



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Cost-Effectiveness of Rotavirus Vaccination in France—Accounting for Indirect Protection

Dan Yamin, PhD^{1,2,*}, Katherine E Atkins, PhD^{2,3}, Vanessa Remy, PharmD, MSc⁴, Alison P Galvani, PhD²

¹Department of Industrial Engineering, Faculty of Engineering, Tel Aviv University, Tel Aviv, Israel; ²Center for Infectious Disease Modeling and Analysis, Yale School of Public Health, New Haven, CT, USA; ³Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; ⁴Sanofi Pasteur MSD, Lyon, France

ABSTRACT

Background: Vaccination against rotavirus has shown great potential for reducing the primary cause of severe childhood gastroenteritis. Previous economic evaluations of rotavirus vaccination in France have not modeled the potential impact of vaccines on disease burden via reduced transmission. **Objective:** To determine the cost-effectiveness of the introduction of pentavalent rotavirus vaccination into the French infant vaccination schedule. **Methods:** We developed an age-structured model of rotavirus transmission calibrated to 6 years of French gastroenteritis incidence and vaccine clinical trial data. We evaluated the cost-effectiveness of pentavalent rotavirus vaccination considering that 75% of infants would receive the three-dose vaccine course. **Results:** Our model predicts that rotavirus vaccination will decrease rotavirus gastroenteritis incidence and associated clinical outcomes in vaccinated and unvaccinated individuals, delay the seasonal peak of infection, and increase the age of infection. From the societal perspective, our base-case scenario predicts that vaccination coverage would be cost-effective at €115

or €135 per vaccine course at €28,500 and €39,500/quality-adjusted life-year (QALY) gained, respectively, and suggests that almost 95% of the financial benefits will be recouped within the first 5 years following vaccination implementation. From the third-party payer perspective, incremental cost-effectiveness ratios ranged from €12,500 to €20,000/QALY, respectively. Our uncertainty analysis suggests that findings were sensitive to various assumptions including the number of hospitalizations, outpatient visits, and the extent of QALY losses per rotavirus episode. **Conclusions:** Introducing pentavalent rotavirus vaccination into the French infant vaccination schedule would significantly reduce the burden of rotavirus disease in children, and could be cost-effective under plausible conditions.

Keywords: cost-effectiveness of rotavirus, herd immunity, rotavirus model, rotavirus vaccination.

Copyright © 2016, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.

Introduction

Rotavirus infection, the primary cause of gastroenteritis in children worldwide, carries a significant disease burden [1]. In the absence of oral rehydration therapy, rotavirus gastroenteritis (RVGE) can cause rapid dehydration, which may lead to death [2]. In developed countries, rotavirus infection is associated with low mortality, but is responsible for high morbidity. France faces a significant societal and economic burden due to rotavirus infection, with 19,200 hospitalizations and 131,200 ambulatory visits annually due to RVGE among children younger than 5 years [3].

Rotavirus vaccines have been introduced into infant vaccination schedules in several developed countries since their licensing in 2006, including the United Kingdom and Germany. In France, the Haut Conseil de Santé Publique recently published its recommendation for the implementation of national rotavirus vaccination for infants younger than 6 months [4]. Data from Australia [5], the United States [6–8], Belgium [9], and Israel [10] suggest that vaccination is highly effective in decreasing RVGE. Moreover, in countries where universal vaccination has been introduced, a 20% reduction in RVGE cases has been observed

among unvaccinated children [11]. These reports indicate that there is a substantial RVGE case reduction due to both direct and indirect effects of vaccination. However, none of the previous studies assessing the cost-effectiveness of rotavirus vaccination in France [3,12–15] has modeled the effect of herd protection.

We developed a dynamic model of rotavirus transmission in France to evaluate the population-level impact of introducing universal pentavalent vaccination into the infant vaccination schedule in France. Using the predictions from the dynamic model, we evaluated the cost-effectiveness of pentavalent rotavirus vaccination from the third-party payer (TPP) and societal perspectives. This study could help to inform policy decisions in predicting the outcomes of a universal pentavalent rotavirus vaccination program in France.

Methods

Dynamic Model

We developed an epidemiological population-based model of rotavirus transmission in France (detailed in the supporting

* Address correspondence to: Dan Yamin, Department of Industrial Engineering, Tel Aviv University, Ramat Aviv 69978, Tel Aviv, Israel. E-mail: yamind@post.tau.ac.il.

information). The dynamic model structure (Fig. 1) takes into account that the risk of infection depends on both the number of previous infections [16] and the age at exposure [17]. The model includes 19 age groups: 0 to 2, 2 to 4, 4 to 6, 6 to 12, ..., 22 to 24 months and 2 to 3, 3 to 4, 4 to 5, 5 to 25, 25 to 45, 45 to 65, older than 65 years, and distinguishes between primary, secondary, and subsequent infections. Infection may be either asymptomatic or symptomatic with either mild or moderate-to-severe RVGE [16]. Following infection, we assume there is temporary complete immunity [18] that lasts for an average of 18 and 24 months following first and second infections, respectively [19,20]. The infectiousness of an infected individual is based on the viral shedding of the infected individual [21]. The extent of viral shedding depends on both the immunity of the infected individual that has been built up from previous exposures and on the severity of the disease. In our sensitivity analysis, we considered three additional waning scenarios (from 6 months to 3 years) (Table 1). Contact rates between age groups were parameterized using age-stratified European physical contact data [22]. We assumed that a vaccine dose is either effective or not effective, and that each effective vaccine dose confers the same protection as a single natural infection. We estimated the per-dose vaccine efficacy by calibrating the dynamic model to the pentavalent vaccine efficacy data from the 2-year clinical trial [23], assuming a given duration of temporary immunity following each dose. These trials showed that vaccinated individuals have their risk of any RVGE reduced by 68% and their risk of moderate-to-severe RVGE reduced by 86.7%.

To estimate empirically unknown epidemiological parameters (Table 1), we calibrated our model to weekly national acute gastroenteritis incidence from 2008 to 2013 in France. These data were collected from the French Sentinels network, detailing the incidence of acute diarrhea stratified by yearly age groups [24]. We converted these incidences to RVGE by considering the proportion of those with acute gastroenteritis who test positive for rotavirus each month [24–30] to capture the seasonal pattern of rotavirus in France. For individuals younger than 5 years, we scaled the age-specific incidences of RVGE with the following age groups: 0 to 6 months, 6 to 12 months, 1 to 2 years, 2 to 3 years, and 3 to 5 years to ensure that the age distribution among RVGE

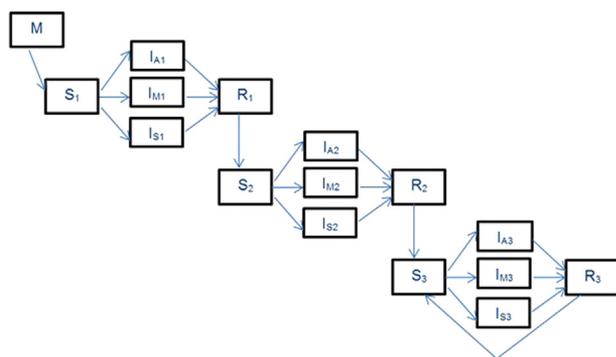


Fig. 1 – State diagram of epidemiologic model, with arrows corresponding to possible transition between states as a result of infection, recovery, or immunity waning. Individuals are born with temporary maternal immunity (state M). This immunity wanes and individuals move to the susceptible state (S₁). Infections can be asymptomatic (I_{A1}), mild RVGE (I_{M1}), or severe RVGE (I_{S1}). Individuals recover from infection to become temporarily immune (R₁). This immunity wanes to allow repeat infections with either a secondary infection or a subsequent infection. Each effective vaccine dose confers protection equal to natural infection. RVGE, rotavirus gastroenteritis.

infected will match that in previous RVGE studies in France [26,27,29]. Given that not all cases are reported, we scaled the incidence by a fixed factor such that the overall mean annual number of RVGE in children younger than 5 years will be 296,500, as suggested by the High Council for Public Health in France [3].

To estimate the RVGE infection for individuals older than 5 years, we used prospective data from the Netherlands that estimate that the age-specific proportion of gastroenteritis cases attributable to rotavirus for individuals aged 5 years and older lies between 1.5% and 3.3% [31,32]. Given that the reported rates of RVGE in France are similar to the ones observed in the Netherlands (see, e.g., [29]), we assumed the same proportion of RVGE for those with gastroenteritis episode as the ones observed in those prospective studies [31,32]. This assumption leads to around 27.5% of all RVGE cases in France in individuals 5 years and older. Overall, our approach ensures that for our model calibration, the data used will capture the actual seasonal patterns, RVGE age distribution, and the total number of cases (both reported and unreported) in France.

Clinical Outcomes

The epidemiological results generated by the dynamic model were integrated into an economic evaluation to estimate the cost-effectiveness of pentavalent rotavirus vaccination introduction into the French infant vaccination schedule. For the economic evaluation, we considered four clinical outcomes: 1) general practitioner (GP) visit, 2) hospitalization (due to a community or a nosocomial infection), 3) emergency department (ED) visit, and 4) death. A proportion of severe RVGE cases were assumed to be hospitalized, attend the ED, or die. A proportion of any (severe or mild) RVGE cases were assumed to require a GP visit. Specifically, in the absence of vaccination, we assumed that among individuals with severe RVGE infection, 19,200 will be hospitalized, 5,460 will attend the ED, and 13 will die annually [26,33]. Among individuals with any RVGE, 131,200 will visit the GP (Table 3) [26,33]. Clinical trials suggest that a full three-dose course of pentavalent vaccination prevents 95.6% of hospitalizations, 93.8% of ED visits, and 87.2% of GP visits in vaccinated individuals [34]. We combined both these clinical trial data with model predictions to estimate the proportion of clinical outcomes averted because of both direct and indirect effects (see Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2016.05.011>).

In our univariate sensitivity analysis, we included the risk of intussusception consistent with a recent US study that found that within a birth cohort of 4.3 million infants vaccine-associated intussusception could cause an excess 0.2 (range 0.1–0.3) deaths, 45 (range 21–86) hospitalizations, and 13 (range 6–25) cases managed in short-stay or ED settings [35].

Quality of Life

In the base-case analysis, we considered a loss of 0.003274 and 0.001715 quality-adjusted life-years (QALYs) per severe and mild RVGE episode for a child, respectively. This is based on the observation that each RVGE episode lasts for 5.4 and 6.5 days, with a daily utility of 0.816 and 0.884 for a mild case and a severe case, respectively [36,37], consistent with previous French economic analyses [13,36,37]. In the sensitivity analysis, we varied the QALY loss by $\pm 20\%$. On the basis of previous studies that showed substantial parental QALY losses due to an RVGE infection of their child [38,39], and in line with previous cost-effective studies on rotavirus in France and elsewhere [14,40–42], we also considered the same QALY loss for one caregiver in our base-case scenario.

Table 1 – Epidemiological parameter values and distributions where applicable.

Parameter	Symbol	Base-case value			Distribution (range) used in uncertainty (sensitivity) analysis	Source
Initial population size (millions)	N	65.63				[1]
Birth rate (annual per 1000 individuals)	<i>f</i>	12.8				[1]
Probability of severity given infection	<i>d</i>					[2,3]
		Asymptotic	Mild	Severe		
Primary infection		0.53	0.34	0.13		
Secondary infection		0.75	0.22	0.03		
Subsequent infection ≤65 y		0.8	0.2	0		
Subsequent infection >65 y		0.4	0.3	0.3		Estimated
Duration of infection (d)	$1/\gamma$					[3,4]
First infection		7				
Second/subsequent/asymptomatic infection		3.5				
Relative infectiousness	ρ	RVGE				[2,3]
		Asymptotic	Mild	Severe		
First infection		0.1	1	1		
Second/subsequent infection		0.1	0.5	0.8		
Relative susceptibility following:	σ					[3,4]
Primary infection		0.62			Uniform (0.56–0.68)	
Second/subsequent infection		0.37			Uniform (0.34–0.4)	
Seasonal offset (radians)	θ	1.355				Estimated
Seasonal amplitude	A	0.0685				Estimated
					Alternative waning scenarios	
Duration of immunity (mo)	$1/\omega$				A B C	
Maternal antibodies		3			3 3 3	
First infection		18			4 9 27	
Second/subsequent infection		24			6 12 37	
Susceptibility rate for age range (probability of infection per infectious contact)	<i>b</i>				A B C	Estimated
0–6 mo		0.283			0.275 0.278 0.286	
6–24 mo		0.52			0.489 0.497 0.525	
24–60 mo		0.13			0.096 0.109 0.146	
5–65 y		0.01			0.009 0.009 0.009	
>65 y		0.02			0.017 0.017 0.017	
Per-dose vaccine efficacy	<i>r</i>	0.35			Baseline: Uniform (0.31–0.39)	Estimated
					A: Uniform (0.38–0.43)	
					B: Uniform (0.34–0.38)	
					C: Uniform (0.3–0.35)	
Vaccination coverage	ϕ	0.75				[5]

The distributions were sampled during the global uncertainty analysis. Ranges are given when the parameter is varied in the univariate/multivariate sensitivity analysis.

Severity of infection is defined by physicians on the basis of a 20-point scoring system [6], with 10 as threshold between mild and severe infections.

Costs

Consistent with other studies, we conservatively only included the costs and benefits attributable to children younger than 5 years because the vast majority of reported rotavirus cases occur in children younger than 5 years, and there is much uncertainty about the clinical burden and severity of RVGE in older children and adults [29,33,42,43]. Costs were compiled from available published sources in France and were inflated to 2015 euros [44,45] (Table 2). For comparison with other studies, we present cost-effectiveness results for two representative vaccine course prices of €115, corresponding to the lowest official price available for the pentavalent rotavirus vaccine in the European private market, and €135, corresponding to the current out-of-pocket advised price of RotaTeq in the French private market. Given that

the rotavirus vaccine would be administered concomitantly with other childhood vaccines as part of the existing French vaccination schedule, or during a routine ambulatory visit, no cost of vaccine administration was considered [3,13]. However, because 1% of vaccinated infants may be brought back for a follow-up visit to their GP, attributable to the rotavirus vaccine, we increased the cost of each vaccine course by 1% of a GP visit to reflect this extra cost.

Economic Analysis

To allow comparison with standard measures of cost-effectiveness in France, the results are presented in cost per QALY gained from introducing the pentavalent rotavirus vaccine into the infant schedule assuming 75% vaccine uptake [13] in

Table 2 – Cost-effectiveness parameter values and distributions where applicable.

Parameter	Base-case value	Distribution (range) used in global uncertainty (univariate/multivariate sensitivity) analysis	Source
Annual incidence rate of symptomatic RVGE in children <5 y before vaccination (per 1000 individuals)		Uniform (0.8–1.2)	[7]
Office visits	31.4		
ED visits	1.3		
Hospitalization	4.6		
Nosocomial infection	2.89		
Deaths	0.0031		
Discount rate	4% for the first 30 y and linearly decreasing to 2% after 50 y		
Costs (adjusted to €2013)	Perspective TPP SP	Total costs × gamma (11.36, 0.098)	[8,9]; Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.05.011
GP consultations	36.64 67.5		
ED visits	86.2 142.2		
Hospitalizations/deaths	1331.5 1385.5		
Nosocomial infections	1178.6 1503.8		
Other direct costs (travel costs, extra diapers, childcare)	0 16		
Vaccination follow-ups	0.37 0.68		
Mortality	A life expectancy of 1; 20; 41.3 minus patient's age with probability of 1/3 each		[10]
The distributions were sampled during the global uncertainty analysis. Ranges are given when the parameter was varied in the univariate/multivariate sensitivity analysis. ED, emergency department; GP, general practitioner; SP, societal perspective; TPP, third-party payer.			

comparison to the status quo of no national vaccination. The analysis was performed in accordance with Haute Autorité de Santé guidelines [46]. We evaluated the cost-effectiveness of rotavirus vaccination from two perspectives: 1) the TPP perspective: quantifying all direct medical costs, 65% of vaccine purchase payable by the national health insurance, and quality of life lost because of RVGE for those younger than 5 years and one caregiver, and 2) the societal perspective (referred to as the “collective” perspective in Haute Autorité de Santé guidelines), which includes all direct costs due to RVGE episodes, all vaccine purchase costs, and quality of life lost due to RVGE for those younger than 5 years and one caregiver. Conservatively, we did not incorporate losses of productivity [47,48].

The discounted costs and benefits of a rotavirus vaccination program were evaluated over a time horizon of 50 years. Consistent with the guidelines, all costs and QALYs were discounted at a rate of 4% annually for the first 30 years, decreasing linearly to 2% annually by 50 years [46].

We performed univariate sensitivity analyses on the following parameters: 1) QALY losses due to RVGE and the number of caregivers, 2) vaccination coverage, 3) clinical outcome costs, 4) waning rate of the vaccine, and 5) discount rate. With respect to discounting, as most cost-effectiveness analysis guidelines suggest, we considered in our base case equal discounting for cost and effects [49]. Nevertheless, given that cost and effects need to be depending on distinct quantities such as the growth

rates of national income and healthy life expectancy, lowering the discount rate for effects relative to that of costs is recommended [49]. Accordingly, in our sensitivity analysis, we conducted a differential discounting by fixing the costs to 4% and varied the effects between 2% and 4%. Additional sensitivity analyses were performed on the probabilities of the respective clinical outcomes. A probabilistic global uncertainty analysis was also conducted to incorporate empirical uncertainty in epidemiological, costs, and vaccine-related parameter values (Table 1).

Results

Dynamic Model

Analysis of our base-case scenario predicts that the introduction of rotavirus vaccination in France will decrease RVGE incidence and the requirement for clinical outcomes in both vaccinated and unvaccinated individuals. The mean reduction in children younger than 5 years ranges from 62% to 65% (2 years after vaccine introduction) to 71% to 75% (10 years after vaccine introduction), depending on the clinical outcome (Table 3).

Our model predicts a delay in peak incidence of around 1 month relative to no vaccination (Fig. 2A,B). The median age of infection for children younger than 5 years is expected to increase by 2 months after 3 years of vaccination. Because of

Table 3 – Estimated mean annual number of infected among children <5 y and demand for medical outcomes following vaccination predicted from the base-case parameter values.

Annual no. of clinical outcomes	Mild RVGE	Severe RVGE	GP visits	ED visits	Nosocomial infection	Hospital visits	Deaths
No vaccination	142,834	153,665	131,200	5,460	9,913	19,200	13
Average at 2 y	54,315	56,677	48,105	1,924	3,460	6,702	5
Average at 5 y	41,229	42,340	35,821	1,401	2,507	4,855	4
Average at 10 y	40,963	42,048	35,571	1,391	2,487	4,817	4

ED, emergency department; RVGE, rotavirus gastroenteritis.

reduced transmission, our model predicts up to 60.5% reduction in infection among the unvaccinated elderly in the long-term following vaccine introduction.

Cost-Effectiveness

From the societal perspective, our base-case analysis predicts that the incremental cost-effectiveness ratios (ICERs) are €28,500

and €39,500/QALY gained for per-course vaccine prices of €115 and €135, respectively (Table 4). From the TPP perspective, where the government covers 65% of the vaccine price, the ICER drops to €12,500 and €20,000/QALY gained for €115 and €135 per vaccine course, respectively (Table 4). If transmission dynamics are neglected, our static model suggests that the cost per QALY may increase by up to 19% from the societal perspective when considering a vaccine course price of €115.

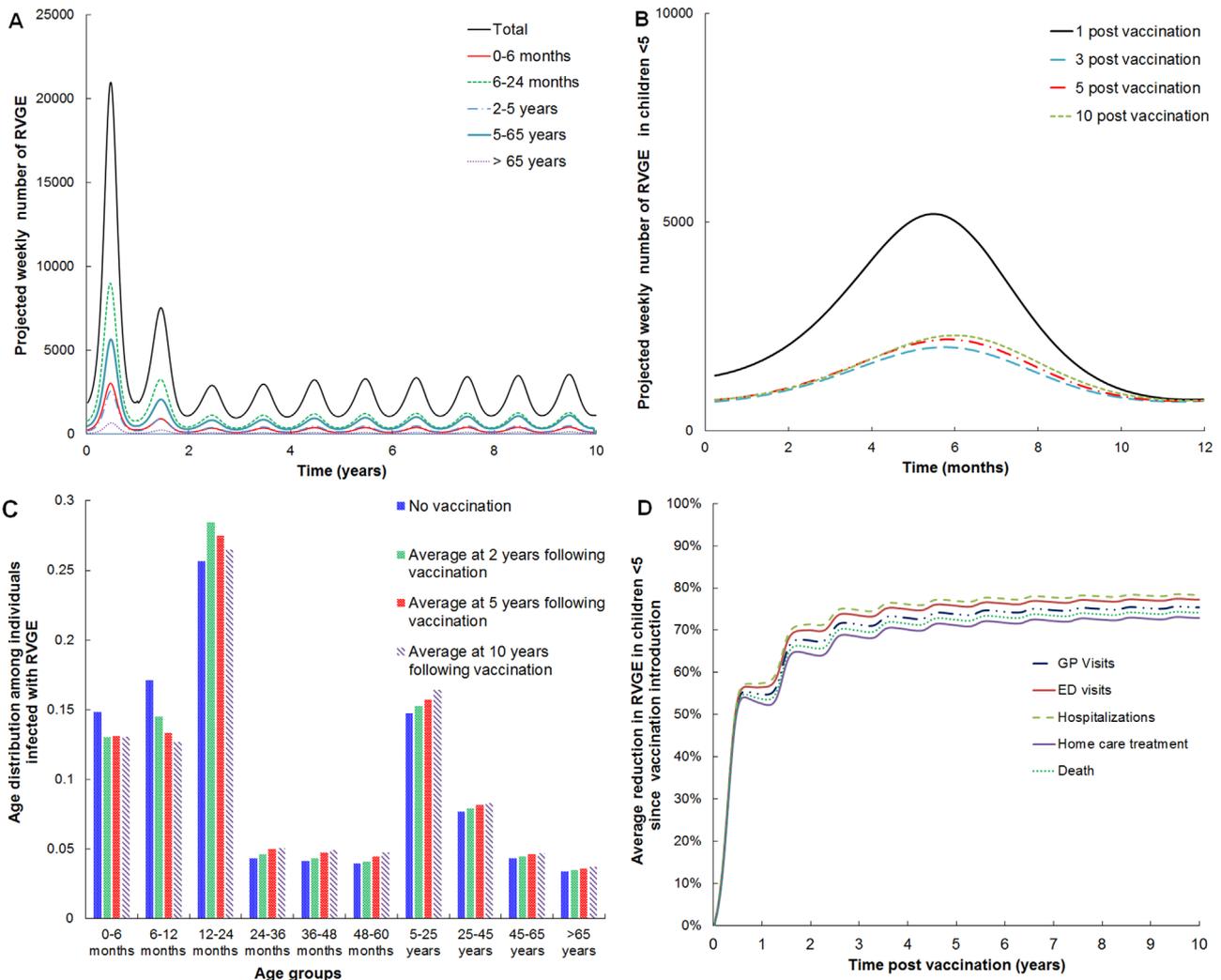


Fig. 2 – Base-case predictions following vaccination. (A) Projected weekly number of RVGE cases. Rapid decline is projected by 2 years postvaccination. (B) Comparison of prevalence given years postvaccination, characterized by a delay in the peak of infection. (C) Age distribution among individuals with RVGE postvaccination is characterized by an increase in the age of infection. (D) Average reduction varies across different clinical outcomes, and gradually plateaus following 5 years postvaccination. ED, emergency department; GP, general practitioner; RVGE, rotavirus gastroenteritis.

Table 4 – Results of cost-effectiveness analyses.

Discounted costs (€2013 million)	No vaccination	Dynamic model	Static model
	<i>Third-party payer</i>		
GP consultations	132.5	42.0	45.7
ED visits	14.0	3.7	4.1
Hospitalizations	757.1	188.7	214.0
Nosocomial infections	346.0	86.2	98.0
Deaths	0.51	0.15	0.18
Home care treatment	0.0	0.0	0.0
Total costs (excluding vaccine course)	1250	320.7	361.9
Vaccine course costs to the third-party payer* (€115 × 65%)	0.0	1,335	1,335
Vaccine course costs to the third-party payer* (€135 × 65%)	0.0	1,566	1,566
Cost-effectiveness (ICER, €/QALY)			
€115 per vaccine course		12,500	16,000
€135 per vaccine course		20,000	24,000
	<i>Societal perspective</i>		
GP consultations	244.1	77.4	84.3
ED visits	23.0	6.0	6.8
Hospitalizations	787.6	196.3	222.5
Nosocomial infections	441.5	110.0	124.7
Deaths	0.58	0.17	0.2
Home care treatment	51.6	16.0	16.4
Total costs (excluding vaccine course costs)	1548.4	405.9	454.9
Vaccine course† (€115)		2,056	2,056
Vaccine course (€135)		2,410	2,410
Total discounted QALYs	46,478	14,163	18,153
Cost-effectiveness (ICER, €/QALY)			
€115 per vaccine course		28,500	34,000
€135 per vaccine course		39,500	46,500
Threshold cost-effective price (€)			
Willingness-to-pay threshold of 30,000 €/QALY		118	108
Willingness-to-pay threshold of 50,000 €/QALY		154	140
ED, emergency department; GP, general practitioner; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.			
* Includes 65% coverage of the cost of vaccine course, and the costs of the third-party payer for GP follow-up visit in 1% of the vaccinated.			
† Includes costs of vaccinations and GP follow-up visit in 1% of the vaccinated.			

Univariate sensitivity analyses indicate that the ICERs are sensitive to the effect of the epidemiological, quality-of-life, and cost assumptions (Fig. 3). The most influential parameter is the QALY consideration for caregivers. For example, assuming no QALY losses for a caregiver would elevate the ICER to €51,000/QALY from the societal perspective.

Our analysis predicts that the ICER is highly sensitive to the incidence of nosocomial rotavirus infections. For example, assuming 4,460 annual cases of nosocomial infection, which is consistent with the lowest limit from a previous epidemiological study [4], the ICER can increase to €35,000/QALY. In contrast, with 14,370 nosocomial infection episodes, which is in the range of previous estimates [4], the ICER drops to €23,500/QALY gained.

Given the uncertainty surrounding the duration of immunity conferred from natural infection and vaccination, we also calibrated our model to alternative waning rates from 6 months to 3 years, compared with 2 years in the base case. The ICER was robust under changes to plausible variation in waning protection rates (Fig. 3). Results were also robust across the discount rate and vaccine coverage. The QALY losses had a small-to-moderate impact on the ICER. For example, when using a discount rate of 2.5% as recently recommended in France [50], the ICER is estimated at €28,000/QALY from the societal perspective. Accounting for possible intussusception due to vaccination had a minimal impact, with an increase in the ICER for €50/QALY gained at most.

To quantify the certainty and robustness of our results to policymakers, we conducted a global probabilistic uncertainty analysis (Table 1). At a vaccine course price of €115, the probability of national rotavirus vaccination being cost-effective is 99% and 99.9% from the societal perspective and the TPP perspective, respectively, for a threshold of €50,000/QALY. For a price of €135, the cost-effective probabilities remained high at 88% and 99.9%, respectively (Fig. 4).

We conducted a budget impact analysis to determine how quickly the vaccine costs to the TPP and the society, respectively, are recouped as a result of the decrease in RVGE clinical outcomes-related costs. We found that at a vaccine course price of €115, 65% and 52% of the vaccine costs are predicted to be recouped. Given that rotavirus is primarily a childhood disease, the time to reach this payback is relatively short, with almost 95% of the overall gain being recouped within the first 5 years (Fig. 5).

Discussion

We developed a dynamic population-based model of rotavirus transmission to determine both the effectiveness and the cost-effectiveness of introducing pentavalent rotavirus vaccination into the national infant immunization schedule of France. Our study is the first to integrate a dynamic model of rotavirus transmission with a cost-effectiveness analysis of rotavirus vaccination in France. Our approach makes it possible to account

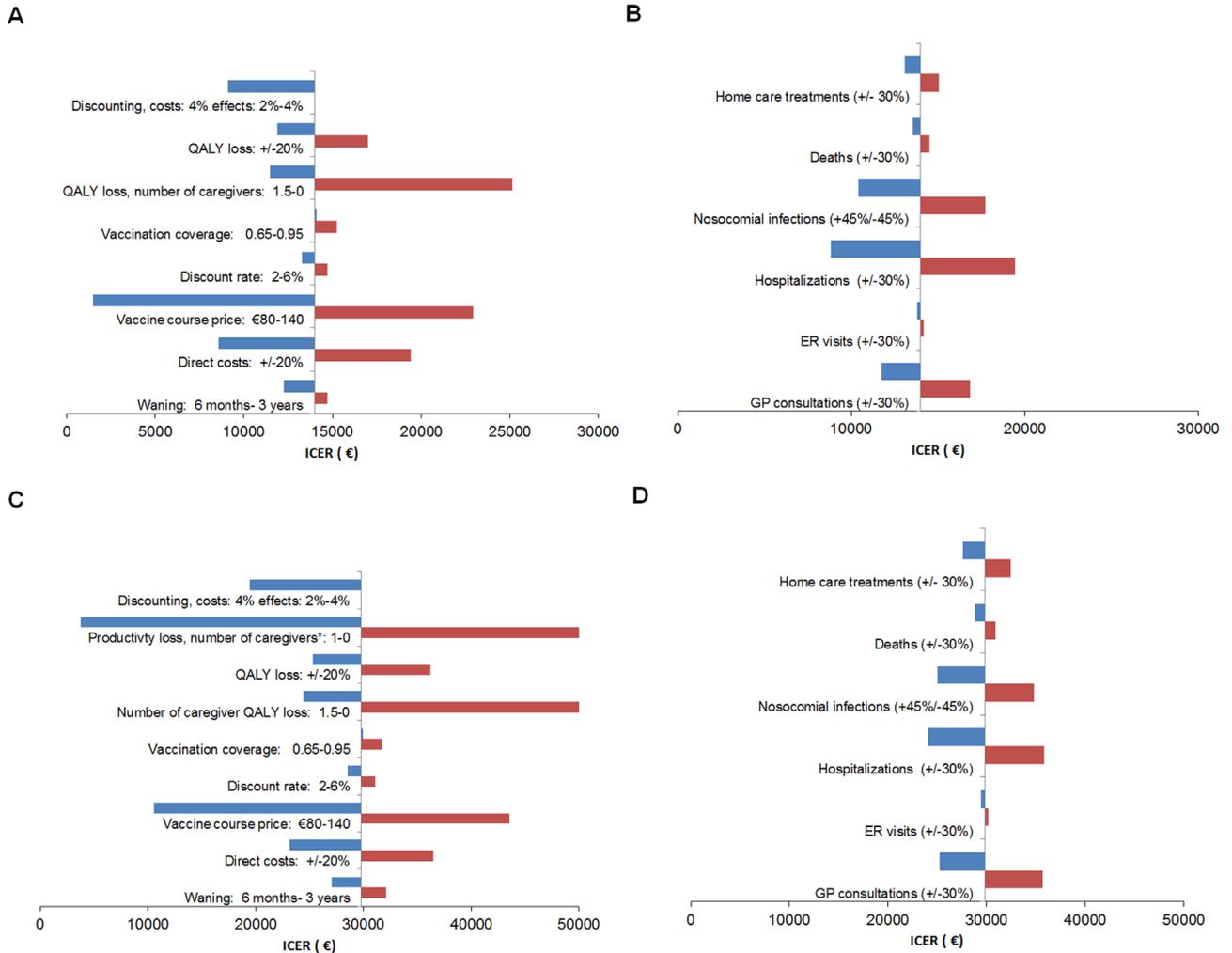


Fig. 3 – Univariate sensitivity analysis of the ICER assuming vaccine course price of €115 in (A) and (B) from the perspective of the third-party payer, and (C) and (D) from the society perspective. ED, emergency department; GP, general practitioner; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

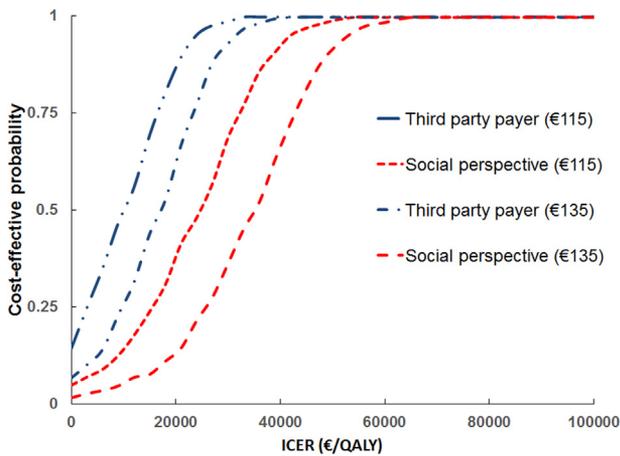


Fig. 4 – Global uncertainty analysis results. Threshold curves showing the effect of vaccine course price on the probability that rotavirus vaccination is cost-effective in France from the social perspective and the third-party payer perspective at prices of €115 and €135 per course, respectively. DALY, disability-adjusted life-year; ICER, incremental cost-effectiveness ratio.

for indirect protection through herd immunity and therefore to assess both the epidemiological and economic impacts of a national vaccination program.

Our epidemiological model replicates several trends that have been observed following universal vaccination implementation in other countries. For example, in line with observations in several countries following the implementation of universal rotavirus vaccination program [8,51,52], the epidemiological model component of our analysis predicts that RVGE infection in unvaccinated elderly is reduced substantially, a benefit conservatively not considered in our cost-effectiveness analysis. Consistent also with previous observations [9,53], our model predicts that vaccination would delay the peak RVGE incidence by 1 month. In France, the current RVGE peak overlaps with that of other gastroenteritis and respiratory infections in February and early March [25]. Thus, both preventing and delaying RVGE cases may ease the seasonal pressure on hospitals when high occupancy is expected by reducing the demand for hospital beds, reducing the cost of medical personnel overtime, as well as preventing nosocomial infections due to overcrowding [54].

We integrate the uncertainty surrounding key epidemiological and vaccine parameters into our predictions by using Monte-Carlo sampling and explain the resulting implications for the impact of vaccination. In particular, to incorporate the high

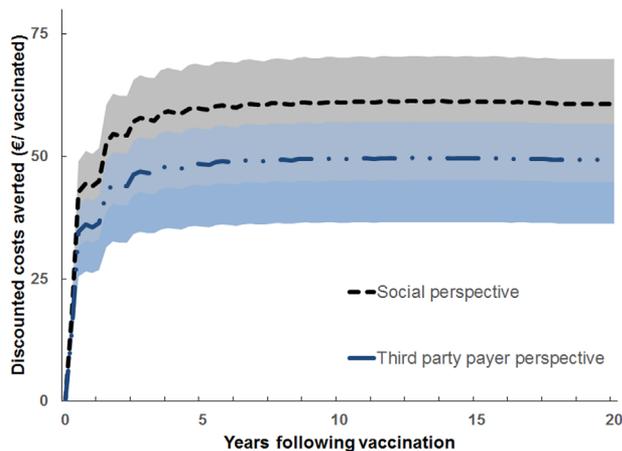


Fig. 5 – Return on investment. Costs averted per vaccinated throughout 20 years following vaccination implementation. The beneficiary of averted costs is presented from the third-party payer perspective and the social perspective.

uncertainty with respect to the annual number of clinical outcomes before vaccination, we used uniform (i.e., naive) distributions. The most influential parameters are the consideration of caregivers' quality of life and the incidence of nosocomial infections and hospitalizations. Nevertheless, with the exception of the scenario removing QALY losses for a caregiver entirely, all univariate sensitivity analyses for €115 led to ICERs below €50,000/QALY. Thus, the probabilistic analysis confirms the robustness of our findings.

As for any model, there are inevitably simplifications in the model structure as well as uncertainty regarding parameterization from empirical data. Given that not all individuals seek medical treatment and some are misdiagnosed, the total RVGE incidence is not known. We assumed the same RVGE cases and likelihood of clinical outcomes as provided in previous studies [4,13]. In line with other dynamic models of rotavirus infection [43], the model assumes temporary and complete immunity following infection. However, the duration of this temporary immunity remains uncertain. We assumed that vaccine-induced protection wanes in the same way as naturally induced protection. For consistency, we also used the same assumptions for quality-of-life parameters as previous cost-effectiveness studies conducted in France [3,13]. However, cost-utility analyses are inherently limited when evaluating childhood diseases because it is extremely difficult to accurately assess quality of life in children. RVGE also impacts the quality of life of parents [37]. In this context, consideration of the burden to the caregiver is pertinent, and should be taken into account when evaluating the economic value of childhood diseases.

Two previous cost-effectiveness analyses conducted for France [3,13,15] suggested higher ICERs than did this study. The discrepancy stems from three important differences: 1) lack of incorporation of herd protection in previous models (leading to a reduction in ICER by ~17%–19%), 2) differences in health outcome costs and vaccine prices, and 3) the extent of nosocomial infections considered. For example, one of the previous studies [13] did not consider nosocomial infections and focused on children younger than 3 years, whereas another previous study [15] accounted for the lower bound of reported nosocomial infections [4]. However, rotavirus vaccination was observed to reduce nosocomial infection by 72% in less than 4 years following vaccination of 72% to 88% of toddlers in Austria and thus should not be neglected or underestimated.

Consistent with other cost-effectiveness studies of rotavirus vaccination, we conservatively only included in our base case the costs and benefits attributable to children younger than 5 years because the vast majority of reported rotavirus cases, and in particular RVGE-related hospitalizations, occur in children younger than 5 years [29,33,42,43]. Nevertheless, in countries where rotavirus vaccination has been introduced into the infant immunization schedule, a significant reduction in RVGE has been observed even among unvaccinated adults [8]. There is limited available data on the extent of RVGE burden in adults in France or in other developed countries. As data become available, future studies should conduct cost-effectiveness analysis that will incorporate the entire population. Nevertheless, even in our analysis when we considered individuals younger than 5 years only, when herd protection is neglected, our static model predicted a 19% increase in the cost per QALY gained. This difference indicates that herd protection even among those younger than 5 years plays a crucial role in determining the cost-effectiveness of universal rotavirus vaccination program.

Conservatively, we did not incorporate the indirect costs of productivity losses for a caregiver in addition to QALYs losses, both of which could be considered in a full societal perspective. Indeed, RotaTeq clinical trials demonstrated an efficacy of 87% in reducing the number of workdays missed by parents to care for their children [55]. This economic burden of productivity loss can contribute to almost 50% of the total cost of RVGE in France. Similarly, the benefits of rotavirus vaccination on the health care system, such as hospital capacity, were not evaluated in the model because these benefits are difficult to quantify monetarily [56]. Therefore, extending our conservative analysis to account for the full economic and societal benefits could further improve the cost-effectiveness profile of pentavalent rotavirus vaccination in France.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at <http://dx.doi.org/10.1016/j.jval.2016.05.011> or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

- Patel MM, Steele D, Gentsch JR, et al. Real-world impact of rotavirus vaccination. *Pediatr Infect Dis J* 2011;30:S1–5.
- Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010;375:1969–87.
- Haut Conseil de la santé publique. Rapport sur la vaccination systématique contre les rotavirus des nourrissons âgés de moins de 6 mois. [Report in French]. French Ministry of Health and Sport Location, Paris, France, 2010.
- Haut Conseil de la santé publique. Rapport sur la place des vaccins contre les infections à rotavirus chez les nourrissons. [Report in French]. French Ministry of Health and Sport Location, Paris, France, 2013.
- Field EJ, Vally H, Grimwood K, Lambert SB. Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. *Pediatrics* 2010;126:e506–12.
- Tate JE, Panozzo CA, Payne DC, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. *Pediatrics* 2009;124:465–71.
- Payne DC, Staat MA, Edwards KM, et al. Direct and indirect effects of rotavirus vaccination upon childhood hospitalizations in 3 US counties, 2006–2009. *Clin Infect Dis* 2011;53:245–53.
- Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. *J Infect Dis* 2011;204:980–6.

- [9] Braeckman T, Van Herck K, Raes M, et al. Rotavirus vaccines in Belgium: policy and impact. *Pediatr Infect Dis J* 2011;30:S21–4.
- [10] Muhsen K, Chodick G, Goren S, et al. The uptake of rotavirus vaccine and its effectiveness in preventing acute gastroenteritis in the community. *Vaccine* 2010;29:91–4.
- [11] Glass RI, Bresee JS, Turcios R, et al. Rotavirus vaccines: targeting the developing world. *J Infect Dis* 2005;192:S160–6.
- [12] Standaert B, Parez N, Tehard B, et al. Cost-effectiveness analysis of vaccination against rotavirus with RIX4414 in France. *Appl Health Econ Health Policy* 2008;6:199–216.
- [13] Melliez H, Levybruhl D, Boelle PY, et al. Cost and cost-effectiveness of childhood vaccination against rotavirus in France. *Vaccine* 2008;26:706–15.
- [14] Jit M, Bilcke J, Mangen M-JJ, et al. The cost-effectiveness of rotavirus vaccination: comparative analyses for five European countries and transferability in Europe. *Vaccine* 2009;27:6121–8.
- [15] Jit M, Mangen M-JJ, Melliez H, et al. An update to the cost-effectiveness of rotavirus vaccination: comparative analyses for five European countries and transferability in Europe. *Vaccine* 2010;28:7457–9.
- [16] Velázquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. *N Engl J Med* 1996;335:1022–8.
- [17] Atkins KE, Shim E, Pitzer VE, Galvani AP. Impact of rotavirus vaccination on epidemiological dynamics in England and Wales. *Vaccine* 2012;30:552–64.
- [18] Pitzer VE, Viboud C, Simonsen L, et al. Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics. *Science* 2009;325:290–4.
- [19] Chiba S, Nakata S, Urasawa T, et al. Protective effect of naturally acquired homotypic and heterotypic rotavirus antibodies. *Lancet* 1986;328:417–21.
- [20] Mäkelä M, Marttila J, Simell O, Ilonen J. Rotavirus-specific T-cell responses in young prospectively followed-up children. *Clin Exp Immunol* 2004;137:173–8.
- [21] Kang G, Iturriza-Gomara M, Wheeler JG, et al. Quantitation of group A rotavirus by real-time reverse-transcription-polymerase chain reaction: correlation with clinical severity in children in South India. *J Med Virol* 2004;73:118–22.
- [22] Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* 2008;5:381–91.
- [23] Vesikari T, Karvonen A, Ferrante SA, Ciarlet M. Efficacy of the pentavalent rotavirus vaccine, RotaTeq(R), in Finnish infants up to 3 years of age: the Finnish Extension Study. *Eur J Pediatr* 2010;169:1379–86.
- [24] French general practitioners' Sentinelles network 2014. Available from: (<https://websenti.u707.jussieu.fr/sentiweb/?page=maladies&mal=6>). [Accessed December 1, 2013].
- [25] Tran A, Talmud D, Lejeune B, et al. Prevalence of rotavirus, adenovirus, norovirus, and astrovirus infections and coinfections among hospitalized children in northern France. *J Clin Microbiol* 2010;48:1943–6.
- [26] Huet F, Chouchane M, Cremillieux C, et al. Prospective epidemiological study of rotavirus gastroenteritis in Europe (REVEAL study): results in the French area of the study. [Article in French]. *Arch Pediatr* 2008;15:362–74.
- [27] Van Damme P, Giaquinto C, Maxwell M, et al. Distribution of rotavirus genotypes in Europe, 2004–2005: the REVEAL Study. *J Infect Dis* 2007;195 (Suppl):S17–25.
- [28] Forster J, Guarino A, Parez N, et al. Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European children younger than 5 years of age. *Pediatrics* 2009;123:e393–400.
- [29] Van Effelterre T, Soriano-Gabarró M, Debrus S, et al. A mathematical model of the indirect effects of rotavirus vaccination. *Epidemiol Infect* 2010;138:884–97.
- [30] Soriano-Gabarró M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J* 2006;25(Suppl):S7–11.
- [31] de Wit MA, Koopmans MP, Kortbeek LM, Wannet WJ, et al. Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. *Am J Epidemiol* 2001;154:666–74.
- [32] de Wit MA, Koopmans MP, Kortbeek LM, et al. Etiology of gastroenteritis in sentinel general practices in the Netherlands. *Clin Infect Dis* 2001;33:280–8.
- [33] Giaquinto C, Van Damme P, Huet F, et al. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. *J Infect Dis* 2007;195:S36–44.
- [34] Itzler R, Koch G, Matson DO, et al. Robustness of the healthcare utilization results from the Rotavirus Efficacy and Safety Trial (REST) evaluating the human-bovine (WC3) reassortant pentavalent rotavirus vaccine (RV5). *BMC Pediatr* 2010;10:42.
- [35] Desai R, Cortese MM, Meltzer MI, et al. Potential intussusception risk versus benefits of rotavirus vaccination in the United States. *Pediatr Infect Dis J* 2013;32:1–7.
- [36] Senecal M, Brisson M, Lebed MH. Burden of rotavirus associated gastroenteritis in Canadian families: a prospective community based study. Winnipeg, Canada: Presented at: Seventh Canadian Immunization Conference, Winnipeg, Canada. December 3–6, 2006.
- [37] Martin A, Cottrell S, Standaert B. Estimating utility scores in young children with acute rotavirus gastroenteritis in the UK. *J Med Econ* 2008;11:471–84.
- [38] Brisson M, Sénécal M, Drolet M, Mansi JA. Health-related quality of life lost to rotavirus-associated gastroenteritis in children and their parents: a Canadian prospective study. *Pediatr Infect Dis J* 2010;29:73–5.
- [39] Marlow R, Finn A, Trotter C. Quality of life impacts from rotavirus gastroenteritis on children and their families in the UK. *Vaccine* 2015;33:5212–6.
- [40] Van der Wielen M, Giaquinto C, Gothefors L, et al. Impact of community-acquired paediatric rotavirus gastroenteritis on family life: data from the REVEAL study. *BMC Fam Pract* 2010;11:22.
- [41] Shim E, Galvani AP. Impact of transmission dynamics on the cost-effectiveness of rotavirus vaccination. *Vaccine* 2009;27:4025–30.
- [42] Atkins KE, Shim E, Carroll S, et al. The cost-effectiveness of pentavalent rotavirus vaccination in England and Wales. *Vaccine*, 2016;30:6766–76.
- [43] Pitzer V, Atkins KE, Blasio BF de, et al. Direct and indirect effects of rotavirus vaccination: comparing predictions from transmission dynamic models. *PLoS One* 2012;7:e423.
- [44] Huet F, Allaert F-A, Trancart A, et al. Economic evaluation of acute paediatric rotavirus gastroenteritis in France. [Article in French]. *Arch Pediatr* 2008;15:1159–66.
- [45] INSEE. France inflation rate. Available from: (<http://www.tradingeconomics.com/france/inflation-cpi>) [Accessed April 1, 2016].
- [46] Haute Autorité de Santé - Choix méthodologiques pour l'évaluation économique à la HAS 2011. Available from: (http://www.has-sante.fr/portail/jcms/r_1499251/en/choix-methodologiques-pour-l-evaluation-economique-a-la-has). [Accessed April 23, 2014].
- [47] Johannesson M. Avoiding double-counting in pharmacoeconomic studies. *Pharmacoeconomics* 1997;11:385–8.
- [48] Blumenschein K, Johannesson M. Economic evaluation in healthcare. *Pharmacoeconomics* 1996;10:114–22.
- [49] Brouwer WBF, Niessen LW, Postma MJ, Rutten FFH. Need for differential discounting of costs and health effects in cost effectiveness analyses. *BMJ* 2005;331:446–8.
- [50] L'évaluation socioéconomique des investissements publics (Tome1) | France Stratégie n.d. Available from: (<http://www.strategie.gouv.fr/publications/levaluation-socioeconomique-investissements-publics-tome1>). [Accessed January 12, 2015].
- [51] Atchison CJ, Stowe J, Andrews N, et al. Rapid declines in age group-specific rotavirus infection and acute gastroenteritis among vaccinated and unvaccinated individuals within 1 year of rotavirus vaccine introduction in England and Wales. *J Infect Dis* 2016;213:243–9.
- [52] Tate JE, Haynes A, Payne DC, et al. Trends in national rotavirus activity before and after introduction of rotavirus vaccine into the National Immunization Program in the United States, 2000–2012. *Pediatr Infect Dis J* 2013;32(7):741–4.
- [53] Theeten H, Hens N, Vandermeulen C, et al. Infant vaccination coverage in 2005 and predictive factors for complete or valid vaccination in Flanders, Belgium: an EPI-survey. *Vaccine* 2007;25:4940–8.
- [54] Hartwig S, Uhari M, Renko M, et al. Hospital bed occupancy for rotavirus and all cause acute gastroenteritis in two Finnish hospitals before and after the implementation of the national rotavirus vaccination program with RotaTeq®. *BMC Health Serv Res* 2014;14:632.
- [55] Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33.
- [56] Brüggjenjürgen B, Lorrot M, Sheppard FR, Rémy V. Do current cost-effectiveness analyses reflect the full value of childhood vaccination in Europe? A rotavirus case study. *Hum Vaccin Immunother* 2014;10:2290–4.