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A critical literature review of health economic evaluations of rotavirus vaccination

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Two licensed vaccines are available to prevent RVGE in infants. A worldwide critical review of economic evaluations of these vaccines was conducted. The objective was to describe differences in methodologies, assumptions and inputs and determine the key factors driving differences in conclusions. 68 economic evaluations were reviewed. RV vaccination was found to be cost-effective in developing countries, while conclusions varied between studies in developed countries. Many studies found that vaccination was likely to be cost-effective under some scenarios, such as lower prices scenarios, inclusion of herd protection, and/or adoption of a societal perspective. Other reasons for variability included uncertainty around healthcare visits incidence and lack of consensus on quality of life (QoL) valuation for infants and caregivers. New evidence on the vaccination effectiveness in real-world, new ways of modeling herd protection and assessments of QoL in children could help more precisely define the conditions under which RV vaccination would be cost-effective in developed countries.

Introduction

Rotavirus gastroenteritis (RVGE) is currently the most common cause of severe gastroenteritis in infants and young children in both developed and developing countries, with seasonal peaks according to latitude and climate. Rotavirus (RV) is transmitted by the faecal-oral route. It infects cells in the intestine, inducing gastroenteritis, leading to severe diarrhea and sometimes death through dehydration.[1-4]

RVGE causes 114 million episodes of diarrhea, 25 million clinic visits, 2.4 million hospital admissions, and more than 500,000 deaths in children up to age 5 y worldwide annually.[3,4] It is estimated that annually in Europe almost 700,000 children younger than 5 y will visit a medical practitioner as outpatients, almost 87,000 will be admitted to hospital, and 231 will die because of RV-associated disease.[5]

Two vaccines are currently available for the prevention of RVGE. RotaTeq (Merck and Co., Inc., West Point, PA USA), is a live pentavalent vaccine that contains five RV vaccine strains produced by reassortment. It is an oral vaccine, which requires three doses between ages 6 and 32 weeks. Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), is a live attenuated monovalent vaccine containing human RV strain RIX4414. It is given orally in 2 doses 4-week apart, between 6 and 24 weeks of age. Both vaccines are indicated for the prevention of RVGE in infants and children.

The cost-effectiveness of these vaccines has been evaluated in many studies, and several literature reviews are available so far. A first review by Bilcke and Beutels was published in 2009.[6] It was based on 19 economic analyses of RV vaccination, in 9 developing and 9 developed countries. The main objectives were to describe and assess methodological and modeling choices, and key conclusions were the need for sensitivity analysis and for accounting for herd protection.

In 2011, Tu et al.[7] published a systematic review that focused on economic studies performed in developing countries. The authors identified 15 studies, and concluded that despite being confirmed as cost effective, this does not imply that RV immunization is affordable in developing countries. For these countries, this would require heavy financial support from international organizations such as the GAVI Alliance's fund (Global Alliance for Vaccines and Immunisation).

In 2011, Plosker[8,9] focused on economic analyses of Rotarix in developed countries, including a discussion of some of the limitations of these studies and possible explanations for the wide variability in results of these analyses, many of which involved indirect comparisons with RotaTeq. Explanations included differences in the selection of data sources or assumptions used to populate the models. Another review published in 2011 focused on economic analyses of Rotarix in developing countries.[10,11] Plosker concluded that the introduction of the vaccine would be very cost effective compared with no RV vaccination program, considering a large range of vaccine prices.

In 2011, Postma et al.[12] reviewed three models[a] used to estimate the cost-effectiveness of RV vaccination, and stated that despite differences in the approaches and inputs, the cost-effectiveness results of the models were quite similar.

The objectives of this article are to provide a comprehensive review of RV economic evaluations, considering both products, for developed and developing countries, and to critically appraise these studies. The differences in methodologies, model assumptions and model inputs were investigated in order to provide insight on reasons for variability in results between studies.

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Search Methodology

This review considered all economic evaluations performed worldwide on RotaTeq and Rotarix published between October 2001 and September 2011. Several search engines were used: Pubmed, Google scholar and NHS Economic Evaluation Database (NHS EED). In addition, we looked for abstracts presented at recent conferences, using health economic and clinical congress websites, such as the International Society for Pharmacoeconomics and Outcomes (ISPOR), the European Society for Paediatric Infectious Diseases (ESPID), and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESGHAN). We used the following search strategy in Medline: ("rotavirus"[MeSH Terms] OR "rotavirus") AND ("economic model" OR "budget" OR "economic" OR "cost" or "costs" OR "decision analytic model" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit" OR "cost benefit" OR "cost utility" OR "resource" OR "fees" OR "consumption").

Screening of references and extraction of data were performed by two reviewers independently, and all disagreements were resolved by consensus. Information relevant to epidemiological aspects (e.g., incidence rate, hospitalization rate), immunity and vaccine (e.g., herd protection, efficacy/effectiveness inputs, vaccination coverage rate) and economic evaluation methods (e.g., type of analysis, type of model, type of outcome) was extracted from each manuscript.

Overview of Studies

Table 1 describes the 68 economic evaluations identified by the literature searches and reviewed. 53 of these studies were journal articles. The remaining studies were posters (14 references) or abstracts (1 reference). One study was not vaccine-specific, 34 studies considered only Rotarix, 16 studies considered only RotaTeq, and 17 considered both vaccines. Out of the latter 17 studies, 13 reported distinct results for both vaccines vs. no vaccination, 3 studies considered Rotarix and RotaTeq as equivalent, and 1 compared the two vaccines, reporting an ICER of Rotarix vs. RotaTeq. Eighteen studies were sponsored by GlaxoSmithKline, 9 by Sanofi Pasteur MSD and 3 by Merck; no industry funding was reported for 38 studies. The number of publications increased after 2001 (from 1 in 2001, to 5 in 2006, to 27 in 2009). Out of the 68 studies reviewed, 31 were based in Europe, 10 in Latin America, 18 in Asia/Pacific, 4 in Africa, 3 in the United States and 2 in developing countries across the world.

Fifty-eight studies presented results of a Cost-Effectiveness Analysis (CEA[b]). Outcome measures used in these CEAs included quality-adjusted life-years (QALYs) gained (22 studies), lives saved (27), disability-adjusted life years averted (25), admissions avoided (20), cases avoided (19) and life-years gained (13). The 22 studies reporting an incremental cost per quality-adjusted life years (QALY) gained are also classified as Cost-Utility Analyses (CUA) in **Table 1**.

Fifty-five studies provided results of a Budget Impact Analysis (BIA[c]), i.e., estimated the impact of vaccination on the budget of a health care payer.

Finally, 23 threshold analyses were conducted. A threshold analysis provides the maximum price for which the assessed intervention (vaccination program) is estimated to be cost-effective (or cost-saving), for a given value of the willingness to pay for a QALY or the health outcome of interest.

Results of Economic Evaluations

All costs are presented using the currency of the original study, and are also presented in 2012 euros in brackets.

Developed countries. *Cost-effectiveness and cost-utility analyses.* Tables with detailed results of economic analyses are available as supplementary digital content. These include results of the CEAs or CUAs, vaccine efficacy data, RVGE incidence data, average yearly incidence of RVGE-related hospitalizations (both community-acquired and hospital-acquired), average yearly incidence of physician visits, average yearly incidence of emergency department visits, annual death rates, and inputs and sources used by studies using QALYs and DALYs.

In Europe, variability between countries was large. Jit et al.[43,44] evaluated the incremental cost per QALY gained in Europe, using the same methodology for different countries, and estimated it at €15 000 (2012 euro value: €17 500) in Finland, €88 000 (€100 000) in the Netherlands, €64 000 (€75 300) in Belgium, €65 000 (€72 800) in France and €110 000 (€136 000) for the UK for Rotarix, and at €27 000 (€31 500) in Finland, €94 000 (€107 000) in the Netherlands, €75 000 (€88 200) in Belgium, €84 000 (€94 000) in France and €150 000 (€185 000) for the UK for RotaTeq, from the Third-Party Payer (TPP) perspective. Furthermore, results varied substantially between studies within countries. In the UK, estimations of the ICER for the monovalent vaccine from the TPP perspective varied between £23,298 (€35 400) for Rotarix[42] and £150 000 (€188 300) for RotaTeq,[43] per QALY gained. Substantial differences in incremental costs per case avoided were also noted for the UK, which was largely due to different case definitions. In the Netherlands, results from the societal perspective also showed large variability: one study suggested that vaccination was cost-effective,[32] two that it was not cost-effective,[33,34] and one concluded that it depends on negotiated price.[35] In Belgium, results of different studies seemed relatively close, with cost per QALY gained varying between €51 000 (€63 100) for Rotarix[13] and €75,000 (€88 200) for RotaTeq[43,44] from the TPP perspective.

In the US, results of Widdowson et al. appeared as rather unfavorable to vaccination, with a base case ICER of $197 190 (€188 300) per life-year saved from a societal perspective.[72] However, from the same perspective, Shim et al. predicted that vaccination would be cost-saving.[73] Weycker et al. did not provide any ICER for vaccination vs. no vaccination, but compared Rotarix with RotaTeq, and concluded that Rotarix dominated RotaTeq in health economic terms.[74] Nevertheless it has been shown by Toumi et al. that these results relied on biased assumptions in favor of Rotarix, which are not supported by clinical evidence.[81]

In Australia, Newall et al.[56] examined the cost-effectiveness of both vaccines. The results were only slightly different: Rotarix

Table 1. Overview of included studies

Continent	Ref	Type	Author	Title	Country	Source	Vaccine evaluated	Sponsor	Type of analysis
Europe	13	Poster	Fruytier 2006	Vaccination with RIX4414 is cost-effective in a belgian setting	Belgium	ISPOR 2006	Rotarix	GSK	BIA + CEA (CUA)
	14	Article	Dhont 2008	Burden of rotavirus gastroenteritis and potential benefits of a pentavalent rotavirus vaccination in Belgium	Belgium	Journal of Medical Economics	RotaTeq	SPMSD	BIA
	15	Article	Bilcke 2008	Cost-effectiveness of rotavirus vaccination: exploring caregiver(s) and "no medical care" disease impact in Belgium	Belgium	Medical Decision Making	Rotarix and RotaTeq	Independent	BIA + CEA (CUA) + threshold analysis
	16	Article	Nohynek 2009	Finland introduces rotavirus vaccine into the national vaccination program in September 2009	Finland	Eurosurveillance	Rotarix and RotaTeq	Independent	CEA (CUA)
	17	Poster	Trichard 2007	Budget impact of a universal rotavirus vaccination program with RotaTeq® in France	France	ISPOR 2007	RotaTeq	SPMSD	BIA
	18	Article	Huet 2007	Burden of pediatric rotavirus gastroenteritis and potential beneÿts of a universal rotavirus vaccination program with RotaTeq in France	France	Vaccine	RotaTeq	SPMSD	BIA
	19	Article	Melliez 2007	Cost and cost-effectiveness of childhood vaccination against rotavirus in France	France	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA (CUA)
	20	Article	Standaert 2008	Cost-effectiveness analysis of vaccination against rotavirus with RIX4414 in France	France	Applied Health Economics and Health Policy	Rotarix	GSK	CEA (CUA)
	21	Poster	Bénard 2009	Economic evaluation of a pentavalent universal rotavirus vaccination program in France	France	ESPID 2009	RotaTeq	SPMSD	BIA
	22	Poster	Hammerschmidt 2007	Epidemiologic and economic impact of routine vaccination of infants against rotavirus gastroenteritis in Germany: a preliminary analysis	Germany	ISPOR 2007	Rotarix	GSK	CEA (CUA)
	23	Article	Buesch 2007	Burden of pediatric rotavirus gastroenteritis and potential benefits of a universal vaccination program in Germany	Germany	ISPOR 2007	RotaTeq	SPMSD	BIA + CEA
	24	Poster abstract	Greiner 2008	Potential health and economic outcomes of implementing universal rotavirus vaccination program with RotaTeq® in Europe - the example of Germany	Germany	ESPID 2008	RotaTeq	Independent	BIA
	25	Poster	Brüggenjürgen 2009	Economic evaluation of universal pentavalent rotavirus vaccination program in Germany	Germany	ESPR 2009	RotaTeq	SPMSD	BIA + CEA
	26	Article	Syriopoulou 2011	Evaluation of potential medical and economic benefits of universal rotavirus vaccination in Greece	Greece	Acta Paediatrica	RotaTeq	SPMSD	BIA

BIA, Budget Impact Analysis; CEA, Cost-Effectiveness Analysis, CUA, Cost-Utility Analysis; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

Table 1. Overview of included studies (continued)

Continent	Ref	Type	Author	Title	Country	Source	Vaccine evaluated	Sponsor	Type of analysis
Europe	27	Poster	Redmon 2009	Cost effectiveness of universal rotavirus vaccination in Ireland: a preliminary analysis	Ireland	ISPOR 2009	Rotarix	GSK	BIA + CEA (CUA)
	28	Article	Tilson 2011	Cost-effectiveness of universal rotavirus vaccination in reducing rotavirus gastroenteritis in Ireland	Ireland	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA (CUA)
	29	Article	Panatto 2009	Burden of rotavirus disease and cost-effectiveness of universal vaccination in the Province of Genoa (Northern Italy)	Italy	Vaccine	Rotarix	GSK	BIA + CEA (CUA)
	30	Article	Giammanco 2009	An economic analysis of rotavirus vaccination in Italy	Italy	Vaccine	Rotarix or RotaTeq	Independent	BIA + CEA + threshold analysis
	31	Poster	Welte 2001	Economic evaluation of rotavirus vaccination for the Netherlands	Netherlands	ISPOR 2001	RotaTeq (assumed)	Independent	Threshold analysis
	32	Article	Goossens 2008	The cost-utility of rotavirus vaccination with Rotarix (RIX4414) in the Netherlands	Netherlands	Vaccine	Rotarix	GSK	BIA + CEA (CUA)
	33	Article	Zomer 2008	Assessing the introduction of universal rotavirus vaccination in the Netherlands	Netherlands	Vaccine	Rotarix or RotaTeq	Independent	BIA + CEA + threshold analysis
	34	Article	Mangen 2010	Is it cost-effective to introduce rotavirus vaccination in the Dutch national immunization program	Netherlands	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA
	35	Article	Rozenbaum 2011	Cost-effectiveness of rotavirus vaccination in the Netherlands; the results of a consensus model	Netherlands	BioMed Central	RotaTeq (not explicit)	SPMSD	BIA + CEA (CUA) + threshold analysis
	36	Poster	André 2008	Cost-effectiveness of vaccination with rotarix in Portugal	Portugal	Europediatrics 2008	Rotarix	GSK	BIA + CEA (CUA)
	37	Poster	Rubio-Terres 2008	Cost impact of pediatric rotavirus gastroenteritis (RVGE) and potential benefits of a universal vaccination program in Spain	Spain	ESPID 2008	Rotarix	GSK	BIA
	38	Article	Rubio-Perez 2011	Socio-economic modeling of rotavirus vaccination in Castilla y León, Spain	Spain (Castilla y León)	Le Infezioni in Medicina	Rotarix	Independent	BIA + CEA (CUA)
	39	Poster	Largeron 2006	Cost-effectiveness analysis of rotavirus vaccination program in the UK	UK	ISPOR 2006	RotaTeq	SPMSD	BIA + CEA
	40	Article	Jit 2007	Evaluating rotavirus vaccination in England and Wales Part II The potential cost-effectiveness of vaccination	UK	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA (CUA)
	41	Article	Lorgelly 2008	Exploring the cost effectiveness of an immunization program for rotavirus gastroenteritis in the United Kingdom	UK	Epidemiology and Infection	Rotarix or RotaTeq	Independent	BIA + CEA + threshold analysis

BIA, Budget Impact Analysis; CEA, Cost-Effectiveness Analysis, CUA, Cost-Utility Analysis; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

Table 1. Overview of included studies (continued)

Continent	Ref	Type	Author	Title	Country	Source	Vaccine evaluated	Sponsor	Type of analysis
Europe	42	Article	Martin 2009	Cost-effectiveness of infant vaccination with RIX4414 (Rotarix) in the UK	UK	Vaccine	Rotarix	GSK	BIA + CEA (CUA)
	43	Article	Jit 2009	The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe	Belgium, England and Wales, Finland, France, Netherlands	Vaccine	Rotarix and RotaTeq	Independent	CEA (CUA) + threshold analysis
	44	Article	Jit 2010	The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe	Belgium, England and Wales, Finland, France, Netherlands	Vaccine	Rotarix and RotaTeq	Independent	CEA (CUA) + threshold analysis
Latin America	45	Article	Soárez 2008	Cost-effectiveness analysis of routine rotavirus vaccination in Brazil	Brazil	Panam Salud Publica	Rotarix	Independent	BIA + CEA + threshold analysis
	46	Article	Constenla 2008	Economic impact of a rotavirus vaccine in Brazil	Brazil	Journal of Health Population and Nutrition	Rotarix	Independent	BIA + CEA
	47	Poster	Valentim 2009	Cost estimates in the economic evaluations of vaccination programmes: the cases of rotavirus and varicella in Brazil	Brazil	ISPOR 2009	Rotarix	Independent	CEA
	48	Article	Constenla 2006	Potential cost effectiveness of a rotavirus vaccine in Chile	Chile	Revista Medica de Chile	Rotarix	GSK	BIA + CEA
	49	Article	De la Hoz 2010	Potential epidemiological and economical impact of two rotavirus vaccines in Colombia	Colombia	Vaccine	Rotarix and RotaTeq	GSK	BIA + CEA
	50	Article	Valencia-Mendoza 2008	Cost-effectiveness of introducing a rotavirus vaccine in developing countries: the case of Mexico	Mexico	Biomed Central	RotaTeq	Merck	BIA + CEA
	51	Article	Constenla 2009	Economic impact of a rotavirus vaccination program in Mexico	Mexico	Panam Salud Publica	Rotarix	GSK	BIA + CEA + threshold analysis
	52	Article	Constenla 2008	Economic impact of rotavirus vaccination in Panama	Panama	Annals of Pediatric	Rotarix	GSK	BIA + CEA
	53	Article	Clark 2009	Cost-effectiveness of rotavirus vaccination in Peru	Peru	The Journal of Infectious Diseases	Rotarix	GSK	BIA + CEA

BIA, Budget Impact Analysis; CEA, Cost-Effectiveness Analysis, CUA, Cost-Utility Analysis; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

Table 1. Overview of included studies (continued)

Continent	Ref	Type	Author	Title	Country	Source	Vaccine evaluated	Sponsor	Type of analysis
	54	Article	Constenla 2006	Assessment of the economic impact of the anti-retroviral vaccine in Venezuela	Venezuela	Panam Salud Publica	Rotarix	GSK	BIA + CEA
	55	Article	Rheingans 2007	Potential cost-effectiveness of vaccination for rotavirus gastroenteritis in eight Latin American and Caribbean countries	Argentina, Chile, Dominican Republic, Honduras, Mexico, Panama, Venezuela	Panam Salud Publica	Rotarix	GSK	BIA + CEA
Asia/ Pacific	56	Article	Newall 2007	The cost-effectiveness of rotavirus vaccination in Australia	Australia	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA (CUA)
	57	Article	Wang 2009	Potential cost-effectiveness of a rotavirus immunization program in rural China	China	Clinical Infectious Diseases	not vaccine specific	Independent	BIA + CEA
	58	Article	Ho 2008	Rotavirus vaccination for Hong Kong children: an economic evaluation from the Hong Kong Government perspective	Hong Kong	Archives of Disease in Childhood	RotaTeq	Independent	CEA + threshold analysis
	59	Article	Rose 2009	Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis	India	British Medical Journal	Rotarix	Independent	BIA + CEA
	60	Article	Esposito 2010	Projected Impact and Cost-Effectiveness of a Rotavirus Vaccination Programm in India, 2008	India	Clinical Infectious Diseases	Rotarix	Independent	BIA + CEA + threshold analysis
	61	Article	Chodick 2009	Potential impact and cost-effectiveness analysis of rotavirus vaccination of children in Israel	Israel	European Journal of Public Health	Rotarix and RotaTeq	Independent	BIA + CEA (CUA) + threshold analysis
	62	Poster	Igarashi 2009	Cost-utility analysis of rotavirus vaccine (Rotarix®) in Japan	Japan	ISPOR 2009	Rotarix	Independent	BIA + CEA (CUA)
	63	Poster	Kang 2010	Public Health and Economic Impact of Rotavirus Vaccination in Korea	Korea	ISPOR 2010	RotaTeq	Merck	BIA
	64	Article	Flem 2009	Costs of diarrheal disease and the cost-effectiveness of a rotavirus vaccination program in Kyrgyzstan	Kyrgyzstan	The Journal of Infectious Diseases	Rotarix	Independent	BIA + CEA + threshold analysis
	65	Article	Milne 2009	Budget impact and cost-effectiveness of including a pentavalent rotavirus vaccine in the New Zealand childhood immunization schedule	New-Zealand	Value in Health	RotaTeq	Merck (partial)	BIA + CEA (CUA) + threshold analysis
	66	Article	Wu 2009	Cost-effectiveness analysis of rotavirus vaccination program in Taiwan	Taiwan	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA + threshold analysis
	67	Article	Chotivitayatarakorn 2010	Cost-effectiveness of Rotavirus vaccination as part of the national immunization program for Thai children	Thailand	Southeast Asian Journal of Tropical Medicine Public Health	Rotarix	Independent	BIA + CEA + threshold analysis

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Table 1. Overview of included studies (continued)

Continent	Ref	Type	Author	Title	Country	Source	Vaccine evaluated	Sponsor	Type of analysis
	68	Article	Isakbaeva 2006	Rotavirus disease in Uzbekistan: cost-effectiveness of a new vaccine	Uzbekistan	Vaccine	Rotarix (assumed)	Independent	BIA + CEA
	69	Article	Fischer 2005	Health care costs of diarrheal disease and estimates of the cost-effectiveness of rotavirus vaccination in Vietnam	Vietnam	The Journal of Infectious Diseases	Rotarix	Independent	CEA + threshold analysis
	70	Article	Kim 2009	Cost-effectiveness of Rotavirus vaccination in Vietnam	Vietnam	Biomed Central	Rotarix	Independent	BIA + CEA + threshold analysis
	71	Article	Podewils 2005	Projected cost-effectiveness of rotavirus vaccination for children in Asia	Asia	The Journal of Infectious Diseases	Rotarix	Independent	BIA + CEA + threshold analysis
USA	72	Article	Widdowson 2007	Cost-effectiveness and potential impact of rotavirus vaccination in the United States	USA	Pediatrics	RotaTeq	Independent	BIA + CEA + threshold analysis
	73	Article	Shim 2009	Impact of transmission dynamics on the cost-effectiveness of rotavirus vaccination	USA	Vaccine	Rotarix and RotaTeq	Independent	BIA + CEA (CUA) + threshold analysis
	74	Article	Weycker 2009	Cost of routine immunization of young children against rotavirus infection with Rotarix vs. RotaTeq	USA	Vaccine	Rotarix vs RotaTeq	GSK	BIA
Africa	75	Article	Ortega 2009	Cost-Benefit analysis of a Rotavirus Immunization program in the arab republic of Egypt	Egypt	The Journal of Infectious Diseases	Rotarix	Independent	CEA (although presented as CBA)
	76	Article	Tate 2009	Rotavirus disease burden and impact and cost-effectiveness of a rotavirus vaccination program in Kenya	Kenya	The Journal of Infectious Diseases	Rotarix	Independent	BIA + CEA + threshold analysis
	77	Article	Berry 2010	The Cost-Effectiveness of Rotavirus Vaccination in Malawi	Malawi	The Journal of Infectious Diseases	Rotarix	Independent	BIA + CEA
Africa	78	Article	Tate 2011	Projected health benefits and costs of pneumococcal and rotavirus vaccination in Uganda	Uganda	Vaccine	Rotarix	Independent	BIA + CEA
All Countries	79	Article	Rheingans 2009	Economic costs of rotavirus gastroenteritis and cost-effectiveness of vaccination in developing countries	Africa, America, Eastern Mediterranean, Europe, Southeast Asia, Western Pacific	The Journal of Infectious Diseases	Rotarix	GSK	CEA
	80	Article	Atherly 2009	Rotavirus Vaccination: Cost-Effectiveness and Impact on Child Mortality in Developing Countries	Region of the Americas, European Region, African region, Eastern Mediterranean region, Southeast Asian region, Western Pacific region, All GAVI Alliance regions	The Journal of Infectious Diseases	Rotarix	Independent	BIA + CEA

BIA, Budget Impact Analysis; CEA, Cost-Effectiveness Analysis, CUA, Cost-Utility Analysis; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

would cost $60 073 (€59 000) per QALY gained and RotaTeq $67 681 (€66 500) per QALY gained from a TPP perspective.

Budget impact analyses. Although most studies suggest that the net costs of vaccination are positive, some concluded that vaccination is cost-saving from a societal perspective (Australia,[56] Belgium,[13] Italy,[29,30] UK,[39,41] and USA[73]). However, the results of these studies were often contradicted by other results for the same countries. For example, for the UK, Largeron et al.[39] and Lorgelly et al.[41] predicted that vaccination would save £5700 (€5580) and £4.5 million (€4,34 million) respectively, from a societal perspective over 5 y, whereas Martin et al.[42] predicted that vaccination would increase net costs by £33.4 million (€31.6 million) over 5 y from the TPP perspective. Net cost estimates from a TPP perspective in the UK ranged from £26.7 million (€25.8 million)[41] to £41.5 million (€40.6 million).[40] The range of budget impact estimates from a societal perspective is also wide for France: Trichard et al.[17] estimated the net cost of vaccination at €22.4 million (€25.5 million), while Melliez et al.[19] estimated it at €68.9 million (€78.4) but it seems that Melliez et al. included only patient copayment and not productivity costs as opposed to Trichard and al.

Threshold analysis. Five studies reported a break-even price in developed countries (3 in Europe, 2 in USA). Estimated break even prices for cost-effectiveness according to Jit et al.,[43] who conducted analyses from a TPP perspective for 5 countries, ranged from €56 (€69) for the UK to €102 (€119) for Finland per full-course vaccine cost of Rotarix, for a willingness to pay threshold of €30,000 per QALY. Unsurprisingly, cost-effective prices are much higher from a societal perspective than from a TPP perspective. Estimates of the threshold price for cost-effectiveness in the Netherlands were €67 (€76) per full course of Rotarix vaccination and €63.30 (€72) per full course of RotaTeq vaccination (for a willingness to pay threshold of €30,000 per QALY) according to Jit et al.[44] from the TPP perspective and €77.71 (€84) (for €20,000 per QALY) according to Rozenbaum et al.[35] per full course of vaccination from a societal perspective.

Developing countries. *Cost-effectiveness and cost-utility analyses.* In January 2000, with global immunization rates stagnating, the GAVI was launched to fund vaccines for children in the world's 70 poorest countries. In GAVI-eligible countries, Atherly et al.[80] projected the cost-effectiveness of introducing RV vaccination to help policy makers in prioritizing resources to gain the greatest health improvements for their constituencies. For the baseline scenario, the estimated incremental cost-effectiveness ratio of RV vaccination was $43 (€33) per DALY averted for the entire period during 2007–2025, suggesting RV vaccination was very cost-effective.

In Latin America, results were clearly favorable to RV vaccination for all countries, except Chile. The primary reason for higher ICERs in Chile is the relatively low mortality estimate. Three studies were published for Brazil, and presented incremental costs per life-year gained a from TPP perspective ranging from €504 (€797)[47] to approximately €790 (€1248).[45] From a societal perspective, estimates varied from €292 (€461) to €520 (€820) per life-year gained. Rheingans et al. found that the incremental cost per DALY averted was higher for 'lower-middle income countries' than for 'upper-middle income' countries. Nevertheless, all results for cost per DALY averted were below $350 (€360) in both the Rheingans and Atherly studies,[79,80] considering vaccination with Rotarix.

For Asian and Oceanic countries, vaccination was found to be cost-effective. Two studies provided incremental costs per DALY averted for Vietnam; for a full course vaccination cost of $10 (€8), the estimated ICERs were $91 (€70) in one study[69] and $550 (€420) in another,[70] from a TPP perspective. The study by Podewils et al.[71] showed that cost-effectiveness at different prices is highly dependent upon the level of income of studied countries. ICERs are more sensitive to price in developed countries: they can be relatively high as vaccination benefits in terms of life-years saved or DALYs averted are smaller, due to low RV-associated mortality, but also very low as potential cost offsets related to hospitalization avoided are larger than in developing countries. This comparison between developing and developed countries should be interpreted with caution, however, since results are not adjusted for purchasing power parities and the willingness to pay per DALY averted differs between these countries.

In Africa, all studies evaluated the cost-effectiveness of Rotarix, and found vaccination was very cost-effective.

Two studies evaluated the cost-effectiveness of Rotarix in Eastern European countries. In the base-case analyses, incremental costs per DALY averted were below $300 (€230) for both studies.[79,80]

Budget impact analyses. Results were consistent in Latin America, with low variability between countries, and within the same country. For example, vaccination is estimated to reduce the economic burden of gastroenteritis due to RV significantly in Brazil, with 76%,[46] 79%[45] or 84%[55] of the total healthcare cost avoided with introduction of vaccination. However a substantial net financial investment would be required. In Asian and Oceanic countries, Podewils and al.[71] distinguished between low-income, middle-income and high-income countries. There was variability in the percentage of costs avoided by vaccination (58% for low-income countries, 72% for middle-income and 83% for high-income countries, from a TPP perspective). In all cases, the cost of vaccination was higher than medical costs averted by vaccination.

Threshold analyses. Thirteen studies reported a break-even price in developing countries (10 in Asia,[58,60,61,64-67,69-71] 2 in Latin America[45,51] and 1 in Africa[76]). In Asia, estimated break even prices, under which vaccination would be cost-saving, ranged from $0.56 (€0.70) in India[60] to $55 (€49) in Hong-Kong[58] per full course, and was highly dependent on country features. In Kenya, the costs of vaccination were estimated to equal the costs prevented when the full course vaccine price was $2.07 (€3.68).[76]

Assumptions and Inputs of Economic Evaluations

Given the wide range of results between studies, main assumptions and inputs used in the studies were reviewed to identify the main sources of variability.

Models structure. *Type of models.* Most existing models are classified as 'static model', as opposed to 'transmission-dynamic models', i.e., they do not account for the potential reduction in

force of infection (incidence among non-immune individuals) over time. The only identified transmission-dynamic model was the model developed in 2009 by Shim and Galvani,[73] for the US. It may be noted that the model by Ho et al.[58] was also presented as a dynamic model. However, this was a 'dynamic model' in the sense that new individuals entered the model every year (births), and some individuals were removed (deaths). Other models were mainly decision trees or Markov models.

Most models followed a single cohort of children, born over a period of 12 mo, from birth or vaccination to age 5 y. For some models the cohorts are divided into monthly sub-cohorts in order to account for seasonality. A few models[34,58,65] considered multiple successive yearly birth cohorts.

Herd protection and transmission-dynamic models. Potential herd protection effects may benefit unvaccinated children.[82] Only one model, Shim and Galvani[73] assessed the cost-effectiveness of RV vaccination in the US based on a model accounting for the transmission-dynamics of RV infection. The comparison between results from Shim et al.[73] and Widdowson et al.,[72] based on similar epidemiological input data but different model structures, indicates that indirect effects of vaccination would account for a reduction in of 41% in incidence of mild cases and 24% in incidence of hospitalizations (the transmission-dynamic model predicted a reduction in hospitalizations of 90% vs. 66% for the static model). Also, Shim et al.[73] concluded that RV vaccination was cost-effective, whereas Widdowson et al. reported an ICER close to $200 000 (€190 000) per QALY gained. Authors argued that the substantial difference in their results compared with those of Widdowson et al.[72] was due to herd protection.

Timeframe. Most analyses (56/68) were conducted over a 5-y time-horizon, but accounted for life-years gained over a lifetime horizon. Benefits occurring beyond age 5 y are small, since the incidence of severe RVGE beyond 5 y is low.[83] A few studies[15,21] looked at the evolution of incremental benefits or ICERs over time and confirmed that a 5-y timeframe was appropriate. Five studies used longer time-horizons: 7 y,[50] 10 y,[65] 18 y[74] and 20 y, including the study by Shim et al. based on a transmission-dynamic model,[34,73] respectively.

RV seasonality. Seasonality was not frequently integrated in the studies included, though incidence of RVGE tends to be highest during cooler and drier months in most developed settings.[84] Only a few models accounted for RV seasonality, with a minimal impact, as based on sensitivity analyses.[13,19,20,36,50]

Natural immunity. Natural immunity (also referred as acquired immunity) was also integrated in some models. One Markov model have explicitly accounted for partial immunity provided by RV infections using different health-states for first, second and subsequent infections.[70]

Vaccine-specific data. Efficacy inputs were rarely comparable between Rotarix and RotaTeq. Large trials have been conducted for both vaccines, and demonstrated that the two vaccines are highly efficacious through two full RV seasons.[85-87] Clinical trials have demonstrated different levels of efficacy in countries with different income and mortality levels. Indeed, RV vaccine efficacy ranges from 90% in developed countries to 50% in developing ones, which could be partially explained by differences in RV strains circulation and infections' characteristics.[88,89]

All models referred to results of these clinical trials. However, several forms of extrapolation of vaccine efficacy were used in models, in particular when both vaccines were considered, as the trials used different endpoints, different observation periods, and different regions.

Waning of vaccine protection over time was considered in several studies. Assumptions varied substantially between models, and waning rates were found to have moderate to large impact on results. For example, Giammanco et al. evaluated the impact of waning rate in their sensitivity analysis.[30] Vaccine efficacy was assumed to decrease by 10% every year in the base case, and this rate varied from 5% to 15% in best and worst case scenarios. Results did not change significantly. Kim et al. estimated that vaccine efficacy against severe gastroenteritis reduced from 77% to 43% after 4 y, and found that results were moderately sensitive to waning.[70] However, Bilcke et al. found that waning was one of the parameters with strongest influence on the ICER for vaccination vs. no vaccination.[15] They had used relatively large confidence intervals around efficacy parameters from the second season to account for waning (99 to 49% against hospitalizations, 75 to 44% against physician visits). Jit et al. accounted for waning by fitting an exponential decay curve to the first and second season vaccine efficacy for all RVGE cases, and reported for example that the ICER of €27 000 (€31 500) per QALY gained for RotaTeq in Finland would decrease to €17 000 (€19 800) when waning is not considered.

Efficacy between doses and efficacy of partial vaccination refer to two different concepts but were generally not distinguished in reviewed models. Efficacy between doses has shown to be high, roughly comparable to efficacy after a complete vaccination course,[90] while efficacy of partial vaccination in the long-term is more uncertain. Assumptions varied between the 14 studies that accounted for it (for example for Rotarix, Podewils et al. used a 50% efficacy after 1 dose,[71] and Tate et al. used a 25% rate[78]). These assumptions were found to have little impact on results for both RV vaccines, but substantial impact on comparisons between vaccines. Serotype and genotype of RV were considered in one study, for the UK, using bootstrap sampling.[40] This led to an increase of efficacy, compared with crude trial estimates.

Side effects of vaccination were not considered in most of the studies reviewed. Only a few models accounted for them, with a minimal impact on results when considered in sensitivity analysis.

Epidemiological inputs. Comparing inputs between models was not always possible, or at least not straightforward, due to differences in model structures. Furthermore, important differences exist in epidemiology and health care resource utilization inputs of developed and developing countries which make models inputs and outputs highly different. Indeed, most of the deaths due to RVGE happen in developing countries with poorer access to care whereas most of the burden in developed countries is linked to hospitalizations.

Authors used several sources, mainly surveillance systems, large health system databases, and the REVEAL study[91] (prospective epidemiological study of RVGE in Europe).

In the studies reviewed, RVGE incidence rates could be month- or age-specific, and varied according to countries: annual incidence rates ranged from 4.7% in Spain[37] to 24.4% in Thailand.[67] It was found to be a pivotal parameter of some models, in which probabilities of hospitalizations, physician visits, emergency department visits and death were highly conditional upon RVGE incidence.

Annual hospitalization rates were also highly variable between countries, ranging from 0.0102% in Uganda[78] to 3.36% in Kyrgyzstan.[68] The input values were generally consistent within countries (except for France and Netherlands), because most values were obtained from the same local data sources. However, hospitalization rates were often surrounded with uncertainty, related to under-reporting in hospital statistics and the fact that the presence of RV is not systematically tested in cases of gastroenteritis. In addition, the REVEAL study,[92] which was the major data source for several studies, was performed during a season with relatively high incidence. The influence of hospitalization incidence on the results of economic evaluations is largely related to cost offsets due to hospitalization avoided, rather than QALY or DALYs changes associated with hospitalizations. The impact varies between developed and developing countries, with a smaller impact in developed countries.

Annual incidences of physician visits were also difficult to compare because of the differences in model structures (authors considered GP visits, GP or pediatrician visits, primary care…). The variability between countries was large, with annual rates ranging from 0.18%, for Uganda,[78] to 17.8%, for Kenya and Korea.[57,76] Most of the values were based on large surveillance networks or large databases of physician records. There was also some variability within countries, but the impact on results was relatively small.

Emergency department (ED) visits was not a frequently reported outcome. First this might be linked to different health systems. Moreover, published data on emergency department visits are scarce. Authors often derived the incidence of ED visits based on a proportion of ED visits assumed to be attributable to RV, or referred to previous cost-effectiveness studies published for the same country or a close country. The variability in yearly incidence of ED visits between countries was moderate, ranging from 0% for France,[14] to 2.65% for Belgium,[18] and the impact on results was small.

Annual mortality rate was also found to be highly variable between developed and developing countries, with a low rate for developed countries (e.g., 0.0004% for France,[18] 0.000246% for Finland[16]), and a high rate for developing countries (e.g., 0.034% for Colombia,[49] 0.05% for Peru[53]). The mortality rate has a very high impact in developing countries, but more surprisingly, the impact is also important for developed countries. For developed countries, mortality was determined using data from national hospital discharge or death notification databases. For developing countries, diarrhea mortality was often used to estimate RVGE mortality. Secondary sources and reviews were also used due to the lack of or limitations of surveillance systems.

Nosocomial infections (also designated as hospital-acquired infections) were explicitly considered in 28 studies, all concerning developed countries. RVGE is responsible for up to 40% of pediatric gastroenteritis nosocomial infections, leading to a mean increase in the length of stay of between 3 and 5 d.[93] Lack of data about its incidence or costs was the most frequently cited reason for not considering them.

Costs. Most of the studies reviewed clearly specified the perspective used for the analysis. TPP, societal, government or patient perspectives were the most frequently used perspectives.

Categories of direct medical costs varied according to model structures and could include GP consultations, pediatrician consultations, specialists consultations, hospitalizations, emergency visits, hospital acquired RVGE cases (nosocomial infection), vaccinations (vaccine acquisition and vaccine administration, plus in some cases costs related to side effects), medication, laboratory tests, over the counter medications, dietary products, diagnostic tests and other relevant medical procedures. Hospitalizations costs are the less transparent (and least described) costs. The length of hospital stay was not homogeneous between countries, with a range from 2 to 5 d. Costs of nosocomial infections are mostly made up of extra hospital days. As for hospital length of stay, extra days for nosocomial infections were not similar between studies. Drug consumption was often based on expert opinion.

It is of importance to make the distinction between the vaccination costs (vaccine plus administration of vaccine when relevant) and the vaccine costs (vaccine regimen only). These costs were not always clearly reported in the studies. Hypothetical prices were used in 61 out of 68 studies. Listed prices were used in only 6 studies. Administration costs, mostly provided by dose, were considered in 41 studies, and included nurse time, secretarial employment for vaccination cost of healthcare personnel and training, cold-chain, storage space, and public education. Administration costs ranged from €2 to €10 per dose according to the country.

Direct non medical costs include transportations, nappies, parents' accommodations, swipes, travel and other miscellaneous costs. This was usually based on published observational studies or expert opinion.

Indirect costs are mostly constituted of costs of lost productivity, due to caregivers (parents) taking time off work during illness because of treatment, illness or death. Different valuation approaches are used: lost wages (human capital) or lost productivity (friction costs, for Netherlands only).

Health-state utilities. The QALY measure was often used for developed countries, whereas the DALY measure was used for developing countries, as well as the Netherlands. DALY can be thought of as one lost year of healthy life, whereas as the QALY would represent one year gained in full health. An important distinction between QALYs and DALYs is that life-years gained are adjusted for quality of life in the QALY approach but not in the DALY approach (therefore DALYs averted are generally expected to exceed QALYs gained).[94,95]

Several sources of utility data for RVGE are available.[96-99] The most frequently used source was Brisson et al., using Health Utilities Index 2 (HUI-2) utilities for children (rated by caregivers) and EQ-5D utilities for caregivers. There were some differences in the way the data were used: some studies included QALY changes for 1 or 2 caregivers per child while others ignored the Health-Related Quality of Life (HRQOL) of caregivers. Some studies accounted for the reduction in HRQOL for cases for which no medical care is sought (generally the same studies that ignored the HRQOL of caregivers) while others did not.

Sensitivity analyses conducted by several authors showed that parameters surrounding QALYs were among those with largest impact on ICERs.[20,31,35,40,43,56,65] In particular, results were found to be highly sensitive to inclusion of cases without medical attention.

Discount rate. Health benefits and costs were discounted at a rate of 3% in most studies. Impact of discount rate may be substantial when costs or benefits occur over a long period of time, which is the case for example when deaths are avoided in children.

Comparisons of RotaTeq vs. Rotarix. Fourteen studies distinguished the two vaccines, to compare both RotaTeq and Rotarix to no vaccination (13 studies), or to compare the two vaccines with each other (1 study). ICER values for Rotarix vs. no universal vaccination program were more favorable than those for RotaTeq when the two vaccines were evaluated separately in the same study, mainly because of favorable efficacy and price inputs.

All but one[19] of the 14 studies distinguishing the two vaccines used different prices, and 8 studies reported higher prices for RotaTeq, although the actual prices at which the vaccine would be acquired in the context of mass vaccination programs were not known for any of the vaccines. Administration costs also have an important impact on cost-effectiveness conclusions given that the numbers of doses required for the two vaccines are different.

Discussion

This section provides a critical analysis of the assumptions and inputs used in the reviewed economic evaluations. A summary of what is done in studies, critical evaluations and our recommendations for future studies is available in **Table 2**.

Model structure. The existence of herd protection effects associated with RV was found to be subject to controversy; however, data collected through surveillance systems implemented to monitor effects of vaccination (large-scale vaccination programs) has provided first insights into potential indirect effects of vaccination. For example, two reviews of vaccination impact studies in the US and Australia suggest that there is some evidence of herd protection after the introduction of RV vaccination.[100,116] For example, Payne et al. reviewed data collected in the US following the implementation of vaccination with RotaTeq and found that the impact of RV vaccination exceeded the expected reduction related to vaccination coverage rate and effectiveness only, thus supporting the hypothesis that vaccination would provide substantial herd protection effects.[103]

Only one economic model integrated herd protection,[73] suggesting that indirect effects of vaccination would be substantial, and could be almost as high as direct effects against mild infection. However more sophisticated transmission-dynamic models, not used for the purpose of economic evaluation, suggested that indirect effects may be more modest than those predicted by Shim et al.[73] A weakness of the model of Shim et al. was that it did not account for the progressive build-up of natural immunity with successive infections. The model by Van Effelterre et al.[101] predicted that indirect effects of vaccination would induce a reduction of 20 to 25% in RVGE incidence for coverage rates between 70 and 90%, and a reduction of 13 to 19% in moderate-to-severe RVGE. Two more recent publications using transmission-dynamic models tend to confirm that RVGE vaccination would provide both direct and indirect protection: Atkins et al. shows that herd protection accounts for about a quarter of the reduction in RVGE incidence,[102] and Atchinson et al.[103] showed that at 91% vaccine coverage, there was an additional 3% reduction in reported cases is predicted compared with direct effects of vaccination alone.

The wider modeling community now very much acknowledges that herd protection needs to be included when evaluating RV vaccination and, although this should be rigorously tested as part of any sensitivity analysis and scenario analyses; it is fundamental to the thorough and complete assessment of cost-effectiveness. It is also essential to evaluate the impact of vaccination coverage. However, the impact of including herd protection, as inferred from the study of Shim et al., which is the only cost-effectiveness analysis based on a transmission-dynamic model, might be overestimated. Jit et al.[43] have conducted sensitivity analyses incorporating herd protection effects predicted by Van Effelterre et al. They found that this has a "moderate impact" on the cost-effectiveness ratios; it changed the conclusion of the analysis for one country out of five. Therefore we would suggest that transmission-dynamic models should now be used, in order to evaluate the cost-effectiveness of vaccination under some limiting but transparent assumptions. Given the remaining uncertainty on the level of herd protection, it would also be essential to perform sensitivity analyses around this parameter.

RV seasonality was ignored in some models. As stated by Pitzer et al.,[84] RV tends to be more common in cooler, drier months in most settings, but seasonal peaks have been noted to occur year-round in developing countries, and can vary over time in the same country. Additionally, the winter peak of RV infections may have an important impact on the health care systems organization. Concomitant epidemics of RV, influenza and respiratory syncytial virus infections are responsible for hospital overload and increased risk of nosocomial infections. Even if some models accounted for fluctuations in RVGE incidence between seasons, those issues of hospital overload and consequences in terms of nosocomial infections were usually ignored. When no local data are available, sensitivity analyses surrounding the effects of nosocomial infections should be performed, using data from comparable countries.

Natural immunity was generally not explicitly accounted for in models, except in the model by Kim et al.[70] The immune

Table 2. Summary of what is done, critical evaluation and recommendations for future studies

Aspect	Summary of what is done in studies	Critical evaluation	Recommendations for future studies
Model structure	Most models are static Markov models, using a 5- year timeframe.	• Herd protection generally ignored.	We recommend developing dynamic models to account for herd protection effects of vaccination. A 5-y timeframe is appropriate for static models, but a longer timeframe is recommended for dynamic models.
Vaccine-specific data	Most evaluations used efficacy data from clinical trials, sometimes considering waning of vaccine protection.	• Effect of the vaccine in real life could be different from the effect measured in clinical trials, especially for developing countries. • The effect of Rotarix in preventing outpatient visits was not measured in clinical trials. • The efficacy in preventing deaths was assumed equal to efficacy against hospitalizations.	We recommend using effectiveness data considering waning of vaccine protection, with adjustment on serotype if possible. Efficacy between doses and efficacy of partial vaccination should be differentiated.
Epidemiology	Main sources used included surveillance systems, large health system databases, and the prospective observational study REVEAL.	• There is an under-reporting issue in administrative databases. • REVEAL study was performed during season with high incidence. • There are little data in developing countries, and the population accessing to vaccination programs may not be the children at highest risk of complications.	We recommend using recent national real-life data whenever possible. Ideally the incidence rates of clinical events should be derived from prospective observational studies conducted over several seasons. Adjustments for under-reporting should be considered when using administrative databases.
Costs	Included costs, in addition to vaccination, were generally physician visits and hospitalizations, and sometimes ED visits, as well as lost productivity. Vaccine costs were often assumed by authors.	• Sensitivity analyses around vaccine price often not reported, although the price was not known. • Lack of data about the probability of taking time off work and duration of absence for parents.	We recommend conducting sensitivity analysis on vaccine costs. Data should be collected on workdays lost as lost productivity account for a large proportion of costs from societal perspective.
Health-state utilities	Sources for children were based on utility instruments.	• Utility instruments are not validated for children under 5. • There was only one source for caregivers' utility, or for mild RVGVE. • No utility data for non-consulting cases.	Further research on the utility associated with RVGE in young children should be conducted, using choice-based technique. The disutility associated with mild cases in particular should be assessed.

correlate of protection from RV infection and disease are not fully understood.[104] The degree and duration of protection will depend on age, host status and associated health conditions, and on the number of RVGE infections.[104,105] Most models accounted for the fact that the incidence of RVGE decreases with age, from birth to 5 y. This appears to be an adequate way to account for natural immunity in static models. However, for dynamic models, it is recommended to explicitly consider the protection conferred by an infection, and in particular differences in severity between primary and secondary infections.

Serotype might also be important to be taken into account. The range of RV strains circulating in Europe is diverse, and predominant and emerging strains vary between regions and from year to year.[83] Currently in Europe, 5 common G/P combinations of RV predominate G1P,[8] G2,[4] G3P,[8] G4 P[8].[106] In that context, it seems appropriate to adjust efficacy on the distribution of genotypes in the study setting.[107]

Finally, negative indirect effects of vaccination might also occur, such as serotype replacement,[108] but there is no evidence at this time. This information will be useful for determining the necessity to incorporate such effects into future economic models, and if need be, for developing such models.

Vaccine efficacy and effectiveness. Although the efficacy of the two vaccines has been clearly demonstrated in large clinical trials, one may wonder whether vaccine effectiveness, referring to effect of vaccine in real life, is close to vaccine efficacy, as measured in clinical trials. There are several reasons why the effect of the vaccine in real life could be different from the effect measured

in clinical trials. First, most patients received a full vaccine course in clinical trials. The effect of the vaccine in reality will depend on the proportion of patients receiving a full course of vaccination, and on the effect among patients who receive only a partial course of vaccination. These data might have been missing at the time of some evaluations but are now available, for example based on data collected following implementation of vaccination in the US.[103,109-111] Second, efficacy was measured over pre-specified time windows in clinical trials, such as one year following last dose or one season following last dose. In economic evaluations, it is necessary to account for effects of vaccination between doses, and up to 5 y or seasons following vaccination. Efficacy estimates from clinical trials were lower for 2nd year/season after vaccination than for 1st year/season.[86,112] Waning rates were derived from these data and used for several models. However, a later study among Finnish children vaccinated with RotaTeq found that vaccine efficacy was sustained over 3.1 y,[113] which led Jit et al. to report results of cost-effectiveness analyses without waning. Third, the effect of vaccine in real-life will depend on the distribution of RV serotypes and genotypes in the studied setting. As this distribution changes over time, it may become increasingly important to account for it.

Real-life data did not always exist in the context of the economic assessment of vaccines, but several recent studies analyzed the effectiveness of vaccination in countries or regions where vaccination programs were implemented. A review of these studies showed that the routine use of RotaTeq has led to 81% to 100% reduction in RV hospitalizations and/or emergency department visits, which is consistent with results of clinical trials in developed countries.[82,88,114] However, vaccination effectiveness in developing countries was relatively low,[115] suggesting that cost-effectiveness ratios might be under-estimated in studies using the efficacy measured in trials as a proxy of effectiveness. This impact may be negligible for developed countries.

Thus, it seems appropriate to use efficacy estimates from pivotal trial publications for developed countries, but it is important to also take into consideration results of later analyses about effect of vaccination between doses, effect of partial vaccination and waning.

Epidemiology. Uncertainty exists around epidemiological inputs in all models. In developed countries, many inputs were obtained from administrative databases, but rotavirus may be underreported among patients admitted in hospital with diarrhea. Assessing mortality associated with rotavirus is also difficult because RVGE is sometimes reported as a secondary diagnosis among patients dying in hospital, but it is not known whether the patients would have survived in absence of RV infection. An observational study, REVEAL, we performed to assess the burden associated with rotavirus in European countries, but the season when it was conducted (2004–2005) was not representative of an average season. In developing countries, little data are available. Another issue is the lack of data sources for numbers of lost workdays per case and especially lost workdays assumed for cases without medical attention. This is important as lost productivity accounts for a large proportion of disease-related costs from societal perspective.[15,72]

Health-state utilities. There are a large number of issues surrounding elicitation of preference-based values for childhood health states. The main sources of utilities for children used were Brisson et al.,[99] using HUI-2 which is not validated for children under 5, and Martin et al.,[102] using a non-validated adaptation of EQ-5D. A number of issues are worth mentioning here.

First, dimensions of health status to incorporate into health state descriptions may not be the same for children as for adults. For example, the 'mobility' dimension of the widely used EQ-5D instrument[116] (I have no problems walking about/I have some problems walking about/I am confined to bed) has little relevance for children who are not yet able to walk. The same issue can be raised for the 'self-care' dimension. Furthermore, due to rapid developmental changes in childhood, it is difficult to identify a common set of dimensions across developmental stages.

A second issue is that of the individuals who should describe and value health states. Health state ratings should ideally be elicited from children themselves, but using proxies is sometimes unavoidable. A widely accepted view is that values should reflect preferences of the general population, and be elicited using a choice-based technique, such as time trade-off or standard gamble.[117,118] This would require people to imagine being in the health state of interest, as young children, which is not really possible. Therefore, we would suggest using alternative approaches, such as person trade-off or a contingent valuation study, in a representative sample of the general population, which would be asked to act as the social decision maker. The premise is that the participants in the valuation exercise are motivated by some notion of what is good for the society of which they are part. It would also be defensible to ask a group of parents to provide the values, but parental altruism may bias the resulting utilities.

Although there is no consensus on QALYs for caregivers, the assumption that the quality of life of parents is reduced due to RVGE episodes affecting their children seems acceptable. For example, parents may not be able to accomplish their usual activities (such as work) when they are caring for a sick child and may feel very anxious when his child is hospitalized. However whether the level of health that affects parents is very uncertain.

Finally, QALYs for RVGE cases not seeking medical attention are currently missing and are an obvious area for future research.

Vaccine prices. A majority of authors used assumptions in their input values, for vaccines prices because prices of the 2 vaccines are subject to uncertainties for mass vaccination programmes (where vaccine prices are subject to negotiation or tenders). Therefore, authors used hypothetical prices or did not report sources. This is particularly problematic for studies comparing both vaccines, using different hypothetical prices and reporting separate results for the two vaccines. Healthcare payers acknowledge in tender markets (such as the UK) that prices are different from the list prices. In a context of uncertainty surrounding vaccine prices, reporting threshold analyses (i.e., to determine the prices at which the vaccine is cost-effective for an accepted cost-effectiveness threshold), might be more relevant for use in decision-making than reporting a single cost-effectiveness ratio for a hypothetical price.

Comparisons of RotaTeq vs. Rotarix. It seems legitimate to conduct scenario analyses using vaccine efficacy data either from RotaTeq trials or from Rotarix trials. However, the basis for differentiating the two vaccines in some studies was not relevant. Indeed, no evidence of difference in efficacy between the two vaccines exists since case definitions, designs and endpoints used in respective clinical trials were different and no head-to-head trials have been conducted to allow a robust comparison of clinical efficacy. Furthermore, little difference in impact is expected between the two vaccines.[106] Additionally, given that RV vaccines are very likely to be administered concomitantly with other pediatric vaccines, in particular in developed countries, differences in administration costs are likely to be small whereas many economic studies considered they were on average 50% higher for RotaTeq (3 doses) than Rotarix (2 doses). Lastly, in situations where prices are not known, one cannot rule out the possibility that the difference in administration in costs is offset by a difference in price. Therefore, we believe that cost-effectiveness direct comparisons between the two vaccines are not informative unless prices are known and further evidence is gathered on the relative effectiveness of one vaccine vs. another.

Conclusion

68 economic evaluations of RV vaccination were reviewed, including 58 cost-effectiveness analyses and 22 cost-utility analyses. Half of the studies concerned Europe. Other evaluations have been conducted in all other parts of the world. All studies for developing countries concluded in favor of vaccination, but conclusions for developed countries varied between studies. Some of this variability is expected: for example, the impact depends on disease burden, which is different between developed and developing countries (higher mortality in developing countries, limited access to care…). One of the key factors explaining such variability was the perspective used for estimating costs: analyses from a societal perspective consistently lead to more favorable results than analyses from a TPP perspective, as savings in terms of productivity loss avoided was taken into account. Furthermore estimates of QALYs gained were highly sensitive to the inclusion of cases without medical care attention (mild cases) and utility lost by caregivers. Thus, the variability around results of cost-effectiveness studies is not only related to methodological issues or insufficient data, but also to varying value judgments, with respect to the perspective from which costs, benefits and quality of life should be valued.

At the time of economic analyses, uncertainty existed around the cost-effectiveness of RV vaccination in developed countries. Further epidemiological research and observation of the impact of vaccination in real-world conditions has led to reduce this uncertainty. To consider the full RV vaccination economic value, we suggest transmission-dynamic models to be used to account for herd protection. Further research into the impact of RVGE on quality of life in young children would also be valuable. Lastly, in a context of uncertainty surrounding vaccine prices, reporting results of threshold analyses on prices might be more relevant than a fixed cost-effectiveness ratio.

Although CEAs are useful to inform decision makers, the incremental cost per QALY gained has some limitations, in particular in the context of the assessment of interventions for young children for whose quality of life evaluation is still controversial. Therefore, it would also be interesting to use other types of complementary analyses (cost-benefit, budget impact analyses or willingness-to-pay approach for example) to consider the full potential societal and economics benefits of RV vaccination.

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Endnotes

[a]Developers of models were contacted by a WHO officer to invite them to participate in the model comparison. The process resulted in three models provided to the authors: Roxanne (Rotarix™ Analyses of Economics) designed by GSK Pharmaceuticals, POLYMOD, developed by public financing within a European-Union project and CoRoVa (Consensus Rotavirus model Vaccination) designed by Sanofi Pasteur MSD but developed by the University of Groningen within the context of an unrestricted grant.

[b]CEA is a form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action. Typically the CEA is expressed in terms of a ratio where the denominator is a gain in health from a measure and the numerator is the cost associated with the health gain. CUA is a CEA using years (QALY) as outcome measure.

[c]BIA is a tool used to predict and understand the potential financial consequences of introducing a new health-care intervention into a drug reimbursement system given inevitable resource constraints.

Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/journals/vaccines/article/24253

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