4414 (Rotarix™).

Main outcome measure: The primary outcome measure was the incremental cost per quality-adjusted life year (QALY).

Results: Vaccination with RIX4414 incurred an incremental cost of € 44,583/QALY at a public price of €57 per vaccine dose. Univariate sensitivity analyses showed that the parameters with the largest influence on the results were: the transition probabilities of severe diarrhoea, seeking medical advice and emergency visits; utility scores of diarrhoea (mild) in children & infants; the discount rate for benefits. Probabilistic multivariate sensitivity analysis confirms these results. The acceptability curve indicated that 94% of the results were under an informal threshold of € 50,000/QALY. Comparing our results with those of a recently published study using pooled data for two rotavirus vaccine products in France, the main differences are explained by differences in model structure and in data input values. They include: a different age-distribution of the infection, shorter duration of the at-risk period (3 years instead of 5 years); different vaccine efficacy; different unit cost data; different disease duration; and different disutility values

for the health states in the model. There is a need for agreed standards to improve comparability of results from different studies.

Conclusions: The results demonstrate that a generalized vaccination strategy with RIX4414 would be cost-effective in France from a limited societal perspective and depending on the base-line assumptions on disease progression and on utility scores selected. The limited societal perspective includes direct medical costs paid out-of-pocket or by third-party payers as well as the proportion of direct medical costs reimbursed by the health authorities, but does not include indirect costs.

INTRODUCTION

Rotavirus infection is a major cause of severe diarrhoea and gastroenteritis in children under the age of 5 years worldwide [1;2]. In the Western world the infection has a seasonal peak during the winter period [3] and the severe consequences of rotavirus gastroenteritis (RVGE) are most frequently observed under the age of 2 years, after which the number of new infections and diarrhea events decreases. Successive infections confer natural immunity [4] and severe rotavirus diarrhea events are rarely seen after the age of 5 years.

Rotavirus is very contagious and its spread is difficult to control despite the application of primary hygiene measures. As a result, rotavirus epidemics are a well-known annually recurrent public health problem from November until March of each year. In France the number of diarrhoea events caused by rotavirus infection is estimated at 300,000 each year in children aged up to 5 years [5].

New vaccines against rotavirus, such as RIX4414 (Rotarix™, GlaxoSmithKline Biologicals, Rixensart, Belgium), are now available. A strategy of vaccinating children before the age of 6 months has the potential to provide protection against rotavirus infection over a period of at least two years. RIX4414 is a two-dose oral vaccine [6], and a phase III clinical trial in Europe has shown that this vaccine has a good safety profile and is highly effective against severe RVGE and hospitalizations caused by RVGE [7].

Health authorities need information on cost-effectiveness of a vaccination strategy compared with the current situation in order to make reimbursement decisions. In 2005, Melliez et al. published a model of rotavirus infection in France that provided estimates of the costs and burden of illness [5]. Recently, the same group reported a cost-utility evaluation of rotavirus vaccination in France, based on the 2005 model and using pooled data on vaccine efficacy and cost for two rotavirus vaccine products [8]. We have further developed a similar model by including modifications such as a combined age-related and seasonal variation in the infection. Using this model, we conducted a cost-utility evaluation of a rotavirus vaccination strategy using a specific vaccine product, RIX4414. In this paper we present the results of our cost-utility analysis and discuss the issues raised from a comparison of the two models.

METHODS

We selected the Markov cohort model that was first published in 2005 by Melliez et al. [5]. The model was constructed in Tree-Age Pro software to simulate rotavirus diarrhoea events and their associated outcomes in a hypothetical birth cohort of children aged up to 5 years (see Figure 1). The basic 'Melliez et al.' model structure was robust, but we refined it by adjusting the model to enable the calibration of the epidemic spread of the disease as a function of age of the child and to account for seasonality of the infection within one model structure (see Figure 2). In one arm of the model children could be vaccinated with RIX4414, and in the other no rotavirus vaccination was allowed. The modelled costs and outcomes were compared between the two arms to estimate the cost-effectiveness of rotavirus vaccination.

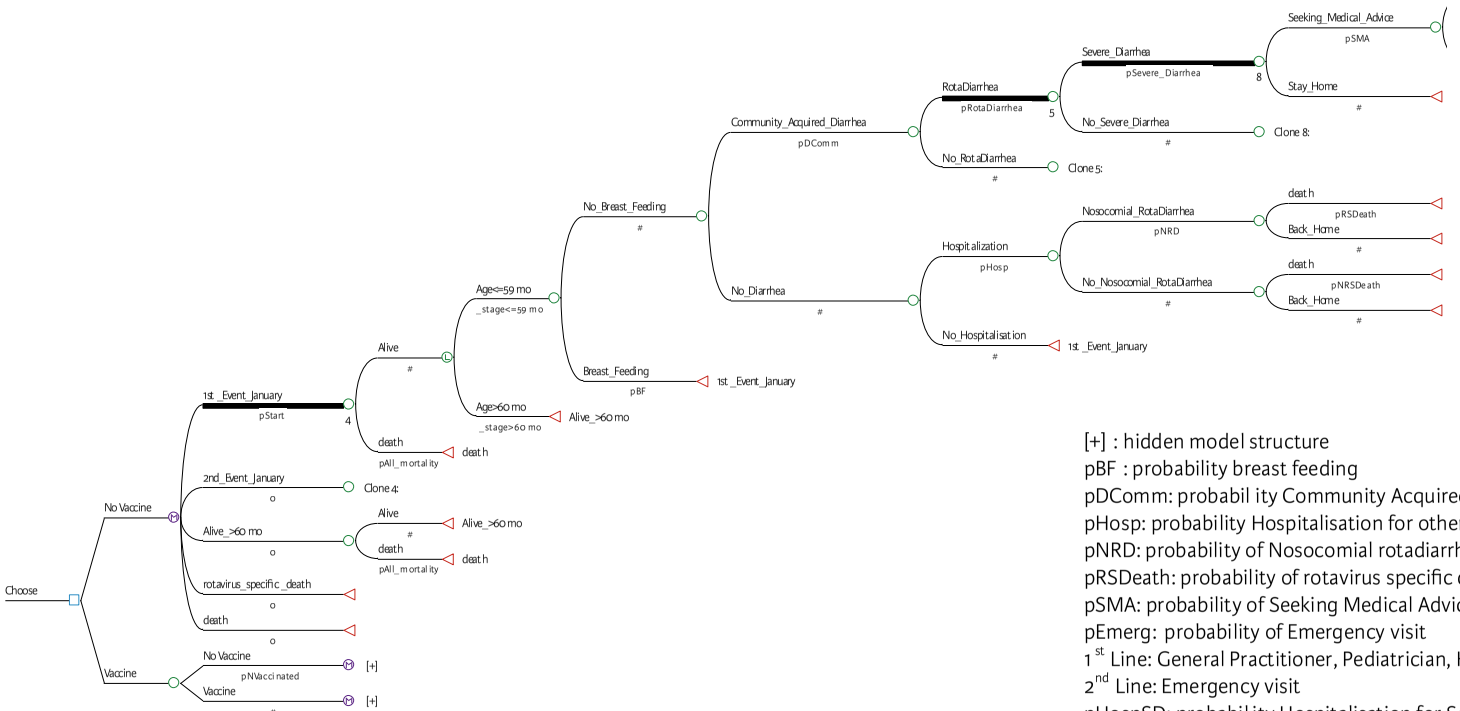
To allow for the higher probability of infection during the winter period, the cohort entry was subdivided into monthly entrants with an equal number of subjects born each month from January to December. Monthly age-adjusted transition probabilities for the risk of infection and diarrhea were then applied for the cohort until the age of 5 years. Fully breast-fed children were assumed to be protected against infection. The total running period of the model was the average life-time of a subject in France, in order to capture the vaccine benefit of avoided deaths caused by rotavirus (number of cycles = 936 months or 78 years).

The tree was constructed as a time-driven, dichotomized event-related process with a cycle time of one month. In each month, the starting cohort has a risk of a first episode of rotavirus-induced diarrhoea. The diarrhoea event could lead to consultation of a medical practitioner, either first line (general practitioner (GP), home care or paediatrician) or second line (emergency visit). A first line medical visit could be followed by an emergency visit and/or by hospitalization. During hospitalization, death caused by the infection could occur. Once discharged from hospital or after a first event, a subject younger than 5 years faced the risk of contracting a second episode of rotavirus infection leading again to diarrhoea. A second infection was assumed never to lead to hospitalization or a second line visit. It was assumed that no further infections would occur after the age of 5 years.

Rotavirus infections can be transmitted between patients in hospital, so children who have been hospitalized for other reasons may be at risk of contracting hospital-acquired (nosocomial) rotavirus infections from rotavirus-infected children in the same paediatric unit. The model added branches to the tree in the "no diarrhoea" arm to allow for the possibility of nosocomial rotavirus-induced diarrhoea in children hospitalized for a non-rotavirus related event. This applied only to the winter period, reflecting the seasonal peak of rotavirus infection.

The tree was duplicated in the vaccine arm into a vaccinated and a non-vaccinated arm, which allows the model to test different rates of vaccine coverage for budget impact analysis.

Figure 1 Overall model design for the January birth cohort only



[+] : hidden model structure
pBF : probability breast feeding
pDComm: probabil ity Community Acquired Diarrhea
pHosp: probability Hospitalisation for other reason than rotadiarrhea
pNRD: probability of Nosocomial rotadiarrhea
pRSDeath: probability of rotavirus specific death
pSMA: probability of Seeking Medical Advice
pEmerg: probability of Emergency visit
1st Line: General Practitioner, Pediatrician, Home visit
2nd Line: Emergency visit
pHospSD: probabil ity Hospitalisation for Severe rotaDiarrhea

DATA INPUT

Each event in the model (diarrhoea or not, medical visit or not, emergency visit or not, hospitalization or not, etc.) was considered as a health state in the Markov process. Each of these health states was assigned a cost (Table 1a) and a utility score (Table 1b). All costs were estimated for the year 2005. Unit costs were obtained from official French financial databases [9]. The cost of hospitalization was calculated by identifying cases coded as A080 (rotavirus gastroenteritis) for the main diagnosis in children aged <5 years. Using these cases and the national hospital costs database (Echelle Nationale des Coûts; ENC) [10], an average weighted cost (€ 518.7 per day) and an average weighted length of stay (3.0 days) were calculated, which were combined to estimate the average cost per hospitalization. This calculation integrated structure costs, and therefore captured the full cost of hospitalization.

Table 1a Costs* per health state and by cost perspective

Health State	Type	Limited Societal
Consultation	General Practitioner (GP) (67%)	25.00 €
	Pediatrician (PED) (17%)	28.00 €
	Home visit of GP (16%)	35.00 €
	Drugs	12.00 €
Emergency	Emergency visit	82.78 €
Hospitalization	Community acquired	1,556.00 €
Nosocomial infection	Nosocomial	1,556.00 €
	Vaccine cost per dose (public price)	57.00 €

* year 2005 costing values

Table 1b Utility scores per health state

Health State	Age	Utility Score (SD)	Duration (days)	Work days lost
Diarrhea	≤ 18 mo.	0.891* (0.132)*	4	4
	> 18 mo.	0.844* (0.172)*	4	4
Diarrhea severe	≤ 18 mo.	0.891* (0.132)*	+3	+3
	> 18 mo.	0.844* (0.172)*	+3	+3
Consultation	≤ 18 mo.	0.781 (0.263)	+1	+1
	> 18 mo.	0.688 (0.345)	+1	+1
Emergency		0.425 (0.243)	+1	+1
Hospitalization	≤ 18 mo.	0.425 (0.243)	+3	+3
	> 18 mo.	0.200 (0.386)	+3	+3
Nosocomial infection	≤ 18 mo.	0.425 (0.243)	+3	+3
	> 18 mo.	0.200 (0.386)	+3	+3
Death		0.000		

*adjusted values; mo.: months

The cost of the vaccine was set at € 57 per dose, the same cost reported by Melliez et al. for the price of RIX4414 (Rotarix™). In sensitivity analysis a maximum cost of € 75 per dose was selected [8]. No additional cost for dose administration was considered as the vaccine can be given at the same time as the combined

diphtheria-tetanus- pertussis-Hib-poliomyelitis vaccine. As no French utility data are currently available, the utility scores to calculate the quality-adjusted life years (QALYs) were taken from a survey conducted in the UK in which GPs and paediatricians rated the impact of RVGE on the affected child's QoL [11]. The values were expressed as disutility scores in the model (disutility is the difference between the utility score of the disease condition and perfect health). For cases for which no medical care was sought, to be conservative the disutility was taken as half the value assigned to the disutility of cases for which medical care was sought. The disutility scores were multiplied by the disease duration expressed in days and transformed into a monthly time scale.

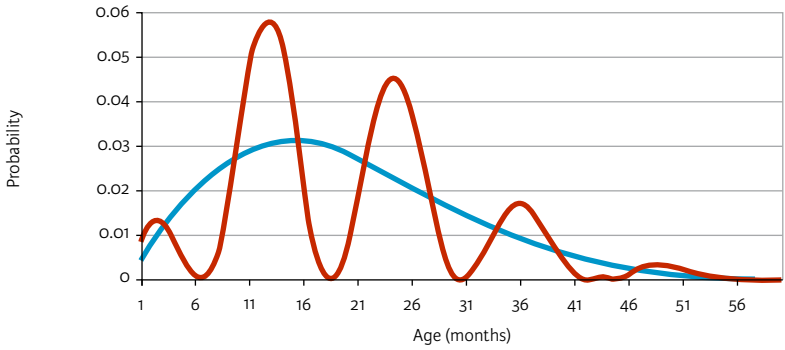
Transition probabilities in the model express the likelihood of getting diarrhea over time, followed by the subsequent event of seeking medical advice. The probabilities of getting diarrhoea were age- and month- dependent to allow for the seasonality of rotavirus infection (more frequent during the winter period, following a normal distribution of the epidemic spread from November until March each year) and the increase in immune protection with age that makes the child most vulnerable between 3 and 24 months of age [12;13]. Data collected from literature indicate that rotavirus infection and the associated diarrhoea events in children under 5 years old approximately follow a Weibull distribution (shape coefficient of 1.5; scale coefficient of 24.2) as illustrated in Figure 2 [5;14;15]. The transition probabilities in the model replicated this distribution and the influence of seasonality as closely as possible (see Figure 2). The sum of the area under the curve for any of these transition probability distributions over the time period of 5 years was equal to 1. Finally, the transition probabilities were different with or without breast-feeding (breast-feeding assumed to protect against infection), and for the initial and subsequent diarrhea events (much lower transition probabilities for the second event). Other age-dependent transition probabilities in the model were the natural mortality rate, the rate of hospitalization with and without diarrhea, and the rate of contracting nosocomial rotavirus diarrhoea.

The effectiveness of RIX4414 was taken from the results of a clinical trial conducted in Europe (eTrack102247/NCT140686) [7], and is listed in Table 2. The protection rate against nosocomial infection was assumed to be the same as that against hospitalization.

Table 2 Vaccine effectiveness

Variable	% reduction 1st year (95% CI)	% reduction 2nd year (95% CI)
Rota specific diarrhea reduction	87.1 (79.6-92.1)	71.9 (61.2-79.8)
GP visits	91.8 (84.0-96.3)	76.2 (63.0-85.0)
Hospitalization	100 (81.8-100)	92.2 (65.6-99.1)
Nosocomial infection	100 (81.8-100)	92.2 (65.6-99.1)

Figure 2 Distribution of diarrhoea events as a function of age and seasonality (January birth cohort only)



Blue = Weibull distribution of diarrhea events as a function of age
Red = Normal distribution of events as a result of seasonality

MODEL ASSUMPTIONS

The overall death rate per month was obtained from the National Statistics database expressed as monthly probabilities [16]. The true total number of diarrhoea events caused by rotavirus is often unknown as only the cases where medical support is sought appear on official lists or in databases. It was therefore assumed in the model that as a base case the total number of diarrhoea events was twice the number of medical visits reported [5] .

The cost perspective considered was a "limited societal" perspective. This included direct medical costs paid out-of-pocket or by third-party payers, as well as the proportion of direct medical costs reimbursed by the health authorities (see Table 1a). We did not include in the base case analysis the costs of lost productivity (indirect costs), as there is still controversy in France over how such costs should be accurately reported [17], especially in cost-utility analyses. This is a conservative approach, as it means that a component of societal cost is not captured in the analysis, and thus the base-case perspective is not a true societal perspective. However in the discussion section we estimated the indirect cost in the current setting using a human capital measurement approach.

It was further assumed that around 15% of the parents confronted with an acute diarrhoea will go for an emergency visit directly or indirectly after a medical visit (15). For the practical design of the model, it was assumed that the cost of an emergency visit was separated from the hospitalization cost. The model therefore marginally overestimates the total cost for cases where an emergency visit results in admission, as in such cases the hospitalization cost would include the cost of the emergency visit. However, the effect should be small and this calculation method should not affect the cost-effectiveness conclusions.

Breast feeding as the sole source of nourishment confers protection against RVGE as long as the child receives only breast feeding [18;19]. Fully breast-fed babies were assumed to have 100% protection against RVGE, and the number of fully breast-fed infants was assumed to be 50% at delivery with an exponential decrease over time (β- scale coefficient = 2).

In the base-case analysis, the annual discount rate was 3% for costs and 1.5% for the effect measure. However, alternative rates were used in the sensitivity analysis as currently recommended in France [17].

A vaccine coverage rate of 85% was used in the base-case. This value was subjected to sensitivity analysis using a coverage range that is normally observed with paediatric vaccines in France.

For all non-rotavirus related hospitalizations, an age-specific nosocomial rotavirus-induced diarrhoea rate was included in the model, varying from 3% to a maximum of 5% per age group and limited to events during the winter period only (maximum 6 months per year). A recent literature review reported the rate of nosocomial rotavirus infection ranging from 2.9% to as high as 19.4% of total admissions, with most results in the 2.9–6.6% range [20].

The transition probability for mortality after rotavirus hospitalization was <0.0005 risk of death per rotavirus hospitalization [5].

OUTCOME MEASURES

The primary outcome measure reported was the incremental cost of vaccination (IC) per incremental quality-adjusted life year (IC/QALY). We selected a threshold of less than or equal to € 50,000 per incremental QALY for cost-effectiveness [21]. Some alternative incremental cost-effectiveness measures are also reported, such as the incremental cost per case averted, per hospitalization averted, and per death avoided.

SENSITIVITY ANALYSIS

Due to the lack of unequivocal reference values, many variables in the model were subjected to sensitivity analyses. These are shown in Table 3 with the minimum and maximum estimate for each. Probabilistic multivariate sensitivity analyses were also reported for several variables (Table 3). This analysis indicates the range over which variables may fluctuate and the probability that vaccination remains cost-effective.

COMPARISON WITH THE 'MELLIEZ ET AL.' MODEL

When comparing our results with the data obtained from Melliez et al. [8], we listed the variables and values that could be identified as different in the two analyses, and then applied distribution variables with uniform distribution ranges of minimum and maximum values (see Table 4) to our model. We then conducted a separate probabilistic multivariate sensitivity analysis to assess which of the variables had the highest impact on the IC/QALY using multiple regression

Table 3 Variables tested in sensitivity analyses

Variables	Base Line	Minimum	Maximum	Distribution Type
1st line cost*	25.00 €	25.00 €	45.00 €	uniform
Emergency visit cost*	82.78 €	82.78 €	90.00 €	uniform
Hospital cost*	1,556 €	1,400 €	1,715 €	uniform
Nosocomial cost*	1,556 €	1,400 €	1,715 €	uniform
Coverage	85%	75%	90%	uniform
Vaccine efficacy 1st year RV diarrhea reduction Hospitalization reduction	85.1% 100%	75% 80%	95% 100%	uniform uniform
Hospitalization for other reason than rotavirus-diarrhea	0.01%	0.005%	0.02%	uniform
Discount rates (cost; effect)	3%; 1.5%	3%; 0%	3%; 3%	uniform
Probability severe diarrhea event°	0.530	0.315	0.745	normal** (0.53; 0.11)
Probability seeking medical advice with severe diarrhea	0.690	0.555	0.825	normal (0.69; 0.069)
Probability emergency visit after 1st line visit with severe diarrhea°	0.514	0.128	0.265	normal (0.514; 0.128)
Utility diarrhea (mild/severe) < 18 mo°	0.891	0.635	1	truncated normal (0.891; 0.132)
Utility diarrhea (mild/severe) > 18 mo°	0.844	0.51	1	truncated normal (0.844; 0.172)
Utility consultation visit < 18 mo°	0.781	0.27	1	truncated normal (0.781; 0.263)
Utility consultation visit > 18 mo°	0.688	0.01	1	truncated normal (0.688; 0.345)
Utility emergency visit°	0.425	0	0.9	truncated normal (0.425; 0.243)
Utility hospital/nosocomial < 18 mo°	0.425	0	0.9	truncated normal (0.425; 0.243)
Utility hospital/nosocomial > 18 mo°	0.200	0	0.96	truncated normal (0.200; 0.386)
Breast feeding	exponential decrease from 50%	exponential decrease from 50%	exponential decrease from 60%	exponential (?-scale coefficient = 2)

* year 2005 costing values;

** first value the mean; second value standard deviation; truncated = maximum value of 1; minimum value of 0)

° month; minimum and maximum values are the 95% Confidence Intervals

Table 4 Values & variables selected for the comparison between the Base Case Model with Melliez et al Model in a probabilistic sensitivity analysis

Variable	Minimum	Maximum	Distribution Type
Vaccine Price	57 €	75 €	Uniform
Duration diarrhoea mild	4 days	5.4 days	Uniform
Vaccine Efficacy (rotavirus-diarrhoea reduction 1sty)	70%	87.10%	Uniform
Discount Effect	1.50%	3%	Uniform
Nosocomial rotavirus diarrhoea prevalence	0%	0.42%	Uniform
Disutility Diarrhoea Score in Children	-0.156	-0.116	Uniform
Cost Hospitalization	1 240 €	1 556 €	Uniform
Duration Severe Diarrhoea	+ 1.1 days	+3 days	Uniform
Duration Hospitalisation visit	+ 1.1 days	+3 days	Uniform
Duration Emergency visit	0	+ 1 day	Uniform
Disutility Severe Diarrhoea in Infants	-0.186	-0.575	Uniform
Duration GP visit	0	+ 1 day	Uniform
Disutility Emergency Visit in Infants	0	-0.575	Uniform
Disutility Hospitalisation Visit in Infants	0	-0.8	Uniform
Disutility Hospitalisation Visit in Children	0	-0.575	Uniform
Disutility Emergency Visit in Children	0	-0.575	Uniform

analysis. The output of that analysis is normalized beta-regression coefficients. It allowed us to define a systematic process for moving step by step from our base case model to the Melliez et al. model by adjustment of the variables in the model. Because Melliez et al. used a different time scale to evaluate the rotavirus problem (3 years instead of 5 years), we adjusted the Weibull distribution to the relevant time scale.

STATISTICAL ANALYSIS

The cost-effectiveness model was run in cohort mode first. This is the conventional approach that directly delivers cost-effectiveness measures such as the incremental cost per QALY per subject. To create the acceptability curve, the cohort mode was run in a 2nd order Monte Carlo simulation program with the distribution curves for the variables mentioned in Table 3 & 4. The number of iterations was 1,000 runs.

The statistical analysis plan was identical when running in either manner, but the end-results could differ slightly because of the Monte Carlo iteration process.

RESULTS

Number and cost of rotavirus infections and events

Table 5 shows the numbers of rotavirus-related events predicted by the model for a birth cohort of 750,000 with and without vaccination, together with the numbers of events derived from literature [5] as well as from our model construction. Table 5 also presents the predicted reduction in RVGE-related diarrhoea events, medical visits, hospitalizations and deaths associated with the implementation of a generalized vaccination strategy with RIX4414 in France with 85% coverage rate. Without vaccination the estimated total direct medical cost of rotavirus disease management in France was around € 41 million per year, mainly related to hospitalization costs (see Table 6).

Table 5 Literature review and model predicted rotavirus events with and without vaccination (cohort of 750,000 newborns followed until the age of years)

	Literature Review	Predicted (No vaccination)	Predicted (Vaccination)	% Reduction*
Diarrhoea events < 5y	300,000 (5)	299,956	113,829	62.05
Severe diarrhoea events < 5y		141,932	29,609	79.14
Seeking medical advice	138,000 (5)	137,965	41,460	69.95
Emergency visits	45,000 (15)	44,956	9,379	79.14
Hospitalization	18,000 (5)	17,932	3,061	82.93
Nosocomial diarrhoea	3,123 (20)	3,129	70	97.77
Death	9 (5)	9	2	77.78

* compared with no vaccination

Table 6 Total direct medical cost estimates for France per year for reimbursement authorities without vaccination

Cost Item	Cost*	% of total
First-line consultations	€ 5,718,365	14%
Emergency visits	€ 3,561,059	9%
Hospitalizations	€ 26,776,381	66%
Nosocomial diarrhoea	€ 4,749,642	12%
Total costs	€ 40,805,447	

* Year 2005 costing values

Cost-effectiveness

Table 7 shows the incremental cost, incremental gain in QALYs and incremental cost/QALY for vaccination with RIX4414 compared with no vaccination. The maximally estimated, discounted QALY gain per subject in the vaccinated group reached 0.001181 over a lifetime, and the incremental cost/QALY was € 44,583. The incremental cost for other effect measures was as follows: € 212 per RVGE-case avoided; € 2,656 per hospitalization avoided; and € 5,435,097 per death prevented.

Sensitivity analyses

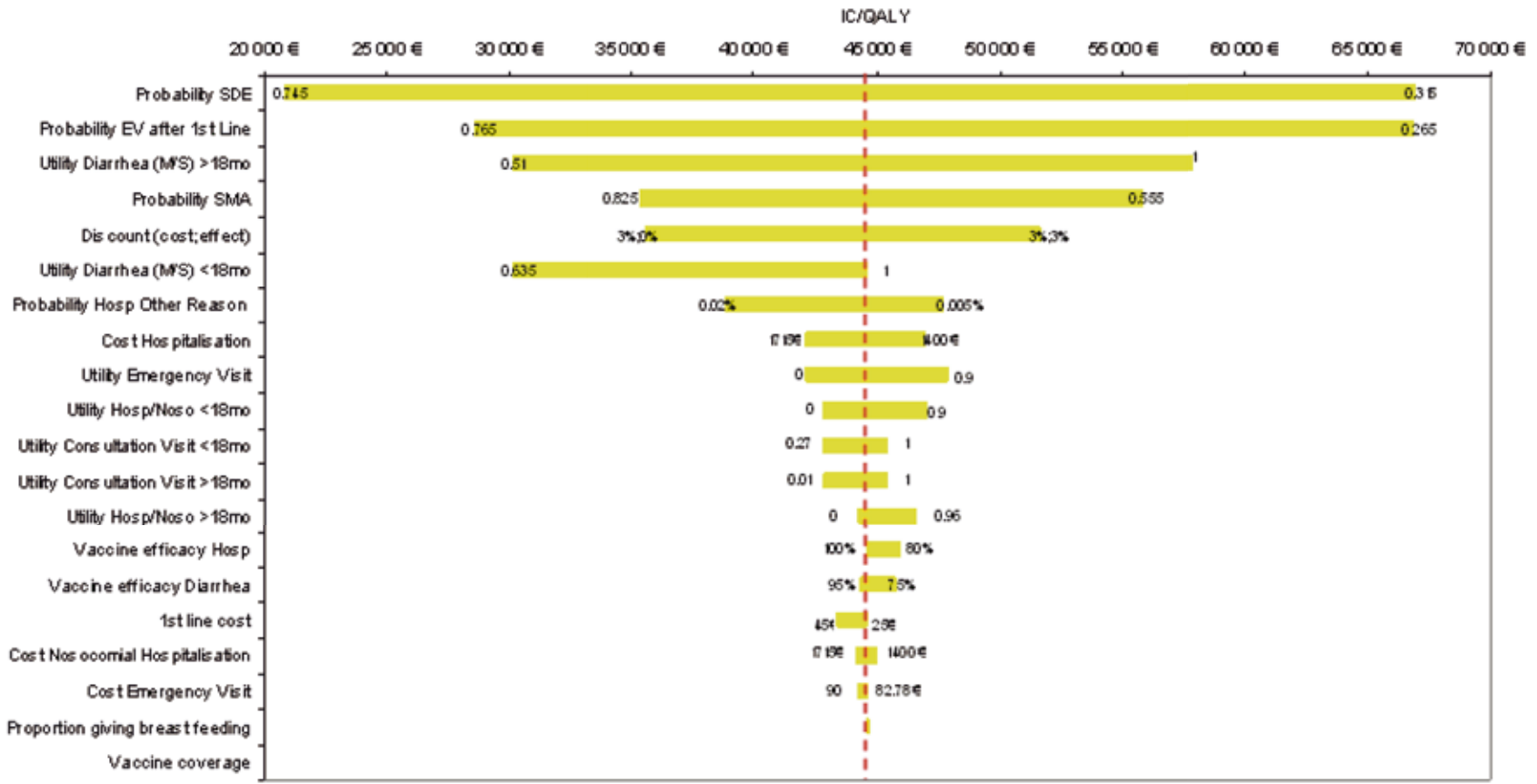
Figure 3 shows the univariate sensitivity analyses for each minimum and maximum value of the variables tested (Table 3). Four groups of variables had a large impact on the end result: the probabilities of moving from diarrhoea to severe diarrhoea, of seeking medical advice, and of going to an emergency clinic; the utility scores for diarrhoea events in children and infants; the rate of non-RV-related hospitalizations; the discount rate applied to the effect measure; and finally the hospitalization cost. Other univariate sensitivity analyses indicated little to no change in the end-result (Figure 3).

The multivariate probabilistic sensitivity analysis resulted in an acceptability curve showing the proportion of results meeting the threshold value as a function of the value set for the threshold (Figure 4 A & B). A total of 94% of the analysis results were under the threshold of € 50,000/QALY. However, the density graph shows a skewed distribution with a tail to the right (Figure 4 B). Analyzing which of the variables may have the largest impact in a combined analysis, indicates again that the probabilities of events and the utility score selection have the biggest impact on the IC/QALY (see Figure 5).

Comparison with the Melliez et al. results

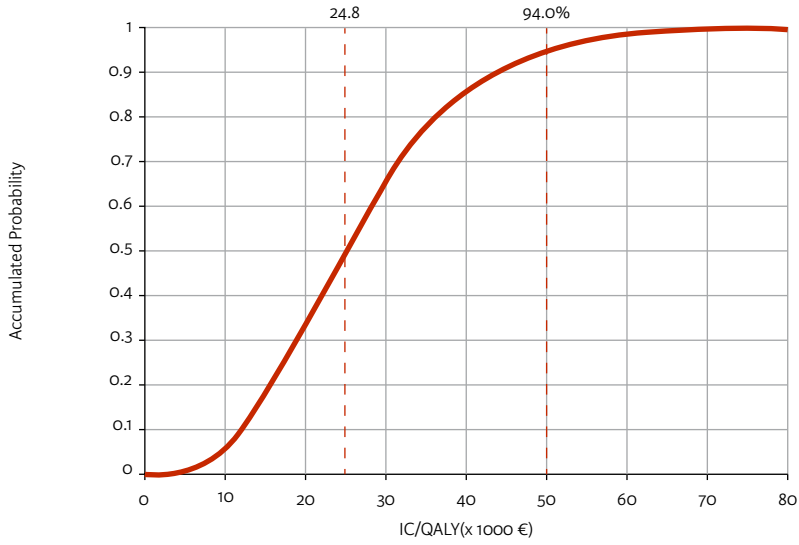
Table 8 presents the differences between the analysis presented here and the analysis published by Melliez et al. [8]. The beta coefficients from the multiple regression analysis are shown in Figure 6. The vaccine price had the highest impact on the ICER results, followed by changes in the duration of diarrhoea, vaccine efficacy, the discount rate applied to the effect measure and the rate of nosocomial infection. Figure 7 and Table 9 show the impact on the ICER of changing the variables in the model in a stepwise fashion, in order of the importance of each variable. Starting from the base case of the present model in a 5 year timescale,

Figure 3 Univariate sensitivity analyses



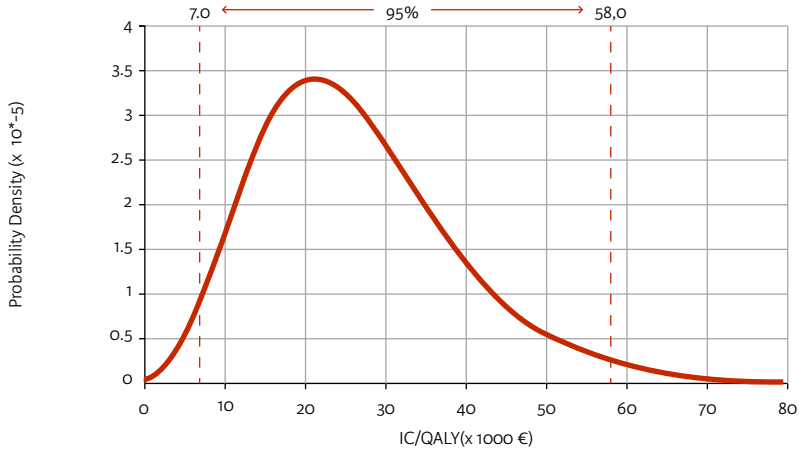
SDE: Severe Diarrhoea Event; EV: Emergency Visit; M: Mild; S: Severe; SMA: Seeking Medical Advice; Hosp: hospitalization; Noso: Nosocomial hospitalisation; Dotted line=base-case

Figure 4a Acceptability curve by function of the threshold value of 50,000€ per QALY



First line: 50% probability
Second line: threshold

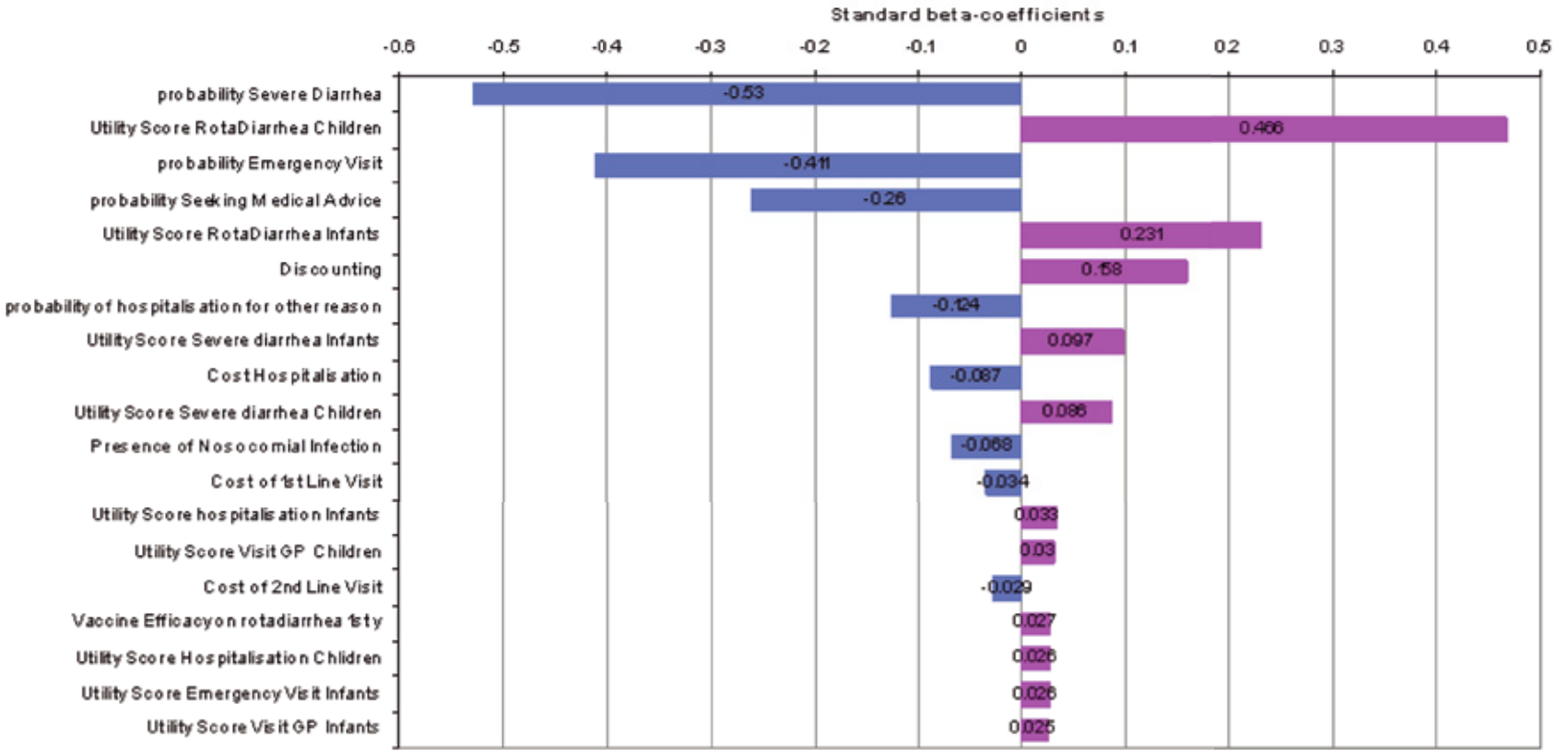
Figure 4b Acceptability curve expressed as a density curve by function of the threshold value of 50,000€ per QALY



First line: 50% probability
Second line: threshold

each variable was changed to its corresponding value in the Melliez et al. model and the resulting ICER calculated. By the time all the values had been set to those used by Melliez, the ICER reported by our model was €147,192/QALY. Similarly, starting from a 3-year timescale with all the values set to those used by Melliez, each variable was changed to the value used in the base case of the present model

Figure 5 Standardized β coefficients of input variables on the output variable (ICER) using multiple regression analysis (probabilistic multivariate sensitivity analysis)



SDE: Severe Diarrhoea Event; EV: Emergency Visit; M: Mild; S: Severe; SMA: Seeking Medical Advice; Hosp: hospitalization; Noso: Nosocomial hospitalisation; Dotted line=base-case

Figure 6 Standardized β coefficients of input variables on the output variable (ICER) using multiple regression analysis (Melliez comparison analysis)

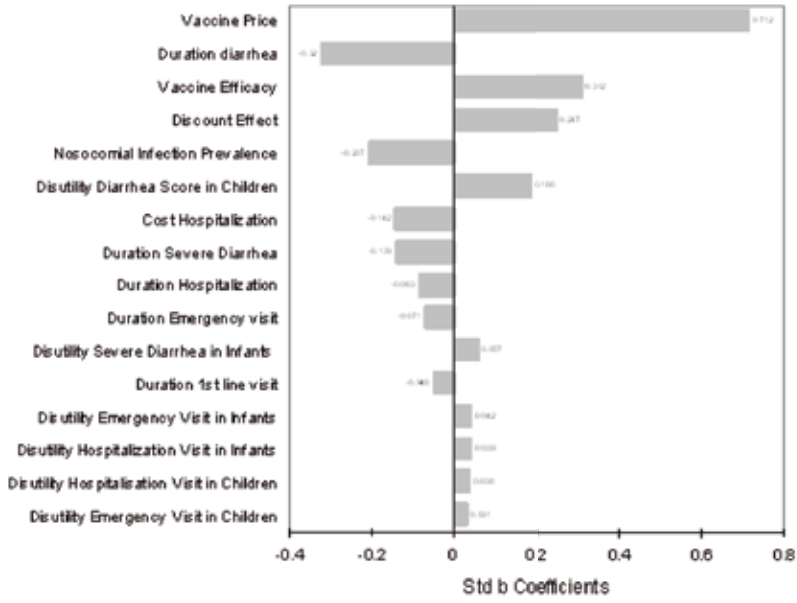
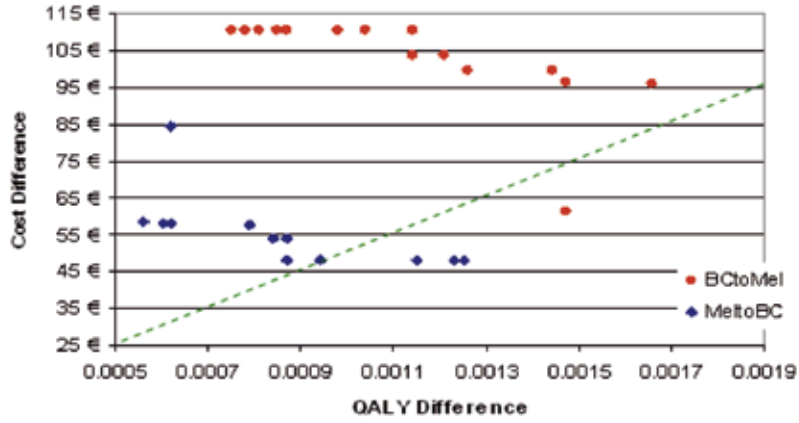


Figure 7 Comparing the ICER-data of the Melliez and the present base-case results



BctoMel = starting from the base-case of the current model and moving to the input values used by Melliez
MeltoBC = 3-year model starting with the values used by Melliez and moving to the input values used in the base-case of the current model

and the ICER calculated. When all the variables had been set to the values used in the present model, the ICER reported by the 3-year model was €38,366/QALY (Table 8). This result is more favourable to vaccination than the result produced by the base case of our model, because the number of QALYs is less affected by the

change in timescale than the costs (12% and 25% change, respectively). A similar effect is seen when working in the opposite direction. Starting from our base case and moving progressively towards the values used in the Melliez analysis, the final ICER of €147,192/QALY was less favourable than the result reported by Melliez et al. [8]. The price and effect differences were smaller when starting with the 3-year timescale and the Melliez values, because of the shorter evaluation period and the lower vaccine coverage rate of 75%.

DISCUSSION

This paper presents the results of a probabilistic model estimating the burden of rotavirus disease and the potential cost-effectiveness of generalized vaccination of infants with RIX4414 in France, compared with the current policy of no rotavirus vaccination. Our model builds on a model previously published by Melliez et al. in 2005 [5]. We have further developed the robust structure of this original model to take account of features of the combined age-adjusted and seasonal variation in rotavirus infection rates. Current epidemiological data on rotavirus disease in France have been used to calibrate the model. Cost figures used come from the limited societal perspective and the utility scores were obtained from research with UK health professionals [11]. The results of the present model indicate that implementing a generalized vaccination strategy with RIX4414 in France would be cost-effective at the indicated public price of € 57 per vaccine dose, with an incremental cost per QALY of € 44 583/QALY (Table 7). The probabilistic multivariate sensitivity analysis shows a more favorable ICER result than the base-line analysis because some of the cost ranges selected such as the cost for 1st Line visit, and emergency visit could only be estimated to a higher end range which will of course positively influence the end result. Meanwhile the importance of this type of sensitivity analysis is mainly to indicate how heavily some of the basic model assumptions on transition probabilities and on utility scores impact the ICER as can be seen from Figures 3 and 5.

Melliez et al. have recently published an estimate of the cost-utility of rotavirus vaccination in France [8]. At first sight, their results appear to produce a less favourable estimate of the cost-effectiveness of rotavirus vaccination than our results, with a base-case cost-effectiveness ratio for vaccination of € 138,000 per QALY gained [8]. However, detailed comparison of the models suggests that the different results are explained by differences in model structure and data input values between the two studies. The main differences we have identified are summarized in Table 8.

Table 9 and Figure 6 show the impact of each of these differences on the model results. It can be seen that applying the opposite set of input parameters to each model can reverse the results; indeed, when our model was run with all the input variables set to the values used by Melliez, it produced a cost-effectiveness ratio that was even less favourable to vaccination than Melliez' own result [8]. Clearly, the values used for the input parameters are crucial in determining the model outputs.

Table 7 Cost-effectiveness results

Strategy	Cost	Incr. Cost	QALY	Incr. QALY	Incr. C/QALY
No Vaccine	52.18 €		43.62997		
Vaccine	104.84 €	52.66 €	43.63115	0.001181	44,583 €
Strategy	Cost	Incr. Cost	RVGE-cases	RVGE cases avoided	Incr. C/RVGE case avoided
No Vaccine	39 135 958 €		299 956		
Vaccine	78 634 989 €	39 499 031 €	113 829	-186 128	212 €
Strategy	Cost	Incr. Cost	Hospitalizations	Hospitalizations avoided	Incr. C/hospitalization avoided
No Vaccine	39 135 958 €		17 932		
Vaccine	78 634 989 €	39 499 031 €	3 061	-14 871	2 656 €
Strategy	Cost	Incr. Cost	Deaths	Deaths avoided	Incr. C/death avoided
No Vaccine	39 135 958 €		9		
Vaccine	78 634 989 €	39 499 031 €	2	7	5,642,719 €

Incr.: Incremental

C: Cost

Table 8 Differences between the present model and the Melliez et al. Model [8]

Parameter	Value(s) used in base case of present model	Value(s) used in base case of Melliez model [8]
Nosocomial infections	Included	Not specifically included
Hospitalization cost	€ 1556	€ 1240
Vaccine cost/dose	€ 57	€ 75
Vaccine coverage	85%	75%
Utility scores	Mild: 0.891 (<18 mo.) 0.844 (>18 mo.) 1st Line visit: 0.781 (<18 mo.) 0.688 (>18 mo.) Hospitalized: 0.425 (<18 mo.) 0.200 (>18 mo.)	Mild: 0.884 Severe: 0.816
Disease Duration	Mild: 4 days Severe: + 3 days Hospitalization: + 3 days Consult: + 1 day	Mild: 5.4 days Severe: 6.5 days
Rotavirus cases with no vaccination	300,000 in children aged <5 yrs.	182,000 in children aged <3 yrs. (= 3/5 of 300,000)
Vaccine efficacy rate	Any severity: 87.1% Hospitalized: 100%	Any severity: 70% Severe: 85%
Time horizon	Lifetime	Up to 35 months of age
Population	Children < 5 yrs.	Children < 3 yrs.
Discount rate	Costs: 3% Benefits: 1.5%	Costs: 3% Benefits: 3%

1st Line: General Practitioner, Paediatrician, Home Visit; mo.: months

The parameters with the greatest impact on the result, as assessed by the multivariate regression analysis, were the vaccine price, duration of diarrhoea, vaccine efficacy, discount rate applied to health benefits, prevalence of nosocomial infection, and the disutility score for rotavirus diarrhoea (Figure 5). Two of these parameters, vaccine price and vaccine efficacy, reflect the fact that in the present paper we investigated a specific rotavirus vaccine, RIX4414, whereas Melliez et al. [8] investigated rotavirus vaccination in general using pooled cost and efficacy

Table 9 Sensitivity analysis on the Melliez data in the present model (incremental cost/QALY)

	5-year model, moving from present base-case values to Melliez values			3-year model, moving from Melliez values to present base-case values		
Variables	**Value**		**ICER**	**Value**		**ICER**
	Base Case	**Melliez**		**Melliez**	**Base Case**	
Start ICER			44,583 €			137 408 €
Vaccine Price	57 €	75 €	69,952 €	75 €	57 €	94,432 €
Duration diarrhoea	4 days	5.4 days	62,559 €	5.4 days	4 days	105,305 €
Vaccine Efficacy	88%*	70%	65,159 €	70%	88%*	96,904 €
Discount Effect	1.50%	3%	74,779 €	3%	1.50%	73,592 €
Nosocomial Prevalence	0.42%	0%	84,178 €	0%	0.42%	64,115 €
Disutility Diarrhoea Score Children	-0.156	-0.116	89,581 €	-0.116	-0.156	62,354 €
Cost Hospitalisation	1,556 €	1,240 €	95,445 €	1,240 €	1,556 €	55,294 €
Duration Severe Diarrhoea	+3 days	+1.1 days	104,102 €	+1.1 days	+3 days	50,924 €
Duration Hospitalisation	+3 days	+1.1 days	111,000 €			
Duration Emergency	+ 1 day	0	124,358 €			
Disutility Severe Diarrhoea Infants	-0.575	-0.186	129,520 €	-0.186	-0.575	41,885 €
Duration GP	+ 1 day	0	136,684 €			
Disutility Hospitalisation Visit Infants	-0.8	0	141,442 €	0	-0.8	39,033 €
Disutility Hospitalisation Visit Children	-0.575	0	147,192 €	0	-0.575	38,366 €

*average vaccine efficacy

data for two different products. Pooling data from different products to arrive at a single input value raises important questions of validity, as the products may differ in effectiveness or cost or both. As the pooled efficacy value used by Melliez et al. was lower than the RIX4414 efficacy, and the average cost was higher than the RIX4414 price, the cost-effectiveness ratio estimated by Melliez et al. for the pooled products would be expected to be less favourable than the RIX4414 cost-effectiveness ratio estimated in the present paper.

Melliez et al. used a higher discount rate for health benefits (3%) than our model. Higher discount rates reduce the value of benefits obtained in the future, and preventive strategies such as vaccination incur immediate expenditure (cost of vaccination) in order to produce future benefits (prevention of infections). Thus, the 3% discount rate used by Melliez et al. would automatically produce a less favourable estimate of the cost-effectiveness of vaccination than the 1.5% rate used in the present model. The optimum discount rate for health effects is still a subject of debate [22-24]. Discounting makes current costs and benefits worth more than those occurring in the future, because there is an opportunity cost associated with receiving money in the future rather than now (money received now can be invested for future gains), and people generally desire to enjoy benefits now rather than in the future. The main argument against discounting health benefits is that health cannot be invested to produce future gains [25]. Many other arguments have been published, and some authors recommend that health benefits should not be discounted [26], while other advice suggests future health benefits should be discounted but at a very low rate of 1.5%-2% [27]. The most conservative approach is to discount benefits at the same rate as costs, but

this tends to discriminate against preventive treatment strategies whose benefits accrue mainly in the future. In the absence of consensus, we felt that a discount rate of 1.5% for benefits reflected a reasonable compromise.

Melliez et al. used higher utility scores for RVGE than our model, which would produce a lower estimate of the number of QALYs gained by vaccination. The utility values used in our model are derived from a study in which health professionals rated QoL for children with different severities of RVGE using a recognized instrument (the Euro-QoL questionnaire). The values used by Melliez et al. were derived from ratings provided by adult caregivers and the source publication did not differentiate between different severities of illness. In both cases, the utility values used were extracted from non-French studies due to the lack of published utility scores for rotavirus gastroenteritis in France. We may question whether selecting physicians is a good alternative for estimating QALY-scores in diseased children instead of parents. It has been reported that medical care-givers overestimate the patient burden but on the other hand they may be best placed to evaluate the total disease impact being confronted on a regular basis with specific health and health care problems [28].

Melliez et al. included only RVGE cases in children <3 years of age, whereas our model covers the larger at-risk population of children <5 years of age. This difference will affect the estimate of the total number of cases of RVGE expected to occur in the population in the absence of vaccination. The number of RVGE cases in children aged <5 years in France was estimated at 300,000 per year by Melliez et al. in an earlier publication [5], and we have applied this estimate in the present study. In their recent model, however, Melliez et al. estimated the number of RVGE cases in children aged <3 years at 182,000 per year [8]. This is difficult to reconcile with the earlier estimate. It is approximately 60% of the earlier estimate for the number of cases in children aged <5 years, which would be plausible if the incidence of RVGE remains stable as a function of age. However, the incidence of RVGE approximately follows a Weibull distribution (Figure 2), and so the number of cases expected in children aged <3 years would be nearer to 90% of the number of cases expected in children aged <5 years. The reasons for this apparent discrepancy between the recent Melliez publication and the earlier paper are not clear, and may indicate an underestimate of RVGE cases in the recent model for the age group up to 3 years.

The fact that two modeling studies evaluating similar vaccination strategies in the same country can produce results that at first sight appear to be contradictory illustrates the difficulties faced in conducting health economic evaluations. A more standardized approach to constructing and populating health economic models would help to make results more easily comparable between different studies [29]. This would help to reduce the confusion caused by publication of apparently conflicting results, which in turn would help to support a rational assessment of the economic value of potential new therapies.

The present analysis may not have captured some potentially important benefits of rotavirus vaccination. For example, peaks of rotavirus gastroenteritis that result in

medical consultations and hospitalization occur during the same period as other commonly occurring childhood diseases that also result in emergency visits, such as influenza and respiratory syncytial virus bronchiolitis [30-32]. It is therefore possible that a reduction in rotavirus-associated emergency consultations and admissions due to vaccination could reduce seasonal pressure on overburdened pediatric emergency wards and physicians' offices, with consequent improvements to patient care. The model also takes no account of any health benefit obtained from herd protection effects in scenarios when vaccine coverage is <100%.

When a parent takes time off work to care for a child with RVGE, the value of the parent's work is lost. These indirect costs were not included in the base-case analysis as there is still a debate in France about the exact method to apply for estimating such costs [17]. However, the model can estimate the number of days of paid work lost due to caring for a child with rotavirus gastroenteritis after the official period of maternity leave (conservatively assumed here to be one year) at 538 303 days per year, based on the proportion of women who are in full-time paid employment (49% in France [33]). In the developed world with a high proportion of working adults, reduction of indirect costs is likely to be an important benefit associated with vaccination against paediatric infections [34].

Our results are conservative compared with some other published studies. For example, Huet et al. [35] reported total direct costs for the burden of rotavirus infection in France of € 63 million to the National Healthcare Payer, compared with € 41 million in this analysis. Huet et al. reported a higher hospitalization rate, consistent with data from the REVEAL study [34-36], whereas our approach conservatively assumes the hospitalization rate considered by Melliez in 2005 [5].

There are no clear guidelines in France on valuing hospital costs. The method used (based on the national hospital costs database) is conservatively the same than the one used by Melliez. The approach is likely to underestimate the true hospitalization costs as DRG costs in France are no full hospital costs.

Finally, the utility values applied in the model estimated the QoL impact of rotavirus gastroenteritis only for the affected child [11], and thus did not capture the QoL impact on other family members. Parents and carers may be adversely affected by the child's illness, resulting in anxiety, stress, and feelings of exhaustion, as others have suggested [37].

Recent cost-effectiveness analyses of the new rotavirus vaccines have been reported in addition to France, for the UK, the Netherlands, Italy and the US [38-41]. The results indicate how difficult it is to pool data of two vaccines seemingly equivalent into one economic analysis. In addition the selected cost perspective and the underlying disease epidemiology will highly affect the end result of cost-effectiveness evaluation by country. But all the analyses suffer from underreporting the disease when not seeking medical advice, unable to define how rotavirus infection affects family functioning, and the imprecise evaluation of the individual patient burden. Meanwhile one interesting study recently highlighted about the estimation of financial rotavirus disease burden in

4 countries in the EU. It appears that in open health care systems such as France and Belgium where there is no limit to consult directly 1st or 2nd line health care levels, the estimated direct medical cost of rotavirus diarrhea is higher compared to the more closed systems in the UK and the Netherlands. However the total estimated societal disease burden including direct and indirect costs per child per year for the 4 countries is more or less the same (23.11 €) [42]. It should therefore be recommended that economic assessment of the vaccine should encompass the total disease burden and not the health care impact only.

In conclusion, the present analysis indicates that universal vaccination of infants against rotavirus infection could be cost effective in France from a limited societal perspective and based on the assumptions introduced in the model regarding disease development and utility scores selected (94% of modelling scenarios generated an incremental cost-effectiveness ratio < € 50,000/QALY). This study supports the findings of the European Rotavirus Vaccination Advisory Committee who advocate, based on currently available evidence, the introduction of rotavirus vaccination into childhood immunization programs [43].

REFERENCES

[1] Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003 May;9(5):565-72.

[2] Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J 2006 Jan;25(1 Suppl):S7-S11.

[3] Brandt CD, Kim HW, Rodriguez WJ, Arrobio JO, Jeffries BC, Stallings EP, et al. Pediatric viral gastroenteritis during eight years of study. J Clin Microbiol 1983 Jul;18(1):71-8.

[4] Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med 1996;335(14):1022-8.

[5] Melliez H, Boelle PY, Baron S, Mouton Y, Yazdanpanah Y. Morbidite et cout des infections a rotavirus en France [Morbidity and cost of rotavirus infections in France]. Med Mal Infect 2005;35(10):492-9.

[6] Vesikari T, Karvonen A, Puustinen L, Zeng SQ, Szakal ED, Delem A, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. Pediatr Infect Dis J 2004;23(10):937-43.

[7] Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet 2007;370(9601):1757-63.

[8] Melliez H, Levybruhl D, Boelle PY, Dervaux B, Baron S, Yazdanpanah Y. Cost and cost-effectiveness of childhood vaccination against rotavirus in France. Vaccine 2008 Jan 30;26(5):706-15.

[9] Official medical tariff list (UCANSS). http://www.ucanss.fr/ 2007

[10] Echelle des Couts (ENC). http://www.atih.sante.fr/?id=000370000FFF 2008

[11] Martin A, Cottrell S. Estimating utility in rotavirus gastroenteritis in children under five in the UK (abstract PIH19). Value Health 2006;9(6):A258.

[12] Bresee JS, Glass RI, Ivanoff B, Gentsch JR. Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. Vaccine 1999 May 4;17(18):2207-22.
[13] Clark HF, Offit PA. Vaccines for rotavirus gastroenteritis universally needed for infants. Pediatr Ann 2004;33(8):536-43.
[14] Fourquet F, Desenclos JC, Maurage C, Baron S. [Acute gastro-enteritis in children in France: estimates of disease burden through national hospital discharge data]. Arch Pediatr 2003 Oct;10(10):861-8.
[15] Martinot A, Dumonceaux A, Grandbastien B, Hue V, Leclerc F. [Evaluation of the ambulatory treatment of acute diarrhea in infants. Reseau interhospitalier d'evaluation des pratigues medicales dans les affections courantes de l'enfant]. Arch Pediatr 1997 Sep;4(9):832-8.
[16] French general practitioners' Sentinelles network. http://websenti.b3e.jussieu.fr/sentiweb/ 2007
[17] College des Economistes de la Sante. French guidelines for the economic evaluation of health care technologies. http://www.ces-asso.org/docs/France_Guidelines_HE_Evaluation.PDF 2004
[18] Clemens J, Rao M, Ahmed F, Ward R, Huda S, Chakraborty J, et al. Breast-feeding and the risk of life-threatening rotavirus diarrhea: prevention or postponement? Pediatrics 1993 Nov;92(5):680-5.
[19] Newburg DS, Peterson JA, Ruiz-Palacios GM, Matson DO, Morrow AL, Shults J, et al. Role of human-milk lactadherin in protection against symptomatic rotavirus infection. Lancet 1998 Apr 18;351(9110):1160-4.
[20] Gleizes O, Desselberger U, Tatochenko V, Rodrigo C, Salman N, Mezner Z, et al. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. Pediatr Infect Dis J 2006 Jan;25(1 Suppl):S12-S21.
[21] Institut de Veille Sanitaire. The fight against HIV/AIDS and sexually transmitted infections in France. 10 years of surveillance, 1999-2005. http://www.invs.sante.fr/publications/2007/10ans_vih/rapport_vih_sida_10ans-7-Prevention.pdf 2007
[22] Bos JM, Postma MJ, Annemans L. Discounting health effects in pharmacoeconomic evaluations: current controversies. Pharmacoeconomics 2005;23(7):639-49.
[23] Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. Value Health 2004 Jul;7(4):397-401.
[24] Smith DH, Gravelle H. The practice of discounting in economic evaluations of healthcare interventions. Int J Technol Assess Health Care 2001;17(2):236-43.
[25] Sheldon TA. Discounting in health care decision-making: time for a change? J Public Health Med 1992 Sep;14(3):250-6.
[26] Parsonage M, Neuburger H. Discounting and health benefits. Health Econ 1992 Apr;1(1):71-6.
[27] Torgerson DJ, Raftery J. Economic notes. Discounting. BMJ 1999 Oct 2;319(7214):914-5.
[28] Martin A, Cottrell S, Standaert B. Estimating utility scores in young children with acute rotavirus gastroenteritis in the UK. Journal of Medical Economics 2008;11(3):471-84.

[29] News from the scientific literature: the cost-utility of rotavirus vaccination with Rotarix (RIX4414) in the Netherlands. V&I News - ECDC Newsletter on Vaccines and Immunisation 2008 Feb;(39):3.
[30] Hjelt K. [Nosocomial virus infections in pediatric departments. Rotavirus and respiratory syncytial virus]. Ugeskr Laeger 1991 Jul 22;153(30):2102-4.
[31] Le Roux P, Marshall B, Toutain F, Mary JF, Pinon G, Briquet E, et al. [Nosocomial viral infections in a pediatric service: example of rotaviral gastroenteritis and respiratory syncytial viral bronchiolitis]. Arch Pediatr 2004 Aug;11(8):908-15.
[32] Maille L, Beby-Defaux A, Bourgoin A, Koulmann L, Eucher V, Cardona J, et al. [Nosocomial infections due to rotavirus and respiratory syncytial virus in pediatric wards: a 2-year study]. Ann Biol Clin (Paris) 2000 Sep;58(5):601-6.
[33] National Institute for Statistics and Economic Studies [Institut Nationale de la Statistique et des Etudes Economiques]. Activité, emploi et chômage selon le type de ménage et le nombre d'enfants. http://www.insee.fr/fr/ffc/chifcle_fiche.asp?ref_id=NATCCF03128&tab_id=490&souspop=2 2008
[34] Giaquinto C, Van Damme P, Huet F, Gothefors L, Van der Wielen M. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. J Infect Dis 2007;195 Suppl 1:S36-S44.
[35] Huet F, Largeron N, Trichard M, Miadi-Fargier H, Jasso-Mosqueda G. Burden of paediatric rotavirus gastroenteritis and potential benefits of a universal rotavirus vaccination programme with RotaTeq in France. Vaccine 2007 Aug 21;25(34):6348-58.
[36] Giaquinto C, Van Damme P, Huet F, Gothefors L, Maxwell M, Todd P, et al. Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004-2005: the REVEAL study. J Infect Dis 2007;195 Suppl 1:S26-S35.
[37] Huppertz HI, Forster J, Heininger U, Roos R, Neumann HU, Hammerschmidt T. The Parental Appraisal of the Morbidity of Diarrhea in Infants and Toddlers (PAMODI) Survey. Clin Pediatr (Phila) 2008;47(4):363-71.
[38] Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. Vaccine 2007;25(20):3971-9.
[39] Goossens LMA, Standaert B, Hartwig N, Hovels AM, Al MJ. The cost-utility of rotavirus vaccination with Rotarix(TM) (RIX4414) in the Netherlands 1487. Vaccine 2008 Feb 20;26(8):1118-27.
[40] Standaert B, Marocco A, Assael B, Gabutti G, Guarino A, Lopalco P, et al. Analisi di costo-efficacia della vaccinazione universale in Italia con il vaccino Rix4414 contro i rotavirus. Pharmacoeconomics 2008;10(1):23-35.
[41] Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Cost-effectiveness and potential impact of rotavirus vaccination in the United States. Pediatrics 2007 Apr;119(4):684-97.
[42] Standaert B, Harlin O, Desselberger U. The Financial Burden of Rotavirus Disease in Four Countries of the European Union. Pediatric Infectious Disease Journal Rotavirus 2008 Jan;217:S20-S27.
[43] Van Damme P, Van der Wielen M, Ansaldi F, Desgrandchamps D, Domingo JD, Sanchez FG, et al. Rotavirus vaccines: considerations for successful implementation in Europe. Lancet Infect Dis 2006 Dec;6(12):805-12.

2.4 SIMPLE VERSUS MORE COMPLEX

Having the ability to evaluate the rotavirus vaccine and its health economic merits in many different places around the world, I observed that in several countries there is a lack of detailed information about the disease. There are some statistics about the disease burden collected by care-givers amongst children <5 years of age, but many researchers are hesitant to assess the economic value of the new vaccine.

I developed a type of back-of-the envelop calculation method for rotavirus vaccine and made the comparison with the more complex cohort model for Turkey. The first model required only 20 variables and one spread sheet in MS Excel®. The second model has more than 120 variables and has 26 spread sheets in MS Excel®.

With the first model called Roxannette decision makers were able to assess with a number of key variables in which direction the economic value of the vaccine should move, given the price they had foreseen in their budget. It is a helpful tool for a first estimate that may drive as well the research program for collecting additional data missing for running the more advanced model [22].

ESTIMATING AND COMPARING THE CLINICAL AND ECONOMIC IMPACT OF PAEDIATRIC ROTAVIRUS VACCINATION IN TURKEY USING A SIMPLE VERSUS AN ADVANCED MODEL

Vaccine, 2013, 31: 979-986

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ABSTRACT

Background: The burden of rotavirus disease is high in Turkey, reflecting the large birth cohort (>1.2 million) and the risk of disease. Modelling can help to assess the potential economic impact of vaccination. We compared the output of an advanced model with a simple model requiring fewer data inputs. If the results are similar, this could be helpful for countries that have few data available.

Methods: The advanced model was a previously published static Markov cohort model comparing costs and quality-adjusted life-year (QALY) outcomes of vaccination versus no vaccination. In contrast, the simple model used only a decision tree. Both models included data on demography, epidemiology, vaccine efficacy, resource use, unit costs, and utility scores from national databases and published papers. Only the perspective of the health care payer was considered in the analysis. The simple model had 23 variables, compared with 103 in the advanced model to allow additional comparisons of different vaccine types, dose schemes and vaccine waning.

Results: With the same input data, both models showed that rotavirus vaccination in Turkey would improve health outcomes (fewer QALYs lost to rotavirus disease).

The projected annual cost offsets were $29.9 million in the simple and $29.4 million in the advanced model. Sensitivity analysis indicated that in both models the main cost driver was disease incidence followed by cost for hospital care and medical visits. Vaccine efficacy had a smaller effect.

Conclusions: Both models reached similar conclusions. Both projected that rotavirus vaccination in Turkey would improve health outcomes and may result in savings in direct healthcare costs to offset the cost of vaccination. The analysis indicated that the simple model can produce meaningful economic results in conditions where few data are available.

Keywords: rotavirus; vaccination; economic evaluation; model; Turkey; paediatric

INTRODUCTION

Rotavirus is a major cause of acute gastroenteritis in young children worldwide, with an estimated 453,000 deaths annually in children aged <5 years, mainly in the developing world [1]. Almost every child will be infected with rotavirus before 5 years of age, with peak incidence at age 6–24 months [2;3]. Countries such as Turkey with a large annual birth cohort (>1.2 million) could experience a high rotavirus gastroenteritis (RVGE) burden, with consequences for health outcomes (mortality and morbidity), healthcare spending (medical visits and hospitalisations), and impaired quality of life (e.g. stress for parents) [3-8].

In the absence of detailed information on rotavirus disease in a country, models are helpful tools to explore the potential impact of new interventions such as vaccination [9]. Many models of rotavirus disease and the projected impact of vaccination have been reported, from simple to advanced [10-13]. Advanced models may include specific aspects of the clinical impact and cost of rotavirus disease over time and various potential vaccine effects, and can compare different vaccine types or estimate indirect vaccine effects.

Decision-makers need to choose an appropriate model for economic assessment of interventions in their country [14]. Model selection depends on three issues: the economic question to be answered; the data available to answer that question; and the audience to whom it is addressed. Simple questions should be answered by simple models that are straightforward to understand and accessible by a range of users. Advanced models can answer more complex questions, but require more data, more assumptions, and more skills to construct, understand and interpret the results. However, an advanced model should also be able to answer simple questions, and its results should not differ greatly from those of the simple model.

In the present paper, we have tested this hypothesis by comparing the results of a simple and an advanced model for estimating cost offsets and gain in quality-adjusted life-years (QALY) for rotavirus vaccination versus no vaccination. We selected Turkey for this study. It is a good example of a country with basic epidemiological data on ambulatory care and hospitalisation that needs to make decisions on healthcare investment. A complete economic assessment, addressing

questions about optimal vaccine type, dose regimen and schedule, and the likely size of the vaccine effect over time, will require an advanced model. However, a simple model can evaluate the economic impact of rotavirus vaccination in the first instance. If a simple model is shown to produce results similar to those of an advanced model, this should help to raise confidence that meaningful assessments can be performed in countries with few data available.

MATERIALS AND METHODS

We developed two models, an advanced model and a simple model deduced from it [13;15;16]. The simple model was designed to address three economic questions: the cost-effectiveness of rotavirus vaccination in infants versus no vaccination; one-way sensitivity analysis to identify the main results drivers; and the budget impact of introducing vaccination. The advanced model can also perform probabilistic sensitivity analysis and address more complex questions, such as the effect of a two- versus three-dose vaccine, different dosing schedules (e.g. 2-3 month dosing versus 3-5 month dosing), waning of vaccine effect over time and indirect protection. Because the objective of the present study was to compare the two model types, we present only results for outcomes common to both. The advanced model has been described elsewhere [13]. Its main features are summarised here.

MODEL STRUCTURE AND DESIGN

Advanced

This static, deterministic, Markov cohort model compared the costs and QALY outcomes of vaccination versus no vaccination of a birth cohort of 1,257,583 infants followed for 5 years in Turkey. The initial model was developed by Melliez and colleagues [17]. We adapted it to address more complex questions, such as dose scheduling, vaccine waning and seasonality [13]. It can include 103 different variables and is presented in 25 Microsoft Excel® worksheets.

Simple

The simple model was a static, deterministic, decision-tree model comparing the costs and QALY outcomes of vaccination versus no vaccination of 5 one-year age groups (0-1 year; 1-2 years; 2-3 years; 3-4 years; 4-5 years), with 1,257,583 children per age-group assessed together over a period of one year [18]. Four health states were included: mild (seeking no medical advice), moderate (visiting a general practitioner [GP] at least) or severe (hospitalised) disease, or rotavirus-related death. It has a maximum of 23 different variables and is presented on a single worksheet (A copy of the simple model is provided as a Microsoft Excel® worksheet in Supplementary Material 1).

As well as the smaller number of variables in the simple model, the models differed in construction. In the simple model, a population up to age 5 years was modelled over one year, whereas in the advanced model a birth cohort aged with time in cycles of 1 month over 5 years. The advanced model allowed more precision about the timing of events. This increased detail allowed the advanced model to identify more clearly the time and age at which projected vaccine benefits occur, which could have consequences for dose scheduling.

DATA INPUT

Demographic data

Both models required the annual number of births or the total birth cohort and birth rate, and average life expectancy at birth, estimated for Turkey at 73.3 years [19].

Epidemiological data

Advanced

Since the distribution of RVGE cases is age-dependent, the disease age distribution simulated in the model followed a Weibull distribution (parametric characteristics alpha=1.5, beta=24.2) over 60 months. Data on medical visits were proportional to that distribution and have the same basic curve shape. However, hospitalisations may have an earlier age distribution than the baseline curve, so age-specific hospitalisation rates for RVGE were included (Table 1).

Non-age-dependent epidemiological variables included the probability of seeking medical advice (probability of a GP visit or a direct emergency room visit, probability of emergency room referral after a GP visit), and the probability of dying after hospitalisation for RVGE (Table 1).

Simple

The simple model did not use any prespecified parametric distribution for age-dependent variables. It estimated age-specific data using a fixed multiplication value for age-specific probabilities for each health state. The initial probability in the first age-group (0-1 year) defined the total number of cases in each health state and probabilities in the subsequent age-groups. The simple model did not account for breastfeeding or distinguish between nosocomial and community-acquired RVGE (both included in severe cases), and included no non-age-dependent epidemiological variables.

Utility data

Utility scores were obtained from a published study [20]. In both models, utility scores were adjusted to the appropriate time period (months for the advanced model, annual for the simple model) combined with the event duration and expressed as disutility scores: disutility score = (utility score–1)*d/unit time (d: days) (Table 1). As disutilities involve otherwise healthy children, assuming a baseline utility value of 1 seems reasonable.

Resource use and cost

Direct medical costs were estimated in each model by multiplying the number of resource units by the unit cost. Vaccine costs were not included in this comparison, because vaccine cost does not differ between the model types and therefore cannot help to explain any differences in model outputs. Rotavirus vaccination was assumed to be administered as part of existing primary vaccination schedules. Table 1 summarises the data used for direct medical costs in Turkey [21;22].

Table 1 Input data for variables in the model

Parameter	Advanced			Simple
	Starting value [a]			Starting value
Age-dependent				
Probability of rotavirus diarrhoea	~ 0.019 [b, c]			0.191
Breastfeeding probability	~ 0.752 [b]			Not included
Hospitalisation probability for rotavirus diarrhoea	~ 0.087 [b]			0.10
Non-age-dependent				
Probability of seeking medical advice	1			
Probability of first-line (GP) visit	0.179			
Probability of second-line visit	0.821			
Probability of dying after hospitalisation due to RVGE	0.00035			
Disutility scores [20]	Age <18 months (m)		Age >18 months (m)	(y)
Diarrhoea	-0.043		-0.027	-0.00285
ER visit	-0.019		-0.019	-0.00158
GP visit	-0.010		-0.007	
Hospitalisation	-0.127		-0.095	-0.00925
Death	-224 d			-225 d
Direct medical cost	Cost	Assumptions		Cost
GP consultation	$ 20	17% go to GP first		$ 20
Emergency room visit	$ 35	83% go to emergency first		$ 35
Hospitalisation RVGE	$ 400	26% pass through emergency		$ 400
Vaccine dose coverage and completion				
1st dose 2 months	95%			95%
2nd dose 3 months	100%			

a Starting values are country-specific and part of the calibration process

b Approximate because the values are age-related

c Probability values differ because the advanced model has a time frame in months and the simple model has a time frame in years, and because of the way probabilities are handled in each model. In the advanced model, probabilities over a 60-month period (5 years) follow a Weibull distribution, influenced in the first six months by breastfeeding, and sum to a cumulative probability of 1 over the period. In the simple model, the starting value is derived from the total number of cases up to the age of 5 years and the proportion of these cases that occur in the first age group (0–1 year).

d Discounted at 5% per year. The disutility scores differ between the advanced and simple model because the way the discount rate is included differs between the two models. The disutility score in the simple model is the mean of the two age groups in the advanced model, divided by 12 because the simple model has a time frame in years and the advanced model has a time frame in months

m: month; d: days; y: years. ER, emergency room; GP, general practitioner; RVGE, rotavirus gastroenteritis

Vaccine effect

Advanced

- The model incorporated both direct and indirect vaccine effects, with indirect effects considered only in sensitivity analysis. The advanced model required the following vaccine efficacy data [23;24]:
- Dose schedule and coverage per dose.
- Vaccine efficacy per dose for mild, moderate, and severe disease assessed over time (Table 2). Vaccine efficacy for mild disease is an estimate, as no precise data are yet available.

Table 2 Vaccine efficacy data after first and second dose of Rotarix®[1] for mild, moderate and severe disease stages over time in the advanced and simple model

	Months	Vaccine efficacy in mild diarrhoea	Vaccine efficacy in moderate diarrhoea	Vaccine efficacy in severe diarrhoea	Vaccine efficacy in nosocomial infections
Advanced					
Before dose 1	1	0.0%	0.0%	0.0%	0.0%
Dose 1	2	78.4%	80.8%	90.0%	90.0%
4 months	4	78.4%	80.8%	90.0%	90.0%
6 months	6	16.3%	16.1%	14.9%	14.9%
12 months	12	0.1%	0.1%	0.1%	0.1%
2 years	24	0.0%	0.0%	0.0%	0.0%
Dose 2	3	87.1%	95.8%	100.0%	100.0%
2nd year	15	74.0%	76.6%	80.0%	80.0%
3rd year	27	62.9%	69.0%	72.0%	72.0%
4th year	39	53.5%	62.1%	64.8%	64.8%
5th year	51	45.5%	55.9%	58.3%	58.3%
6th year	60	41.0%	52.2%	54.5%	54.5%
Simple					
After 2 doses		87%	95%	100%	100%

[1] Rotarix is a registered trade mark of the GlaxoSmithKline group of companies

Simple

The simple model assumed an average vaccine efficacy value for each health state without differentiating by time period or dose number (Table 2), using the maximum vaccine efficacy after 2 doses in the clinical trial [23]. It did not include indirect effects.

Model assumptions

Table 3 shows the key assumptions in both models, the rationale for each assumption and its impact. Outcomes were discounted at 5% and costs at 0% in the simple model and the advanced model base case.

DATA OUTPUT

Although the advanced model had many more outputs than the simple one, we report here only the outputs common to both:

- Rotavirus diarrhoea events within a birth cohort aged ≤5 years: all events; seeking medical advice; hospitalisations;
- Rotavirus-specific deaths;
- Total direct costs excluding vaccine costs (Cost offset = total rotavirus-related direct cost without vaccination minus total rotavirus-related direct cost with vaccination);
- Total QALY loss.

Both models considered the payer-only perspective (Ministry of Health). No cost-effectiveness result was reported as the analysis did not include vaccine cost.

Table 3 Assumptions used in construction of base case for each model

Assumption	Rationale	Impact
Adv.: Breastfeeding protects children against rotavirus infection Sim.: No breastfeeding	Adv.: Maternal antibodies are protective against rotavirus infection Sim.: No evidence available for protection by breastfeeding	High proportion of breastfeeding during the first 3 months after birth improves cost-effectiveness
Adv.: Parametric shape of the curve of RVGE events as a function of age (Weibull distribution) Sim.: Linear decrease as a function of age	The disease burden is higher in young infants	Equal spread of the disease over time may result in worse cost-effectiveness because of discounting
Adv.: Herd effect is essentially seen in very young infants (<3 months old) Sim.: No herd effect	Adv.: Data from the impact study in Belgium shows that effect Sim.: Difficult to integrate	Adding a fixed herd effect improves the cost-effectiveness
Adv.: Vaccine efficacy after one dose decreases exponentially Sim.: No specific dose adjustment	Adv.: Not enough data to know what happens in real life Sim.: No precise data available	Exponential decrease in vaccine efficacy after one dose justifies the administration of a second dose being cost-effective
Adv.: Cohort modelling is appropriate for demonstrating the vaccine effect over time Sim.: 1-year cross-sectional up to the age of 5 years	Adv.: As long as there is no demographic change in the population one can opt for a cohort approach Sim.: Simulates one year	Is a more conventional way of reporting the economic value of a new intervention over time
Adv.: No good data exist on the frequency of RVGE events that do not seek medical advice. The results are based on an approach of infection rates that manifest clinical symptoms (e.g. 60% first infection, 40% second infection) Sim.: same approach	Adv.: No observed data available other than this approximation Sim.: same rationale	To be tested in sensitivity analysis

Adv., advanced model; Sim., simple model; RVGE, rotavirus gastroenteritis

SENSITIVITY ANALYSES

One-way sensitivity analyses evaluated the robustness of the model results related to the underlying parametric assumptions (see Supplementary Material 2 for parameters and ranges). Sensitivity analyses used realistic ranges for each of the base-case parameters, derived from published sources wherever possible. Results are presented as tornado diagrams for cost results only.

STATISTICAL CONSIDERATIONS

Five datasets on RVGE in children aged ≤5 years should be collected at country level: diarrhoea events; first- and second-line visits; hospitalisations; and deaths. The advanced model calibrated the data against observations. The latter follow a Weibull distribution showing more cases at earlier ages before children reach 2 years old. This is important, as most RVGE cases occur before the age of 2 years and failure to adjust may produce less accurate results. The process of calibration in the model was an automated, iterative program in Visual Basic that brought the modelled values close to the observed values (difference of <0.001%).

As the simple model made fewer adjustments for factors such as breastfeeding, herd effect, dose adjustment, vaccine effect, cost discount, etc., the initial comparison was

Table 4 Projected numbers of rotavirus cases by severity, rotavirus deaths, cost and cost offset, and QALYs lost for each model type with and without vaccination

	Unvaccinated	Vaccinated	Difference (%)
Simple			
Mild	539 280	93 565	−445 715 (83%)
Moderate	539 280	52 580	−486 700 (90%)
Severe	36 797	1 840	−34 957 (95%)
Deaths	13	1	−12 (92%)
Cost / Cost offset [a]	$32 480 486	$2 581 784	−$29 898 702 (92%)
QALY lost	−2 973	−369	2 604 (88%)
Advanced (base case)			
Rotavirus diarrhoea events	539 280	36 688	−502 591 (93%)
1st line	96 554	6 569	−89 985 (93%)
2nd line	442 726	30 120	−412 606 (93%)
Emergency visit	9 653	657	−8 996 (93%)
Hospitalisation	36 797	2 257	−34 540 (94%)
Deaths	13	1	−12 (92%)
Cost / Cost offset [a]	$32 483 127	$3 110 586	−$29 372 541 (90%)
QALY lost	−2 663	−254	2 409 (90%)

[a] Unvaccinated and Vaccinated columns show cost, Difference column shows cost offset

made with the fewest of these effects in the advanced model. This estimated the basic difference in cost offset and QALYs between the models, expressed as a percentage. Additional features were then successively added to the advanced model and the percentage deviation from the initial analysis calculated. This was conducted first by evaluating each parameter separately as a one-way sensitivity analysis, then by combining different elements as a multi-way sensitivity analysis. We also reported the results of the advanced model as normally used (including breastfeeding, discounting of costs and effect and waning, but excluding herd protection).

RESULTS

Table 4 summarises the estimated number of rotavirus cases, cost and cost offset and QALYs lost for vaccination compared with no vaccination projected by each model.

The advanced model was adjusted to be comparable with the simple one (i.e. no cost discount, breastfeeding, herd effect or vaccine waning). The number of QALYs gained by vaccination was slightly smaller in the advanced model than in the simple one, because the simple model only discounted the life-years gained when deaths were avoided. The cost offsets were larger in the simple than in the advanced model because of the difference in disease age-distribution and differences in effect and coverage for the first and second doses in the advanced model.

Table 5 shows the effect of introducing into the advanced model the features that differentiate it from the simple one, adding first breastfeeding, then cost discounting at 5%, then waning, and finally herd effect with a 10% improvement in vaccine efficacy. The 'Combined effect' analysis shows the effects of adding

Table 5 Effect of adding each specific feature, separately and combined, to the advanced model (% relative to base case advanced model)

Advanced	No Vaccination	Vaccination	Difference (%) [a]
Breastfeeding			
Cost / Cost offset [b]	$32 483 167	$2 111 214	−$30 371 953 (103%)
QALY lost	−2 669	−177	2 492 (103%)
Cost discounting			
Cost / Cost offset [b]	$30 699 401	$3 013 889	−$27 685 512 (94%)
QALY lost	−2 663	−254	2 409 (100%)
Waning vaccine effect			
Cost / Cost offset [b]	$32 483 127	$3 190 296	−$29 292 870 (99%)
QALY lost	−2 663	−263	2 400 (99%)
Herd effect			
Cost / Cost offset [b]	$32 483 127	$2 977 515	−$29 505 651 (101%)
QALY lost	−2 663	−238	2 425 (101%)
Combined effect			
Cost / Cost offset [b]	$30 598 598	$1 901 138	−$28 697 460 (98%)
QALY lost	−2 669	−163	2 506 (104%)
Normal			
Cost / Cost offset [b]	$30 598 598	$2 080 690	−$28 517 908 (97%)
QALY lost	−2 669	−187	2 482 (103%)

QALY, quality-adjusted life-year

a result expressed as a percentage of the result for the base case of the advanced model in Table 4. 100% indicates no difference

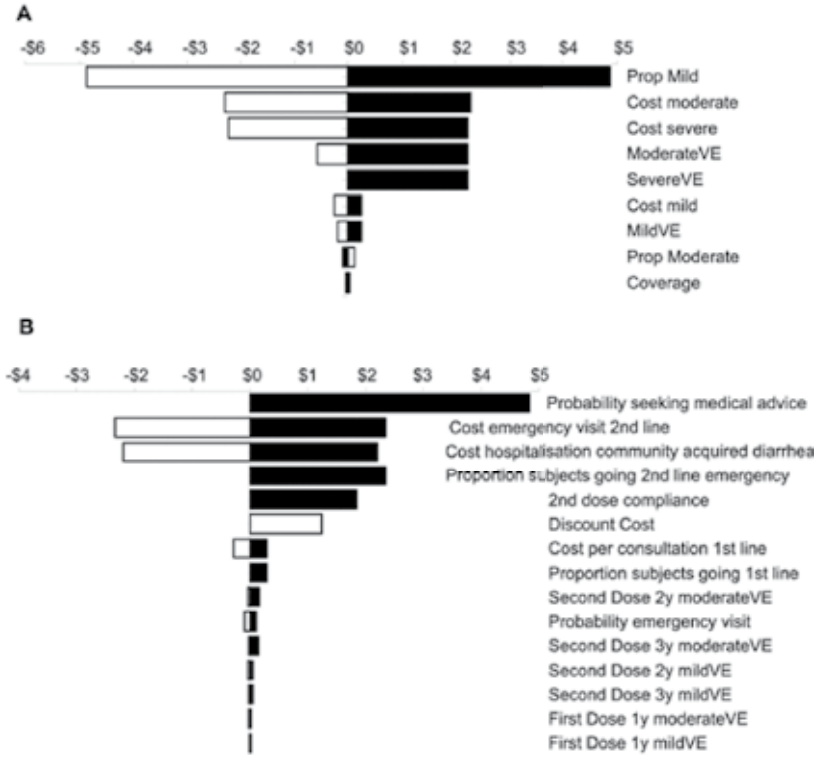
b No vaccination and Vaccination columns show cost, Difference column shows cost offset

all these features together, and the 'Normal' analysis shows the results of the advanced model as normally used (including breastfeeding, cost discounting and waning, but excluding herd effect).

The combined analysis showed the greatest effect (2506 QALYs gained, compared with 2409 in base-case) but it was still smaller than estimated by the simple model (2604 QALY). One reason is that the simple model assumed a greater mortality gain than the advanced model. The greatest cost offset was seen when breastfeeding was included. Breastfeeding is assumed to confer full protection against rotavirus infection, and therefore adds benefit for a limited time after vaccine administration [25]. The lowest cost offset was seen when discounting was applied to cost, but the change was modest because most cost occurs during a small time window of 2–3 years. It is reassuring that the additional features in the advanced model essentially result in more precision in the end result, rather than a radically different end result. Adding herd protection to the model resulted in a slight change in favour of vaccination, and discounting the cost or adding vaccine waning resulted in a larger change that was unfavourable to vaccination.

Figure 1 shows tornado diagrams on the cost offset for the simple (Figure 1A) and advanced (Figure 1B) models.

Figure 1 Tornado diagram on key variables measuring the cost difference in (A) the simple model and (B) the advanced model. Black bars show the effect of decreasing the parameter value; white bars show the effect of increasing the parameter value. Prop, proportion; VE, vaccine efficacy; y, year



In both models the main cost driver was disease incidence, followed by disease-related costs. Vaccine efficacy had a smaller effect, perhaps because vaccine efficacy was high and the input range limited. The advanced model also indicated the importance of cost discounting and dose compliance, but these were not major drivers (Figure 1B).

DISCUSSION

The results of both the simple and advanced models projected that rotavirus vaccination could produce important cost offsets in hospitalisation and medical visit costs in Turkey. This reflects the large medical and QALY disease burden associated with rotavirus in Turkey. Reduction of this burden by vaccination may result in estimated cost offsets of up to $29.5 million per year, a decrease of 92% of the current estimated cost of rotavirus disease.

The conclusion was similar using either a simple or an advanced model. This should be expected, as both models should reach the same conclusion when answering simple questions with the same data input, unless there is a problem with the model construct. The simple model produced more optimistic estimates

than the advanced model in its normal configuration. This is because the simple model had a simplified approach to discounting and age distribution of rotavirus disease, did not adjust vaccine efficacy over time, and made no adjustments for first and subsequent vaccine doses.

As the results from both models in the current study indicated that vaccination would reduce medical costs and improve QALYs, the greater precision offered by the advanced model has limited benefit except to indicate the potential range of cost offsets and QALYs gained. In other situations where one strategy is both more expensive and more costly than the comparator, the ability of the advanced model to adjust for factors such as breastfeeding, changes in vaccine efficacy over time and any herd protection may be important to obtain precise estimates of discounted costs, benefits and incremental cost-effectiveness ratios.

The similarities and small differences between the simple and advanced models in the tornado diagrams are of interest. Both models were affected by disease incidence and cost variables more than by vaccine efficacy. The relatively small impact of changes in vaccine efficacy reflects the characteristics of rotavirus disease. Rotavirus incidence drops dramatically after the age of 24 months, due to age-related behavioural changes and development of natural immunity after repeated infections, so after this age any change in vaccine efficacy has only a small effect on the results. This illustrates the importance of calibrating the advanced model closely with the data to simulate precisely a disease distribution concentrated in young children (aged <24 months) [13].

Both models can include indirect costs if needed, as lost earnings are associated with time missed from work by parents caring for their children.

Both models used life expectancy at birth, rather than natural mortality rates. This assumption is acceptable if the economic evaluation measures health gain only amongst children, and if no large change is expected in population demographic structure. The same approach is used when developing an age-structured dynamic model [26;27].

Recent observational studies on the impact of rotavirus vaccination in real life have indicated that the decrease in vaccine efficacy reported in clinical trials may reflect a reduction in net effect due to development of natural immunity over time, rather than a real decrease in vaccine effect [28]. This supports the use of vaccine efficacy maintained over time in the simple model. Long-term studies may provide definitive evidence on whether vaccine efficacy is indeed maintained over time.

Advanced models have often been used in developed countries such as in the US, France, UK, or the Netherlands. However, attempting to make a straightforward comparison between the results of those models from those countries with the Turkish situation may highlight an issue illustrated by a recent review on the cost-effectiveness of Rotarix vaccination. The health and economic problem caused by rotavirus differs greatly between developed and emerging countries. In developed countries the healthcare cost is high, mainly driven by hospital

costs, and mortality is low. In contrast, emerging markets such as Turkey have a lower cost problem and higher mortality. The review was therefore split into two separate papers, one covering developed countries and one covering developing countries[29]. The economic analysis and the comparison showed that in more developed countries the offsets in QALY loss are limited, due to the low mortality from rotavirus in developed countries. In emerging markets the situation is quite different, as rotavirus mortality is higher and the scope for QALY gains consequently larger. In contrast, the cost offset could be important in both market types. As a consequence it is likely that a new vaccine against rotavirus would be cost-effective in emerging markets, whereas in the more developed world cost minimisation drives the economic end result.

This type of analysis has limitations, and we propose the simple model presented here as an exploratory method for obtaining the best estimates possible with limited available data. It should help decision-makers to orient their choices, but the findings will need subsequent confirmation if vaccination is introduced. It will be helpful to use both models if possible as part of a validation process. The advanced model is more sophisticated than the simple one, and if both produce similar results that should support confidence in the findings. Conversely, large differences in the results may indicate that an explanation should be sought. The simple model with its graphical interface should help decision-makers understand and explain rotavirus disease and the potential impact of rotavirus vaccination. To date, few studies in the literature have compared results between different types of models for the same disease, although it is known that data are scarce in some countries. The present analysis is therefore interesting and helpful for countries that have limited data available, as it shows that they can still perform a meaningful economic analysis of a specific infectious disease and a specific prevention strategy.

CONCLUSIONS

With a large rotavirus disease burden and high vaccine coverage the health benefits of rotavirus vaccination can be overwhelming, producing both improved health outcomes and reduced healthcare costs. If few data are available in a country, the simple model offers a good first step to estimate the potential effects of vaccination, making best use of the data available. The simple model produces results similar to those of a more advanced model when used to answer simple economic questions.

Where more data are available, we recommend using both models in parallel. The combination of two different modelling approaches provides useful validation for the results, and will help to improve understanding of rotavirus disease and its management using new techniques such as vaccination.

REFERENCES

[1] Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2011 Nov;3099(11):1-6.

[2] Bernstein DI. Rotavirus overview. Pediatr Infect Dis J 2009 Mar;28(3 Suppl):S50-S53.
[3] Ceyhan M, Alhan E, Salman N, Kurugol Z, Yildirim I, Celik U, et al. Multicenter prospective study on the burden of rotavirus gastroenteritis in Turkey, 2005-2006: a hospital-based study. J Infect Dis 2009 Nov 1;200 Suppl 1:S234-S238.
[4] Kurugöl Z, Geylani S, Karaca Y, Umay Y, Erensoy S, Vardar F, et al. Rotavirus gastroenteritis among children under five years of age in Ýzmir, Turkey. The Turkish Journal of Pediatrics 2003;45:290-4.
[5] Khoury H, Ogilvie I, El Khoury AC, Duan Y, Goetghebeur MM. Burden of rotavirus gastroenteritis in the Middle Eastern and North African pediatric population. BMC Infect Dis 2011;11:9-20.
[6] Karadag A, Acikgoz ZC, Avci Z, Catal F, Gocer S, Gamberzade S, et al. Childhood diarrhoea in Ankara, Turkey: epidemiological and clinical features of rotavirus-positive versus rotavirus-negative cases. Scand J Infect Dis 2005;37(4):269-75.
[7] Akan H, Izbirak G, Gurol Y, Sarikaya S, Gunduz TS, Yilmaz G, et al. Rotavirus and adenovirus frequency among patients with acute gastroenteritis and their relationship to clinical parameters: a retrospective study in Turkey. Asia Pac Fam Med 2009;8(1):8.
[8] Van der Wielen M., Giaquinto C, Gothefors L, Huelsse C, Huet F, Littmann M, et al. Impact of community-acquired paediatric rotavirus gastroenteritis on family life: data from the REVEAL study. BMC Fam Pract 2010;11:22.
[9] Bilcke J, Beutels P. Reviewing the cost effectiveness of rotavirus vaccination: the importance of uncertainty in the choice of data sources. Pharmacoeconomics 2009;27(4):281-97.
[10] Jit M, Bilcke J, Mangen MJ, Salo H, Melliez H, Edmunds WJ, et al. The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe. Vaccine 2009 Oct 19;27(44):6121-8.
[11] Atchison C, Lopman B, Edmunds WJ. Modelling the seasonality of rotavirus disease and the impact of vaccination in England and Wales. Vaccine 2010 Apr 19;28(18):3118-26.
[12] Atkins KE, Shim E, Pitzer VE, Galvani AP. Impact of rotavirus vaccination on epidemiological dynamics in England and Wales. Vaccine 2012 Jan 11;30(3):552-64.
[13] Standaert B, Parez N, Tehard B, Colin X, Detournay B. Cost-effectiveness analysis of vaccination against rotavirus with RIX4414 in France. Appl Health Econ Health Policy 2008;6(4):199-216.
[14] Postma MJ, Jit M, Rozenbaum MH, Standaert B, Tu HA, Hutubessy RC. Comparative review of three cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. BMC Med 2011;9:84.
[15] Goossens LMA, Standaert B, Hartwig N, Hovels AM, Al MJ. The cost-utility of rotavirus vaccination with Rotarix(TM) (RIX4414) in the Netherlands 1487. Vaccine 2008 Feb 20;26(8):1118-27.

[16] Martin A, Batty A, Roberts JA, Standaert B. Cost-effectiveness of infant vaccination with RIX4414 (Rotarix) in the UK. Vaccine 2009 Jul 16;27(33):4520-8.
[17] Melliez H, Boelle PY, Baron S, Mouton Y, Yazdanpanah Y. [Morbidity and cost of rotavirus infections in France]. Med Mal Infect 2005 Oct;35(10):492-9.
[18] Turkish Statistical Institute. Turkey's Statistical Yearbook 2010. 2011 Apr. 3522.
[19] Turkish Statistical Institute. Life expectancy at birth. http://www.tuik.gov.tr/Gosterge.do?id=3712&sayfa=giris&metod=IlgiliGosterge 2012 [cited 2011 Jun 8]
[20] Martin A, Cottrell S, Standaert B. Estimating utility scores in young children with acute rotavirus gastroenteritis in the UK. J Med Econ 2008;11(3):471-84.
[21] Turel O, Soysal A, Bakir M. Clinical Characteristics and Direct Medical Cost of Diarrhea among Hospitalised children in Istanbul. ISPOR . 2005. Ref Type: Abstract
[22] Turkish Social Security Institution. Social Insurance and Universal Health Insurance Law, Treatment Guidelines. Appendix no. 8. Official Gazette of Republic of Turkey 2010 Mar 25;Report no. 27532 (updated).
[23] Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. The Lancet 2007 Nov 24;370(9601):1757-63.
[24] Jit M, Mangen M-JJ, Melliez H, Bilcke J, Salo H, Edmunds WJ. An update to "The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe". Vaccine 2010;28:7457-9.
[25] Gianino P, Mastretta E, Longo P, Laccisaglia A, Sartore M, Russo R, et al. Incidence of nosocomial rotavirus infections, symptomatic and asymptomatic, in breast-fed and non-breast-fed infants. J Hosp Infect 2002 Jan;50(1):13-7.
[26] Brisson M, Edmunds WJ. Impact of model, methodological, and parameter uncertainty in the economic analysis of vaccination programs. Med Decis Making 2006 Sep;26(5):434-46.
[27] Brisson M, Edmunds WJ. Economic evaluation of vaccination programs: the impact of herd-immunity. Med Decis Making 2003 Jan;23(1):76-82.
[28] Standaert B, Gomez J, Raes M, Debrus S, Velazquez FR, Postma MJ. Impact of rotavirus vaccination on hospitalisations in Belgium: comparing model predictions with observed data. [[In preparation]] 2012.
[29] Plosker GL. Rotavirus vaccine RIX4414 (Rotarix): a pharmacoeconomic review of its use in the prevention of rotavirus gastroenteritis in developed countries. Pharmacoeconomics 2011 May;29(5):439-54.

3 IMPACT STUDIES

The challenge when launching a new vaccine is that the evaluation period of randomized clinical trials often has a short duration for obvious reasons. With short duration I emphasize periods of maximum 2 - 3 years in which the vaccinated group is evaluated separately from the unvaccinated group.

There are two particular points to make here about this approach. One is that there could be additional benefit beyond the period of observation. It is not because the effect of the vaccine is assessed over a certain fixed period that suddenly it stops once the vaccine is not studied anymore as some authorities were claiming when presenting our clinical trial results. Because one was unable to evaluate that effect in a randomized fashion over long enough periods I tried to evaluate the assessment through modelling exercises. But that is a problem for some evaluators on how to precisely model the assumed benefit over time. Sensitivity analysis could help here as well.

Another way to look at the problem is to check whether the model predictions fit with reality by designing impact studies [23]. I was able to develop such a study in Belgium called the RotaBIS (Rotavirus vaccine Belgian Impact Study) study among 11 hospital centres spread all over the country. I reported results at 2, 5 and now 7 years after the introduction of the vaccine. The last evaluation allows starting the comparison of a cross-sectional analysis with a follow-up of vaccinated birth-cohorts over time. Interestingly by doing this comparison I observed a difference in the source of infection over time, from children in baseline at a very young age to parents or other care-givers over a maintained long period of observation (Standaert B et al., submitted, 2015).

Another interesting point is that by doing these impact studies and analysing the data on an infectious disease with a rapid spread such as rotavirus, it is possible to measure a herd effect very early on in the follow-up period of randomised clinical trials. Therefore any trial with duration longer than a year will be under the influence of indirect vaccine effect if that infection follows an annual epidemic spread. As a consequence lower vaccine efficacies were obtained in the second year after the vaccine introduction, because of the calculation method used to assess the vaccine efficacy. The denominator is the number of rotavirus events in the control arm that is decreased due to the herd effect [24].

One recommendation I want to make here is that health economists should be closely involved into the development and design of the epidemiologic studies that evaluate the benefit of vaccines over short and long term periods. They are the ones most interested in understanding and evaluating the indirect benefit that vaccines create. That particular benefit often helps bringing the vaccine over the hurdle of becoming cost-effective.