Budget Impact and Cost-Utility Analysis of Universal Infant Rotavirus Vaccination in Spain

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TITLE PAGE

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INTRODUCTION[1]

Rotavirus is a major cause of acute gastroenteritis in children worldwide (CDC, 2011). Although deaths due to rotavirus occur mostly in less-developed countries (Parashar et al., 2009), a substantial burden of Rotavirus Gastroenteritis (RVGE) has been reported in European countries (Giaquinto et al., 2007). In Spain, RVGE entails important morbidity and considerable resource utilization across all health care settings, as well as for families of patients and their employers (Diez-Domingo et al., 2010). It has been estimated that 181,626 episodes of acute gastroenteritis occur per year among children under 5 years of age in Spain (Díez-Domingo et al., 2010), which translates into 14,342 hospitalizations, 41,701 emergency department visits and 48,320 primary care visits with important implications for families, and society as a whole. Spanish parents miss, on average, 4.6 workdays when their child is hospitalized due to a rotavirus infection (Giaquinto et al., 2007).

Vaccination has proven to be effective in preventing rotavirus infections and limiting their impact (Vesikari et al., 2006). Although there are two rotavirus vaccines authorized for use in the European market, RotaTeq® and Rotarix®, our study has focused only on RotaTeq®, as it is the only vaccine available in Spain (Agencia Española de Medicamentos y Productos Sanitarios, 2010a; Agencia Española de Medicamentos y Productos Sanitarios, 2010b; Agencia Española de Medicamentos y Productos Sanitarios, 2010c). Currently the rotavirus vaccination is not included within the Spanish universal infant vaccination schedule, so RotaTeq® has to be purchased at market prices, as an out of pocket expense, if so desired.

The introduction of a new vaccine into the public immunization schedule would require a high resource investment and significant costs, taking into account that public vaccination programmes are, currently, completely publicly funded.

[1] RVGE: Rotavirus Gastroenteritis
QALY: Quality Adjusted Life Year
SNHS: Spanish National Health System
GP: General Practitioner
REST: Rotavirus Efficacy and Safety Trial
ICUR: Incremental Cost-Utility Ratio
NICE: National Institute for Clinical Excellence

Cost-utility studies have been performed in some European countries, though not in the Spanish setting, estimating the costs of adding a Quality Adjusted Life Year (QALY) with mass vaccination versus no vaccination and adopting time dependence models. The assessments have differed in their assumptions, choice of model, contextual information, and other parameters, but also in their results. Some of them have concluded in favour of the introduction of the universal rotavirus vaccination (Atkins et al., 2012; Jit et al., 2009). However, most of them have come to the conclusion that the introduction of the vaccine would not be efficient with the current conditions, although a lower vaccine price could achieve a cost-effective result(Bilcke et al., 2009; Mangen et al., 2010; Melliez et al., 2008; Rozenbaum et al., 2011; Tilson et al., 2011).

An economic evaluation of rotavirus vaccination has recently been published for a specific region in Spain, "Castilla y León" (Pérez-Rubio et al., 2011). The study estimates the cost-utility ratio based on a decision tree that does not take into account time evolution and second episodes. Our study tries to overcome these limitations, using a Markov model, to compare the cost-utility of the universal infant rotavirus vaccination in Spain using RotaTeq® versus no vaccination. In addition, we assessed the effect on these results of varying different variables that feed the model.

METHODS

A deterministic static Markov cohort model, adopting both the Spanish National Health System (SNHS) and the societal perspective, was developed for a hypothetical cohort of 500,000 newborns, which represents the approximate annual birth rate in Spain (INE, 2012). The model was built using the Tree Age Pro Suite 2011.

Two strategies were compared: one considering a fully publicly funded universal rotavirus vaccination with RotaTeq®, and the other considering no vaccination. In the vaccination strategy, children are vaccinated with RotaTeq®, at 2, 4 and 6 months. A 96% vaccination adherence rate was assumed, which corresponds to the average adherence rate reported for the Spanish infant vaccination programme in previous years (Ministerio de Sanidad, 2012).

The following health states were included in the model as represented in figure 1: 1) no previous infection (being at risk for rotavirus infection for the first time), 2) first rotavirus infection, 3) post first-infection (being at risk for a second rotavirus infection), 4) second rotavirus infection, 5) post second-infection, 6) rotavirus death, and 7) non rotavirus death (death by causes other than rotavirus).

The model´s time horizon was five years with one month time cycles. In each monthly cycle, children in the cohort have a risk of getting rotavirus-induced diarrhoea. Diarrhoea may lead to consultation of a General Practitioner (GP), visit to an emergency service, not seeking any medical attention or death. The GP may send patients to the emergency service or home. Once a patient seeks emergency service attention, they can be hospitalized or sent home. A child can be confronted with a second episode, but this one is assumed not to be severe and never lead to death by rotavirus infection. We also assume that the child is fully immune after two rotavirus infections. Only severe consequences were assumed for a first infection as rotavirus immunity acquisition has been reported (Velázquez, 2009; Ward et al., 1994).

Clinical parameters

The probabilities of getting a rotavirus infection were derived from the Spanish epidemiological data included in the REVEAL study (Van Damme et al., 2007) (table 1). This is a broad sample of Spanish rotavirus infection incidence data, from 2 hospitals, 3 emergency departments and 23 primary care centres that registered rotavirus infections between October 2004 and September 2005, for children under the age of 5. These data were based only on community-acquired infections, excluding nosocomial ones.

Mortality rates for children under the age of 5 were derived from the 2009 mortality data reported by the Spanish Statistical Institute (INE, 2012) (table 1). Transition probabilities regarding natural history and health care utilization after episodes of rotavirus infection are displayed in table 2. Due to the lack of available Spanish data, we assumed the transition probabilities of risk reduction after a first rotavirus infection reported in a rotavirus vaccine trial conducted along two years in the USA (Ward et al., 1994). We assumed the same transition probabilities regarding health care utilization as those found in the French and Finnish economic evaluations (Melliez et al., 2008; Takala et al., 1998).

Regarding efficacy of Rotateq® to avoid rotavirus infection among children, we used data from the Rotavirus Efficacy and Safety Trial (REST) (Vesikari et al., 2006). To the best of our knowledge, this is the only randomized trial that evaluates the efficacy of the vaccine among children of developed countries with a long follow-up period. This randomized controlled trial studied nearly 70,000 children from eleven, mostly developed, countries, reporting 74% higher efficacy for RotaTeq® vaccination compared to placebo in preventing first rotavirus episodes (CI95%: 66.8-79.9). Our base case used the efficacy in the REST trial for all rotavirus infections, regardless of severity. We assumed no herd immunity and no-waning vaccination efficacy during the five year period.

Costs and utilities

The analysis was performed both from the societal and the national health care payer (SNHS) perspectives. The societal perspective analysis included both direct (health care and non-health care) and indirect costs (table 3), but the SNHS perspective included only direct medical costs. Costs are described in table 3 and derive from the estimations for Spain included in the REVEAL study (Giaquinto et al., 2007), and were updated to 2011 using the Laspeyres index, recommended by the Spanish Statistics Institute (INE, 2012).

GP visits, emergency visits, telephone consultations, medication, home assistance, diagnostic and therapeutic procedures during hospitalization were included as direct medical costs. The SNHS perspective included only the direct medical costs reimbursed. However, the societal perspective included both reimbursed and non-reimbursed direct medical costs. Costs of hospitalization procedures were estimated using Diagnostic Related Groups. Medication consumption was estimated based on the average consumption for Spanish patients in the REVEAL study.

Caregiver expenses, extra nappies and transport-related costs were included as direct non-medical costs. Working days lost by parents or caregivers under the age of 65 were also included as indirect costs.

The manufacturer's sales prices for RotaTeq® in September 2011 were used in the base-case analysis (44.5€ per dose). We included the manufacturer's price and not the retail price as it was assumed that this vaccine would be purchased by the public administration and not by individuals themselves.

We assumed the vaccination process would not generate additional administration costs as the vaccine would be given orally to children in the currently planned visits in the Spanish vaccination programme.

As no specific utility data for Spanish children having RVGE were found, recently published data from a prospective Canadian study was used regarding loss of quality of life estimated for children under the age of three who have suffered RVGE, and their parents (Brisson et al., 2010). The Canadian study estimated that a rotavirus infection reduces 0.0022 QALYs per child and 0.0018 QALYs for parents in a year. Therefore, we assumed that a rotavirus infection produces a 0.004 QALY reduction in a year, which is the result of adding the loss of quality of life of a parent to the reduction in quality of life of a child.

Analysis

We calculated the incremental unitary effects (incremental QALY) by calculating the difference between QALY obtained for a vaccinated in comparison with a no vaccinated child. The incremental costs were determined by calculating the difference between the incurred costs for the whole cohort with and without vaccination. The unitary costs are calculated by dividing these quantities by 500,000, which is the number of included children in the cohort. The incremental Cost-Utility Ratio (ICUR) was calculated dividing the incremental unitary cost by the incremental unitary effect. Although there is no explicit acceptability threshold for inclusion in the Spanish NHS Benefits, we assumed 30,000 € per QALY as it is the most quoted figure in the Spanish literature (Sacristán et al., 2002).

One-way sensitivity analyses were performed by modifying parameters, decreasing and increasing values by 50% and checking the consequences on the incremental cost-utility ratio. We tested the following variables, taking into account the parameters introduced for the societal perspective model: vaccine coverage, vaccination price, intervention costs, vaccine efficacy for the first infection, mortality probabilities, risk reduction after a first episode, severity risk, transition probabilities of no care, transition probabilities of outpatient care, transition probabilities of emergency department visits and transition probabilities of hospitalization after emergency consultation.

Following the recommendations of the Spanish Consensus on Health-Care Economic Evaluation Methodology, we adopted discount rates of 3% both for costs and health outcomes (López-Bastida et al., 2008). All costs were expressed in 2011 Euros.

RESULTS

The economic impact for the health care budget of introducing universal infant rotavirus vaccination with RotaTeq® in Spain would be 10.43 million Euros per year (table 4), which results from dividing the incremental costs from the SNHS perspective by five years. On the other hand, the impact from the societal perspective would be lower as the incremental cost per year would be 7.83 million Euros.

Under the base case assumption, the vaccination strategy would be more expensive than the non-vaccination strategy, but it would also mean an increase in the average utility (QALYs) obtained in five years. From the societal perspective, an increase in one QALY per child in the vaccination strategy would cost an average of 210,167€. The ICUR would be even higher from the SNHS perspective, with an average cost of 280,338€/QALY gained.

The univariate sensitivity analyses showed that only variations in vaccine price, vaccination efficacy and utility scores in case of infection could produce appreciable changes in the ICUR. Variations up to 50% of the values for the rest of the parameters did not produce ICUR variations of more than 10%. For the three variables that produced changes greater than 10% in the ICUR, severe reductions of the values were required to reach acceptable ICUR values (considering an ICUR threshold of 30,000€/QALY).

Regarding vaccine price, our base case included a RotaTeq® dose price of 44.5€, resulting in an ICUR of 210,167€/QALY. A decrease by half in the RotaTeq® price (22€/dose) would decrease ICUR to 40,140 €/QALY. If the price were reduced to 21€/dose, the ICUR would decrease to an acceptable threshold of 32,584€/QALY (figure 2).

However, acceptable ICURs remain unreachable despite considering greater vaccination efficacy values. If we consider the 95% confidence intervals of efficacy reported in the REST trial (ie: 67-80% efficacy), the ICUR which results for an efficacy of 80% would be 176,579€/QALY, far from an acceptable threshold in Spain (figure 3). Even, if a 100% efficacy is considered, the resulting ICUR remains unacceptable (105,179€/QALY).

Other variables that produced significant changes in the results include the utility value used to score infection episodes. In the base case, we assumed that a rotavirus infection episode reduces 0.004 QALYs in a year. In our sensitivity analysis, a favourable QALY reduction of 0.006, which is an increase of 50%, did not reach an acceptable ICUR (124,287€/QALY) (figure 4). Even a reduction of 0.009 QALY is still far from an acceptable threshold in Spain for the introduction of the universal infant rotavirus vaccination, as it would mean a cost of 74,150€ to gain an additional QALY.

DISCUSSION

According to our results, the introduction of universal infant rotavirus vaccination using RotaTeq® would not be efficient in Spain and would only lead to a small improvement in quality of life at high costs. From the societal perspective, the gain of an additional QALY would cost an unaffordable amount, which would be even greater from the National Health Service perspective. In addition, the implementation of a vaccination programme against rotavirus offered to all Spanish infants between 2 and 6 months of age using RotaTeq®, would require an increase in the health care budget of more than ten million euros per year.

Our model was stable to changes in most variables. Even significant changes in most variables, did not manage to reach acceptable cost-utility ratios. In order to reach acceptable ICUR values, the laboratory price of RotaTeq® would need to be halved. Variations in other variables were not sensitive enough to decrease ICUR to acceptable values.

Although there are no explicit ICUR threshold values in Spain, our ICUR are significantly higher than those used or proposed in Western countries. The National Institute for Clinical Excellence (NICE) has specified a threshold value between GB£ 20,000 and 30,000 per QALY (NICE, 2008) (which corresponds to 24,645 – 36,968€ using the exchange rate on 17th Dec 2012). Other figures have been mentioned in the literature for other Western countries but they are not official, unlike those specified by NICE.

In the USA, the figure of US$ 50,000/QALY (38,009€, using the exchange rate on 17th Dec 2012) has frequently been quoted (Eichler et al., 2004). In Spain, despite no explicit threshold, the most quoted figure has been 30,000 €/QALY (Sacristán et al., 2002), which was the threshold reference we assumed for our analysis.

Our study is affected by several limitations. There are uncertainties about the epidemiology of rotavirus infection as actual rotavirus infection is difficult to estimate. Our incidence data were based on a rigorous study that investigated incidence from several large centres of the three levels of health care in Spain: hospital, primary and emergency care. As in other countries happen, the incidence of acute rotavirus may be underestimated due of the large amount of infections that usually remain undetected by the health care system. Many patients with AGE may not seek medical treatment. In addition, because detection of rotavirus in stools does not influence treatment, physicians do not collect stool samples from patients, thus leading to underdiagnoses of RVGE in many children.

Because of the scarcity of precise information, we have not included nosocomial or home treated infections in the model. In addition, home treated infections are generally mild, and as our model was stable to changes in variables related to infection probabilities, we would not expect these variables to cause relevant reductions in the cost-utility values. The same as other authors have done, our model assumed that two infections could show the most relevant differences between states related to this infection (Melliez et al, 2008; Bilcke et al, 2009; Jit et al, 2009) although this modelization may lead to an underestimation.

Our model does not take into account herd immunity, which could lead to an underestimation of the vaccine´s effect for the unvaccinated individuals, approximately 4% in Spain, (Ministerio de Sanidad, 2012) and outside the vaccinated cohort. The estimation of the indirect protective effect attributable to rotavirus vaccination is affected by uncertainties, some regarding the existence of accurate parameters but also because of lack of consistency in the results of the studies that took into account herd immunity assessing rotavirus vaccination. Recently, two differing studies that included herd immunity in their models have been published. The England and Wales' study found, after ten years of follow-up, that rotavirus vaccination with RotaTeq® would be efficient for a wide range of scenarios having assumed a threshold of 30,000 £/QALY (Atkins et al., 2012). However, the Dutch evaluation, after a 20 year follow-up, achieved results between 55,000 and 58,000 €/QALY from the societal and healthcare perspective, respectively (Mangen et al., 2010), concluding that only much lower vaccine prices and/or large indirect effects by herd immunity would lead to acceptable ICUR estimates for the Netherlands.

We assumed no waning efficacy due to the lack of evidence for a decreasing efficacy after a five-year follow up (Melliez et al., 2008). In addition, we had to use non-Spanish sources of information to feed transition probabilities into the model due to the scarcity of Spanish-specific information on the parameters related to the natural history and medical management of rotavirus infections.

When comparing with other similar studies, we also found limitations due to the scarcity of accurate information but also differences in the models, assumptions and settings. Bilcke et al performed an evaluation in Belgium using a static model with a seven year follow-up, and taking into account a waning effect on efficacy. They compared the efficiency of a fully funded universal vaccination using RotaTeq® against a scenario of “no vaccination”, and found an ICUR of 30,227€/QALY from the societal perspective and 65,767€/QALY from the healthcare perspective (Blicke et al., 2009).

The results of the base case of the five European countries comparison were based on the following assumtions: a threshold value of 30,000€/QALY gained, vaccination with RotaTeq®, the healthcare provider perspective was considered, no herd immunity was taken into account, and they included in their calculations the quality of life of one caregiver. They found that rotavirus vaccination would be nearly cost-effective for Finland, but clearly not cost-effective for Belgium, England and Wales, France, and the Netherlands (Jit et al., 2009).

Our study evaluated the introduction of rotavirus vaccination in Spain using only Rotateq®, but not Rotarix®, as it is currently not used in Spain. Nevertheless, we would not expect important differences in the results for Spain if the evaluation were based on the alternative vaccine, because the reported differences in terms of efficacy and cost-utility between Rotarix® and Rotateq® appear to be small (Bilcke et al., 2009; Mangen et al., 2010; Tilson et al., 2011).

Our model and assumptions are similar to those that Melliez et al made, in the French setting, to evaluate the introduction of rotavirus vaccination compared to "no vaccination" (Melliez et al., 2008). The study used a static Markov model with a follow-up of three years, and estimated an ICUR of 151.000 €/QALY from the societal perspective. This ICUR would not be radically reduced unless the price of the vaccine decreased considerably. Thus, we should be cautious when comparing the results obtained in different countries using different models and input data.

We have also seen that our results are stable and only radical changes in vaccine price, vaccination efficacy and/or utility scores in the case of infection would achieve acceptable cost-utility values. An additional strength of our study is that we have incorporated the societal perspective, including transport, extra diapers and lost working days as indirect costs, which is determinant in the measurement of the impact of this disease. In addition, our utilities measurement took into account indirect consequences, incorporating information of one caregiver, which is relevant in the evaluation of paediatric interventions.

Our study aimed to provide information for a highly debated topic in Europe nowadays, the prioritization of public health programmes. Currently, there are several positions from different European countries that have already made a decision. Some have introduced mass rotavirus vaccination in public programmes (Austria, Belgium, Luxembourg, Finland and Greece), while others have recommended against the introduction, after an economic evaluation was available (France, England, Wales, Netherlands) (Atkins et al., 2012; Jit et al., 2009). On the other hand, it seems more justified to introduce rotavirus vaccination, and at lower prices, in those countries with higher mortality rates, which do not include western European countries such as Spain (Fischer et al., 2005; Melliez et al., 2007).

Conclusion

According to our model and estimates, the introduction of a universal infant rotavirus vaccination in Spain would cause a large impact on the health care budget and would not be efficient unless large variations in vaccine price, vaccine efficacy and/or utilities took place.

Conflict of interest statement:

The authors declare that there are no conflicts of interest.

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