Burden of paediatric Rotavirus Gastroenteritis (RVGE) and potential benefits of a universal Rotavirus vaccination programme with a pentavalent vaccine in Spain

Javier Diez-Domingo¹, Nuria Lara Suriñach²*, Natalia Malé Alcalde², Lourdes Betegón², Nathalie Largeron¹, Mélanie Trichard³

Abstract

Background: Rotavirus is the most common cause of gastroenteritis in young children worldwide. The aim of the study was to assess the health outcomes and the economic impact of a universal rotavirus vaccination programme with RotaTeq, the pentavalent rotavirus vaccine, versus no vaccination programme in Spain.

Methods: A birth cohort was followed up to the age of 5 using a cohort model. Epidemiological parameters were taken from the REVEAL study (a prospective epidemiological study conducted in Spain, 2004-2005) and from the literature. Direct and indirect costs were assessed from the national healthcare payer and societal perspectives by combining health care resource utilisation collected in REVEAL study and unit costs from official sources. RotaTeq per protocol efficacy data was taken from a large worldwide rotavirus clinical trial (70,000 children). Health outcomes included home care cases, General Practitioner (GP)/Paediatrician, emergency department visits, hospitalisations and nosocomial infections.

Results: The model estimates that the introduction of a universal rotavirus vaccination programme with RotaTeq (90% coverage rate) would reduce the rotavirus gastroenteritis (RVGE) burden by 75% in Spain; 53,692 home care cases, 35,187 GP/Paediatrician visits, 34,287 emergency department visits, 10,987 hospitalisations and 2,053 nosocomial infections would be avoided. The introduction of RotaTeq would avoid about 76% of RVGE-related costs from both perspectives: €22 million from the national health system perspective and €38 million from the societal perspective.

Conclusions: A rotavirus vaccination programme with RotaTeq would reduce significantly the important medical and economic burden of RVGE in Spain.

Background

Acute Gastroenteritis (AGE) is a common disease among children in both developed and developing countries, with rotavirus as the principal etiologic agent[1,2]. As it is a highly contagious virus, almost all children will suffer from paediatric rotavirus gastroenteritis (RVGE) before 5 years of age[3]. Verstraeten et al[4] estimated that 4.5 million episodes of RVGE occur each year in the European Union among children up to 5 years old. The classical symptoms of the disease are diarrhoea, vomiting and fever[5].

Although death due to RVGE is rare in developed countries, there is an important morbidity related to the disease as well as a substantial economic burden associated with its management[6]. RVGE is a major reason for hospitalisation, and it is responsible for an important number of nosocomial infections in paediatric wards, which increase the medical resources required for treating these children with RVGE[7,8]. According to Gil et al[3], the annual incidence of hospital admissions attributable to rotavirus is 1.0 per 1000 children ≤5 years,
although it can be as high as 2.5 per 1000 children ≤5 years during the winter season. Overall, these authors estimated that the annual number of days of hospitalisation attributable to rotavirus exceeds 8,700 in Spain. Another important consequence of the disease is the workdays lost by parents and caregivers[9,10]. This has been estimated to account for 75% of total costs of RVGE in a primary care setting in Italy[11]. Recent publications in different European countries have added information about the burden and costs of the disease as well as the potential benefits of a universal vaccination programme[9,12-19].

An oral, pentavalent rotavirus vaccine (RotaTeq), which has recently been licensed in Europe, has been shown to be highly efficacious and safe in a large-scale phase III trial (Rotavirus Efficacy Safety Trial; REST) [20]. This vaccine offers protection against G1, G2, G3, G4 and P[8] serotypes, which are responsible for 98% of all RVGE episodes[21] in Europe, and is available in Spain. Several published studies have suggested that effective rotavirus immunisation would provide large health and economic benefits in Europe[22,23]; however, no specific data about the potential benefits of a universal rotavirus vaccination programme in Spain were available until now. The objective of this study was to assess the potential health and economic benefits of a universal vaccination with a pentavalent rotavirus vaccine (RotaTeq) from the National Health System (NHS) and societal perspectives in the Spanish setting using a modelling approach. The present study is not a cost-effectiveness analysis.

Methods
Model design
A health-economic cohort model was developed to assess the costs and health benefits of a universal rotavirus vaccination programme with RotaTeq versus no rotavirus vaccination programme by simulating the flow of a hypothetical cohort of infants from birth to 5 years. Under each scenario, children may experience or not a RVGE episode, which may be either community or hospital acquired. When community cases occurred, patients may seek medical attention either at a primary care centre (PCC), at an emergency room (ER) or at hospital. Also, patients may not seek medical attention and only require home care. Hospital acquired episodes (nosocomial infections) were assumed to require additional days of hospitalisation. The “vaccination strategy” arm included children receiving and not receiving the vaccine with a coverage rate of 90%[24]. The structure of the decision model is shown in Figure 1.

Based on incidence data, each children was at risk of RVGE with corresponding resource consumption and costs, which were obtained from different sources: the Rotavirus Gastroenteritis Epidemiology and Viral Types Accounting for Losses in Public Health and Society (REVEAL) epidemiological study[25], the REVEAL costs study[26], the Rotavirus Efficacy & Safety Trial (REST)[20], national statistics[27], and from an extensive literature review[28-35]. A discount rate of 3% was applied to both costs and benefits based on results from recent Spanish pharmacoeconomic studies[36,37].

![Figure 1 Model tree overview - Rotavirus vaccination program versus no Rotavirus vaccination program. PRG: Paediatric Rotavirus Gastroenteritis (RVGE)
Model inputs

Epidemiological data

Epidemiological data for patients seeking medical attention were obtained from the REVEAL study[25], which was the first European-wide epidemiological study about rotavirus, specifically conducted to measure epidemiological consequences and the burden of RVGE. This prospective, multicenter, observational study on children up to 5 years old with AGE was performed between October 2004 and September 2005 in seven European countries including Spain. In Spain, two hospitals, three ERs and twenty-three PCCs participated in the study and a total of 801 children were included. A total of 252 of the 772 stool samples analysed for the presence of rotavirus, by an ELISA test, were positive (32.6%). A questionnaire was completed for each child included to collect data on resource utilisation (consultations, hospitalisations, drug consumption, clinical services, extra childcare, transportation and additional nappies) and number of parental workdays lost. These data were used to estimate annual incidence rates of RVGE consultations at hospital, ER and PCC, and to evaluate the impact of RVGE on the health care system (health care consumption) and the society (productivity loss).

Based on the REVEAL study[25], the annual incidence rates for hospitalisations, ER and PCC consultations in patients with RVGE seeking medical attention were 6.5/1,000, 18.9/1,000 and 21.9/1,000, respectively. Age-specific incidences were calculated for seven age groups (0-3 months, 3-6 months, 6-12 months, 1-2 years, 2-3 years, 3-4 years and 4-5 years) by deriving annual incidences with the specific age group distribution obtained from REVEAL study.

The proportion of children with RVGE who did not seek medical care was estimated to be 41.4%. As such data is not available for Spain; this estimate was taken from the incidence observed in a study performed in a daycare centre in France (Lyon)[33].

The age group distribution for children who did not seek medical care was assumed to be similar to the one observed in children visiting a PCC estimated in the REVEAL study[25].

The incidence of nosocomial infection in children up to 5 years used in the model was 1.6/1,000[29]. The age group distribution was derived from the percentages reported from Gleizes et al[29] and Forster et al[38]. The average extra length of stay due to nosocomial infections was assumed to be 2.4 days based on the average results from two Spanish publications[30,31].

According to the Spanish National Statistics Institute for 2004 (INE)[27], the annual number of births in Spain was 441,283 and life expectancy was 78.7 years (average for males and females, year 1998). UNICEF[28] has reported a mortality rate for children under 5 years in Spain of 4/1,000. The epidemiological parameters for the model are shown in Table 1.

Vaccine parameters

The efficacy and safety of the pentavalent rotavirus vaccine (RotaTeq) have been demonstrated in the REST trial[20], a large-scale, double-blind, placebo controlled, randomised international trial conducted from 2001 to 2004 in 11 different countries which included 70,301 healthy infants aged between 6 and 12 weeks. Children received three doses of the oral vaccine or placebo, at 2, 4 and 6 months, with 4 to 10 weeks intervals between doses.

Per-protocol efficacy data against G1-G4 RVGE cases was used in the model. Based on REST data, a reduction of 95.8%, 93.7% and 86.0% in the incidence of hospitalisations, ER, and GP visits respectively was assumed for all vaccinated children. Although REST data specifically relates to G1-G4 RVGE, the reduction in health care utilisation due to serotypes other than G1-G4 was considered to be the same as for vaccine-contained serotypes[16]. RotaTeq also contains P[8], a predominant genotype and the most common P-type associated with human RV strains in Europe and worldwide. Studies suggest vaccines containing the serotype P[8] may protect against other G-serotypes, such as G9, which was confirmed for RotaTeq in the REST study. G1, G2, G3, G4 and G9 serotypes account for 98% of RVGE cases in Spain[21].

As it was not specifically evaluated in the clinical study, it was assumed that the vaccine efficacy for nosocomial infections was similar to that observed for hospitalisation, and that for patients not seeking medical care was similar to that observed for PCC visits.

Vaccine efficacy was considered to be nil in the 0-3 months age group, and full protection started from the 3-6 months age group.

The model took into account the waning immunity observed in REST[20], which was a 10% decrease in vaccine efficacy 2 years post-vaccination. The vaccine coverage rate was assumed to be 90%, based on the observed coverage for common routine vaccinations in Spain (diphtheria, tetanus and pertussis)[24]. The vaccine parameters used in the model are shown in Table 2.

Cost data

Costs were assessed from both NHS and societal perspectives. Costs for children who were hospitalised, or who had ER and PCC visits were obtained from the Spanish REVEAL study of costs[26]. Cost of nosocomial infections was calculated based on an estimated extra length of stay of 2.4 days and the cost per day of hospitalisation of €310[31]. It was assumed that 68.3% of parents had to take time off work for children who were hospitalised[25]. Costs for children not seeking medical
Table 1 Data for demographics, epidemiological and parental work days lost

| Model parameters                              | Value     | References |
|-----------------------------------------------|-----------|------------|
| **Demographics**                              |           |            |
| Birth cohort size                             | 441,283   | 23         |
| Life expectancy                               | 78.7 years| 23         |
| Mortality rate in case of no vaccination < 5 years | 4/1,000  | 24         |
| % of cases not seeking medical care           | 41.4%     | 29         |
| % of G1-G2-G3-G4                              | 97%       | 17         |
| **RVGE Burden (< 5 years)**                   |           |            |
| Annual hospitalization incidence rate         | 6.5/1000  | 21         |
| Age group distribution (%)                    |           |            |
| < 3 months                                    | 7.69      |            |
| 3-6 months                                    | 5.77      |            |
| 6-12 months                                   | 17.31     |            |
| 12-24 months                                  | 34.62     |            |
| 24-36 months                                  | 21.15     |            |
| 36-48 months                                  | 9.62      |            |
| 48-60 months                                  | 3.84      |            |
| Annual emergency visits incidence rate        | 18.9/1000 | 21         |
| Age group distribution (%)                    |           |            |
| < 3 months                                    | 1.0       |            |
| 3-6 months                                    | 16.0      |            |
| 6-12 months                                   | 22.0      |            |
| 12-24 months                                  | 46.0      |            |
| 24-36 months                                  | 11.0      |            |
| 36-48 months                                  | 3.0       |            |
| 48-60 months                                  | 1.0       |            |
| Annual PCC visits incidence rate              | 21.9/1000 | 21         |
| Age group distribution (%)                    |           |            |
| < 3 months                                    | 3.06      |            |
| 3-6 months                                    | 6.12      |            |
| 6-12 months                                   | 22.45     |            |
| 12-24 months                                  | 39.80     |            |
| 24-36 months                                  | 19.39     |            |
| 36-48 months                                  | 6.12      |            |
| 48-60 months                                  | 3.06      |            |
| Annual nosocomial infection incidence rate    | 1.6/1000  | 25         |
| Age group distribution (%)                    |           |            |
| < 3 months                                    | 31.85     |            |
| 3-6 months                                    | 16.15     |            |
| 6-12 months                                   | 26        |            |
| 12-24 months                                  | 19        |            |
| 24-36 months                                  | 5.5       |            |
| 36-48 months                                  | 1.5       |            |
| 48-60 months                                  | 0         |            |
| **Parental work days lost**                   |           |            |
| (mean number of days/paediatric case)         |           |            |
| Hospitalized RVGE case                        | 3.12      | 21         |
| RVGE case seen in emergency visit             | 2.02      | 21         |
| RVGE case seen in PCC visit                   | 1.37      | 21         |
| RVGE nosocomial infection                     | 1.63      | Assumption based on 21, 26, 27 |
| RVGE not seeking medical attention            | 0.26      | Assumption based on 37 |
care were considered from the societal perspective. It was estimated that an average of 0.26 workdays were lost per episode not involving medical care, based on the assumption that mothers would stop working half a day, and taking into account that 51% of mothers work outside their home[39]. Unit costs from local sources[40-45] were used to value each resource. The cost parameters used in the model are presented at Table 3.

- **Direct medical costs** According to each healthcare setting, direct medical costs for consultations, hospitalisations including, medication and laboratory tests were considered. Hospitalisation costs were calculated using DRG data (Diagnostic-Related Groups).

In Spain, the cost of consultations, hospitalisations and laboratory tests are fully covered by the NHS. The prescribed medication costs are shared between the patients and the NHS based on a fixed percentage (40% for the patients and 60% for the NHS). Over-The-counter (OTC) drugs are not reimbursed by the NHS.

- **Non-medical costs** The non-medical costs included transportation (car or taxi), extra nappies and baby sitting; which were extracted from the REVEAL study[26]. These costs are paid by the patients.

- **Indirect costs** Work days lost by parents seeking medical care for their child was estimated at 3.12 days for hospitalisation, 2.02 days for emergency room visits and 1.37 days for PCC offices visits[26]. For those who did not seek medical care the number of workdays lost was estimated to be 0.26 days based on the assumptions that 51% of mothers work outside the home[39] and that they stopped working for half a day to take care of their children. The cost for one workday lost was 93.3€ based on Eurostat data[44]. Indirect costs were included in the societal perspective.

**Model outcomes**
The model was developed to compare the health outcomes (number of RVGE cases whether or not seeking medical care, number of hospitalisations, number of ER and PCC visits and number of nosocomial infections) and costs from NHS and societal perspectives for the vaccination and not vaccination scenario.

The number needed to vaccinate (NNV) for Spain was calculated using data from the health economic model for a vaccinated birth cohort. This gives the number of children to vaccinate to avoid one child seeking medical care (hospitalisation, ER visit, PCC) due to RVGE. The NNV was calculated following Brisson et al [13] method which assessed the NNV to prevent Human PapillomaVirus (HPV) related diseases. It is defined as the reciprocal of the percentage of children seeking medical care in the group without rotavirus vaccination minus the percentage in the group with rotavirus vaccination.

- **Sensitivity analyses**
Since some parameters may present uncertainty, a one-way deterministic sensitivity analyses was performed, using 95% confidence intervals (CI) when available, data from the literature or varying the base case value with a fixed percentage (± 20%) when no other source could be considered. The variables that were tested were the vaccine coverage rate, the vaccine efficacy in reduction of RVGE cases, the vaccine efficacy annual rate by age, epidemiological data, costs of the disease and discount rates (Table 4).

**Results**
**Burden and costs of RVGE in Spain**
The model estimated that each year, 181,626 children would have an RVGE episode, resulting in 14,342 hospitalisations, 41,701 visits to an ER, 48,320 visits to a PCC, 3,530 nosocomial infections and 210,404 workdays lost.

---

**Table 2 Vaccination parameters**

| Parameters                  | Value | Source     |
|-----------------------------|-------|------------|
| Coverage rate               | 90%   | 20         |
| Vaccine efficacy (%)        |       |            |
| Hospitalizations reduction  | 95.80 | 16         |
| Emergency visits reduction  | 93.70 | 16         |
| PCC visits reduction        | 86.00 | 16         |
| Nosocomial infections       | 95.80 | Assumption: same as hospitalization |
| reduction                   |       |            |
| Cases not seeking care      | 86.00 | Assumption: same as PCC |
| reduction                   |       |            |
| Waning rate after 2 years   | 10%   | Based on REST (16) and expert opinions |

---

**Table 3 Cost per RVGE cases**

| Parameters                  | NHS perspective | Societal perspective | Source |
|-----------------------------|-----------------|----------------------|--------|
| RVGE cases not seeking care | 0 €             | 23.80 €              | Assumption based on 37, 42 |
| Hospitalized RVGE cases     | 1,248.99 €      | 1,551.70 €           | 22     |
| Emergency visit RVGE cases  | 204.29 €        | 408.87 €             | 22     |
| PCC RVGE cases              | 16.61 €         | 165.89 €             | 22     |
| Nosocomial infection cost   | 744 €           | 896.80 €             | Assumption based on 26, 27, 42 |
days lost for the parents. In addition, 73,733 cases would not seek medical care.

The annual costs due to RVGE in children under 5 years old were estimated to be €28.6 million from the NHS perspective, while, from the societal perspective, they were estimated to be €50.0 million.

Expected health and economic benefits from a universal rotavirus vaccination programme
The implementation of a 3-dose universal rotavirus vaccination programme with RotaTeq would have a positive impact on public health in Spain since, assuming a 90% coverage rate, the programme would prevent 136,190 episodes of RVGE annually. This would lead to the prevention of 10,981 hospitalisations (-76%), 34,287 ER visits (-82%), 35,187 consultations with a PCC (-73%), 2,053 nosocomial infections (-58%) and 53,692 RVGE episodes for which no medical care is sought (-73%). Furthermore, the programme would avoid 161,495 work days being lost (-77%) (Table 5).

The model predicted that for every 5 infants vaccinated with RotaTeq, one need for medical care for RVGE (hospitalisation, ER visit, PCC) would be avoided. Based on the benefits of vaccination, the model predicted that the total costs associated with RVGE in a Spanish birth cohort followed up to 5 years of age would be reduced by €22 million for the NHS (-76.3%) and lead to an overall reduction of €38 million from the societal perspective (-76.5%) (Figure 2).

Sensitivity analyses
Health and economic outcomes were most sensitive to changes in the vaccine coverage rate and health care setting incidences. Benefits of a universal rotavirus vaccination programme would be increased if the vaccine coverage was higher, which is an expected finding in the health economic evaluations of vaccines. The same effect would be observed with the increase in the rotavirus incidence at any setting, the vaccine efficacy and the costs.

Hospitalisation incidence was tested based on an assumed 20% variation. For the higher value, the overall number of avoided paediatric rotavirus hospitalisations would be increased in comparison to the base case from 10,981 to 13,184 and consequently the overall avoided paediatric RVGE costs from €22 to €25 million and
from €39 to €42 million from the NHS and the societal perspectives, respectively. Work days lost by parents were more sensitive to the variations in the incidence of emergency visits than to variations in hospitalisations incidence; a 20% increase in emergency visits would result in 14,376 extra days lost in comparison to the base case. The results of the sensitivity analyses are shown in Table 6.

**Discussion**

AGE is a frequent disease, with rotavirus being the main cause in children under 5 years of age. The burden of RVGE is considerable both in terms of clinical and economic considerations[6,46,47]. To our knowledge this is the first study to estimate the burden of paediatric RVGE, the associated direct and indirect costs, and the potential health and economic benefits of a universal rotavirus vaccination programme in Spain. The model predicted that RVGE would be responsible for more than 181,600 infections for every new birth cohort in Spain followed up to 5 years of age and would result in intensive use of health care services as well as more than 210,000 work days lost by parents. The implementation of a universal vaccination programme for infants in Spain could potentially reduce the overall clinical burden of RVGE by 75% and save 76% of costs from both the NHS and the societal perspectives.

We estimate that RVGE is responsible for more than 14,000 hospitalisations a year in children up to 5 years old in Spain. This incidence is higher than that previously reported, which was 9,000 days of hospitalisation a year in children of the same age group[3]. The difference might be explained by the methodology used since in the previous study hospitalisation for RVGE was estimated using data on laboratory reports and hospital admissions due to AGE. Our data were based on the results from a recent prospective epidemiological and cost-of-illness study (REVEAL)[25], which included all children aged up to 5 years old with RVGE over a one year period in one Spanish region, so our estimation might reflect the current burden of hospitalisations due to RVGE in Spain.

**Table 5 Base case health outcomes under the current context and under a universal rotavirus vaccination program for a birth cohort followed until 5 years**

| RVGE cases seeking medical care | No rotavirus vaccination program | With rotavirus vaccination program | Avoided cases with rotavirus vaccination program | Reduction (%) |
|--------------------------------|---------------------------------|-----------------------------------|-----------------------------------------------|---------------|
| Hospitalizations               | 14,342                          | 3,355                             | 10,987                                        | -76%          |
| Emergency visits               | 41,701                          | 7,414                             | 34,287                                        | -82%          |
| PCC visits                     | 48,320                          | 13,133                            | 35,187                                        | -73%          |
| Nosocomial infections          | 3,530                           | 1,477                             | 2,053                                         | -58%          |
| **RVGE cases not seeking medical care** | **73,733** | **20,040**                        | **53,692**                                    | **-73%**      |
| Total RVGE cases               | 181,626                         | 45,420                            | 136,206                                       | -75%          |
| Parental work days lost        | 210,404                         | 48,909                            | 161,495                                       | -77%          |

![Figure 2 RVGE economic burden in Spain with and without a universal rotavirus vaccination program.](image-url)
The annual incidence rates for PCC consultations in patients with RVGE seeking medical attention assumed in this study based on REVEAL, is very similar to the results in other previous studies performed in Spain [48,35].

Furthermore a recent review of prospective studies suggested that the total burden of symptomatic rotavirus infection does not differ significantly between studies in different countries around the world, even though use of health care by infected patients does [49].

A recent study [50] in the Galician area of Spain estimated that the mean indirect cost per case due to RVGE was €428. This cost included productivity loss, travel expenses, cost of caregivers, meals and materials. Although our definition of indirect costs referred only to productivity loss, our model included transportation,

Table 6 Results of the sensitivity analyses

| Number of events avoided | RVGE cases (seeking or not medical care) | Hospitalizations | Nosocomial infections | Emergency visits | PCC visits | Work Days Lost | RVGE costs avoided (M€) | NHS perspective | Societal perspective |
|--------------------------|------------------------------------------|------------------|----------------------|-----------------|------------|----------------|-----------------------|-----------------|---------------------|
| BASE CASE                | 136,190                                  | 10,987           | 2,053                | 34,287          | 35,187     | 161,495        | 21.77                 | 38.19           |
| SENSITIVITY ANALYSES    |                                          |                  |                      |                 |            |                |                       |                 |
| Vaccine coverage rate    |                                          |                  |                      |                 |            |                |                       |                 |
| 50%                     | 75,670                                   | 6,104            | 1,141                | 19,049          | 19,548     | 89,719         | 12.09                 | 21.20           |
| 97%                     | 146,800                                  | 11,841           | 2,213                | 36,954          | 37,924     | 174,055        | 23.47                 | 41.16           |
| Ratio not seeking medical care/seeking medical care |                                          |                  |                      |                 |            |                |                       |                 |
| -20%                    | 125,468                                  | 10,987           | 2,053                | 34,287          | 35,187     | 158,836        | 21.77                 | 37.95           |
| +20%                    | 146,945                                  | 10,987           | 2,053                | 34,287          | 35,187     | 164,415        | 21.77                 | 38.43           |
| Cost and benefit discount rates |                                          |                  |                      |                 |            |                |                       |                 |
| 0%, 0%                  | 136,207                                  | 10,987           | 2,053                | 34,287          | 35,187     | 160,52         | 22.84                 | 40.02           |
| 6%, 6%                  | 136,207                                  | 10,987           | 2,053                | 34,287          | 35,187     | 154,371        | 20.77                 | 36.46           |
| Incidences              |                                          |                  |                      |                 |            |                |                       |                 |
| PCC                     |                                          |                  |                      |                 |            |                |                       |                 |
| -20%                    | 124,197                                  | 10,987           | 2,053                | 34,287          | 35,187     | 151,082        | 21.66                 | 36.96           |
| +20%                    | 148,216                                  | 10,987           | 2,053                | 34,287          | 35,187     | 171,908        | 21.88                 | 39.41           |
| Hospitalization         |                                          |                  |                      |                 |            |                |                       |                 |
| -20%                    | 132,534                                  | 8,789            | 2,053                | 34,287          | 35,187     | 154,633        | 19.17                 | 34.92           |
| +20%                    | 139,880                                  | 13,184           | 2,053                | 34,287          | 35,187     | 168,357        | 24.37                 | 41.45           |
| Emergency visits        |                                          |                  |                      |                 |            |                |                       |                 |
| -20%                    | 125,058                                  | 10,987           | 2,053                | 27,430          | 35,187     | 147,119        | 20.43                 | 35.40           |
| +20%                    | 147,355                                  | 10,987           | 2,053                | 41,145          | 35,187     | 175,870        | 23.12                 | 40.98           |
| Nosocomial infections   |                                          |                  |                      |                 |            |                |                       |                 |
| -20%                    | 135,796                                  | 10,987           | 1,642                | 34,287          | 35,187     | 160,846        | 21.48                 | 37.83           |
| +20%                    | 136,617                                  | 10,987           | 2,464                | 34,287          | 35,187     | 162,143        | 22.07                 | 38.55           |
| Vaccine efficacy in reduction of RVGE cases (95% CI) |                                          |                  |                      |                 |            |                |                       |                 |
| 90.5% hospitalizations, NI | 121,187                                  | 10,379           | 1,939                | 32,494          | 30,236     | 147,707        | 20.54                 | 35.54           |
| 88.8% emergency visits  |                                          |                  |                      |                 |            |                |                       |                 |
| 73.9% PCC and home care |                                          |                  |                      |                 |            |                |                       |                 |
| 98.2% hospitalizations, NI | 144,258                                  | 11,262           | 2,104                | 35,312          | 37,847     | 168,854        | 22.39                 | 39.55           |
| 96.5% emergency visits  |                                          |                  |                      |                 |            |                |                       |                 |
| 92.5% PCC and home care |                                          |                  |                      |                 |            |                |                       |                 |
| Vaccine efficacy annual rate by age |                                          |                  |                      |                 |            |                |                       |                 |
| 10% decrease in year 2 and exponential decrease until year 4 | 135,507                                  | 10,891           | 2,051                | 34,208          | 34,987     | 160,770        | 21.65                 | 37.99           |
| NHS & Societal costs (95% CI) |                                          |                  |                      |                 |            |                |                       |                 |
| Lower values            | 136,190                                  | 10,987           | 2,053                | 34,287          | 35,187     | 161,495        | 19.59                 | 33.57           |
| Higher values           | 36,190                                   | 10,987           | 2,053                | 34,287          | 35,187     | 61,495         | 23.94                 | 44.64           |
extra nappies and baby sitting in terms of non-medical costs. Taking these costs together, our estimated cost is lower, ranging form €139 to €289 (PCC and hospital cases, respectively). The work days lost by parents accounted for 69% and 75% of the overall cost in studies conducted in the United States[51] and in Italy[11], respectively, whereas in our model this was only 39% of the overall cost of €19.6 million. This suggests that our analysis might underestimate the real burden of RVGE in Spain.

Although there are no other studies evaluating the impact of a universal rotavirus vaccination in Spain, our findings are consistent with studies performed in France[12], UK[52] and Germany[13], that estimated that a universal vaccination programme, with a 90% coverage, would reduce the burden of disease by 74% to 75%.

The main objective of the study was to assess the economic burden of rotavirus disease and to describe the potential benefits of rotavirus vaccination, but not its cost-effectiveness. A cost effectiveness analysis is usually used as a decision making tool for resource allocation in a situation of limited resources. In order to perform a cost effectiveness analysis, a reliable vaccine price should be considered. However, the current situation in Spain is that the vaccine is currently available on an out-of-pocket market, i.e., not reimbursed by the national health system with different prices depending on the region. It is consequently difficult to assess the current market price. Also, the expected tender price under reimbursement from national health system would be lower than the current market price. Therefore, using the current market price for the vaccine would substantially unfavour the cost-effectiveness results, and even more, results would not be reliable because of the use of un real vaccine price.

However, a cost-effectiveness analysis would be of interest using various price assumptions and correct methods to assess at best the impact of uncertainty related to rotavirus epidemiology and estimation of quality of life in children aged under five years old on the cost-effectiveness ratios.

As most of economic models, one limitation of this study is that it relies on assumptions for some parameters which induce uncertainty around the estimates. Due to lack of evidence, data from nearby countries was used as proxy for Spain; this is the case for the percentage of working mothers (51%[39]), which is based on Italian data, or the percentage of cases not seeking for medical attention (41.4%[33]), based on French information. In both cases, differences in health behaviour within countries might be observed; for example, it is possible that more than 51% of mothers in Spain work although this parameter did not have any impact in the results. Secondly, we considered a coverage rate of 90% as indicated by the World Health Organization (WHO) [24] for common compulsory vaccinations. However, according to Martin A[53], average paediatric coverage rates might be higher in Spain (97%) due to higher reimbursement rates from the national healthcare payer compared with those in other European countries. This mainly implies that our results are certainly conservative and underestimate the real benefit of the vaccination.

Furthermore, the model did not consider additional indirect benefits due to rotavirus vaccination programme. For example, it is noteworthy that the epidemic peak of RVGE overlaps with that of other seasonal diseases such as influenza and respiratory syncytial diseases thus increasing the load for health services which are already overcrowded at this period[6]. By decreasing substantially the number of RVGE cases, the vaccination contributes to a better organisation of paediatric services at hospital as well as in PCCs.

Potential herd immunity resulting from transmission of vaccine strains has not been considered in this study. As rotavirus is transmitted by infants and children, it spreads within families and day care centres, the possibility of herd immunity would contribute substantially to the burden reduction. Preliminary data from the United States show that 2 years after the introduction of RV vaccination into the immunization schedule, the reduction in severe rotavirus disease appears to approximate that seen in phase III clinical trials. More over there also been reductions in rotavirus disease in older and unimmunised age groups[54,55]. In a recent study performed in five European countries where authors were evaluating cost-effectiveness of the rotavirus vaccination, the results show that incorporating the effect of possible indirect protection has overall a moderate impact on the cost-effectiveness ratio in all the countries. However, in some countries where the vaccination is not cost-effective but near to the threshold of 30.000€ per QALY the inclusion of indirect benefits of the vaccine could change the overall conclusion[56]. Although there have been reports of symptomatic cases due to transmission of vaccine rotavirus reported among family members, we did not take this into account due to the lack of available data. Generally, the limitations discussed would tend to lead to an underestimation of the vaccine benefits.

**Conclusions**

In conclusion, this study shows that the implementation of a universal rotavirus vaccination program with Rotateq would substantially reduce the morbidity due to RVGE among children in Spain, avoiding more than 136,200 cases and reducing spending by €38 million per
birth cohort. Our model could be extended to assess the cost-effectiveness of a rotavirus vaccination program with RotaTeq in Spain.

List of Abbreviations

AGE: Acute GastroEnteritis; DRG: Diagnostic Related Groups; ER: Emergency Room; GP: General Practitioner; LOS: Length of Stay; NHS: National Health System; NNV: Number Needed to Vaccinate; OTC: Over The Counter; PCC: Primary Care Centre; REST: Rotavirus Efficacy and Safety Trial; REVEAL: Rotavirus gastroenteritis Epidemiology and Viral types Accounting for Losses in Public Health and Society; RVG: Rotavirus GastroEnteritis; WHO: World Health Organization.

Competing interests

Authors from IMS received fees from SPMSD to conduct the study Authors from SPMSD has Non-financial competing interests (Commercial being SPMSD employee Diez-Domingo J. has received speaker fees from GSK and SPMSD, and is principal investigator in clinical trials and epidemiological studies financed by these companies. Sanofi Pasteur MSD give us grand support.

Authors’ contributions

JDD carried out the study, and participated in its design and coordination and helped to draft the manuscript, he read and approve the final manuscript. NLS carried out the study, and participated in its design and coordination and helped to draft the manuscript, she read and approve the final manuscript. NM drafted the manuscript she read and approve the final manuscript. LB participated in the design of the study and the analysis and read and approve the final manuscript. NL initiated the study, participated in its coordination and helped to draft the manuscript, he read and approve the final manuscript. MT initiated the study, participated in its coordination and helped to draft the manuscript and read and approve the final manuscript.

Author details

1Vaccine Investigation Area. CSISP Centre for Public Health Research, Avda Catalunya 21, Valencia, (46020), Spain. 2HEOR, IMS Health, Dr. Ferran 25 - 27, Barcelona, (08034), Spain. 3Market Access Manager Sanofi Pasteur MSD, SNC, 8 Rue Jonas Salk, Lyon (69367), France.

Received: 14 October 2009 Accepted: 10 August 2010 Published: 10 August 2010

References

1. Kirkwood CD, Buttery J. Rotavirus vaccines - an update. Expert Opin Biol Ther 2003, 3:975-107.
2. Roberts JA, Cumberland P, Sackett PN, Wheeler J, Rodrigues LC, Sethi D, Roderick PJ, Infectious Intestinal Disease Study Executive: The study of infectious intestinal disease in England: socio-economic impact. Epidemiol Infect 2003, 130:1-11.
3. Gil A, Carrasco P, Jiménez R, San-Martín M, Oyagüez I, González A: Burden of hospitalizations attributable to rotavirus infection in children in Spain, period 1999-2000. Vaccine 2004, 22:2221-5.
4. Verstraeten T, Wollenswinkel Van den Bosch JH: Cost- effectiveness of an immunization programme for rotavirus gastroenteritis in the United Kingdom. Epidemiol Infect 2008, 136:64-55.
5. Hammerschmidt T, Gartner B: Acute rotavirus gastroenteritis: burden of disease and cost of illness among young children in Germany [poster]. Presented at the 7th European ISPOR Congress, Value Health 2004, 7(6):762.
6. Fontana M, Zuin G, Panchen P, Fusco FC, Lambertini A, Berni Canani R, SGEP Working Group on Intestinal Infections: Costs associated with outpatient diarrhoea in infants and toddlers: a nationwide study of the Italian Society of Paediatric Gastroenterology and Hepatology. Dig Liver Dis 2004, 36:523-7.
7. Huet F, Largearon T, Trichard M, Miadi-Fargier H, Jasso-Mosqueda G: Burden of paediatric rotavirus gastroenteritis and potential benefits of a universal rotavirus vaccination programme with RotaTeq® in France. Vaccine 2007, 25:6348-58.
8. Buesch K, Ezaz N, Trichard M, Largearon N: Burden of paediatric rotavirus gastroenteritis and potential benefits of a universal vaccination programme in Germany [poster]. Presented at the 10th Annual European Congress, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Dublin 2007.
9. Hammerschmidt T, Fanter J, Huppertz H, Heininger U, Roos R, Standaert E: Epidemiological and economic impact of routine vaccination of infants against rotavirus gastroenteritis in Germany: a preliminary analysis. [poster]. Presented at the 10th Annual European Congress, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Dublin 2007.
10. Jit M, Edmunds WJ: Evaluating rotavirus vaccination in England and Wales Part II. The potential cost-effectiveness of vaccination. Vaccine 2007, 25:3971-9.
11. Mellezi H, Levybruhi D, Boelle PY, Dervaux B, Baron S, Yazdanpanah Y: Cost and cost-effectiveness of childhood vaccination against rotavirus in France. Vaccine 2008, 26:706-15.
12. Biek J, Van Damme P, De Smet F: The health and economic burden of rotavirus disease in Belgium. Eur J Pediatr 2008, 167:1409-19.
13. Zomer TP, van Duyvenhoven YT, Mangen MJ, van der Maat NL, Vennema H, Boot H, de Meijer HE: Assessing the introduction of universal rotavirus vaccination in the Netherlands. Vaccine 2008, 26:3757-64.
14. Giammanco MD, Congiolo MA, Pignato S, Giammanco G: An economic analysis of rotavirus vaccination in Italy. Vaccine 2009, 27:3904-3911.
15. Vesikari T, Matson DO, Denney P, Van Damme P, Santosham M, Rodriguez Z, Dallas MJ, Heyse JF, Goveia MG, Black SB, Shinefield HR, Christie CD, Ylitalo S, Itzler RF, Coia ML, Onorato MT, Adeyi BA, Marshall GS, Goethelers L, Campens D, Karvenon A, Watt JP, O'Brien KL, DiNubile MJ, Clark HF, Boslego JW, Offit PA, Heaton PM, Rotavirus Efficacy and Safety Trial (REST) Study Team: Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006, 354:23-33.
16. Santos N, Hoshino Y: Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective vaccine, Rev Med Virol 2005, 15:29-56.
17. Welte R, Pager JC, Van Duyvenhoven YTHP, De Wit MAS: Cost- effectiveness of rotavirus vaccination in the Netherlands [poster]. Presented at 6th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Arlington, 2001.
18. Takala AK, Koskenniemi E, Joensuu J, Makela M, Vesikari T: Economic evaluation of rotavirus vaccinations in Finland: randomized, double-blind, placebo-controlled trial of tetravalent rhesus rotavirus vaccine. Clin Infect Dis 1998, 27:272-82.
19. WHO Coverage rate for DTP. [http://www.euro.who.int], Accessed 13 September 2006.
20. Van Damme P, Gaquintu C, Huet F, Goethelers L, Maxwell M, Van der Wielen M, REVEAL Study Group: Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004-2005: The REVEAL Study, J Infect Dis Suppl 2007, 195(Suppl 1):545-516.
21. Gaquintu C, Van Damme P, Huet F, Goethelers L, Van der Wielen M, REVEAL Study Group: Costs of Community-Acquired Pediatric Rotavirus Gastroenteritis in 7 European Countries: The REVEAL Study, J Infect Dis Suppl 2007, 195:36-44.
22. INE, Spanish Institute of Statistics. [http://www.ine.es], Accessed February 2006.
28. Spanish UNICEF statistics. [http://www.unicef.org/spanish/statistics/index_countrystats.html]. Accessed June 2009.

29. Glezies O, Desselberger U, Tatochenko V, Rodrigo C, Salaman N, Mezner Z, Giaquinto C, Grimpel E. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. Pediatr Infect Dis J. 2006, 25(1 Suppl):S12-21.

30. Roman E, Wilhelmi I, Colomina J, et al. Acute viral gastroenteritis: proportion and clinical relevance of multiple infections in Spanish children. J Med Microbiol. 2003, 52:435-40.

31. Diez-Domingo J, Ríos M, Ubeda I, Ballester A. Incidencia y costes de la hospitalización por bronquiolitis y de las infecciones. An Pediatr (Barc). 2006, 65:325-30.

32. Soniano-Gabarró M, Mutukwicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J. 2006, 25(1 Suppl):S7-S11.

33. Floret D, Lina B, Porchet R, Billaud A, Lefèvre F, Langeron N, Bellemain B, Tranq CN, Fau C, Gaspard C, Mamoux V, Marcelin L. Epidemiological and burden of rotavirus diarrhoea in day care centres in Lyon, France. Eur J Pediatr. 2006, 165:905-6. Epub 2006 Aug 10. Erratum in: Eur J Pediatr 2008, 167:255-6.

34. Sánchez-Fauquier A, Wilhelmi I, Colomina J, Cubero E, Roman E. Diversity of group A human rotavirus types circulating over a 4-year period in Madrid, Spain. J Clin Microbiol. 2004, 42:1609-13.

35. Diez-Domingo J, Martín IO, Sanz AB, López AG, Martínez CC, Boronat CP, Del Barrio MJ, García DG, Pons MM, Crespo VA, Esteve PA, Arfella IL, Monrabal IS, Baveira LB, López MG. Rotavirus gastroenteritis among children under five years of age in Valencia, Spain. Pediatr Infect Dis J. 2006, 25:455-7.

36. Asemar F, De Jose M, Lorente M, Moraga F, Clurya V, Arkanic S, Cescasino R, Vento M. A pharmacoeconomic evaluation of seven-valent pneumococcal conjugate vaccine in Spain, Value Health. 2004, 7:36-51.

37. Lenne X, Diez Domingo J, Gil A, Ríos M, Lluch JA, Dervaux B. Economic evaluation of varicella vaccination in Spain—results from a dynamic model. Vaccine. 2006, 24:6880-9.

38. Forster J, Frank HD, Henker H, Stehr K, Rieger C. Eine prospektive nationale Multizenterstudie zur Bewertung von Rotaviruserkrankungen in Deutschland. Monatschr Kinderheilk. 1999, Suppl 2: S148.

39. OECD: Selection of OECD Social Indicators: How does Italy compare? [http://www.oecd.org/dataoecd/35/2/34555477.xls], [homepage on the Internet]. Accessed June 2009.

40. BOT – Spanish General Council of the Official Colleges of Pharmacists. [CD-ROM]. 2006.

41. Gisbert R, Brosa M. Health Care Costs Database. SOIKOS Version 2.2. 2005.

42. Economical information System, regional health care ministry (Valencia).

43. INE (Spanish Statististic Institute), Índice de Costes Laborales (2002). [base de datos de Internet]. Madrid. [http://www.ine.es], Accessed June 2009.

44. Mitag HJ. Labour costs in Europe 1996-2002. Brussels: Eurostat; European Communities 2004.

45. BOE (Spanish Central Government Official Bulletin), 3/12/05, n° 289. Spanish Treasury, Orden EHA/3770/2005. Sec 1:39852

46. Mitag HJ. Labour costs in Europe 1996-2002. Brussels: Eurostat; European Communities 2004.

47. Diez-Domingo J, Martin IO, Sanz AB, Lopez AG, Martin CC, Boronat CP, Del Barrio MJ, Garcia DG, Pons MM, Crespo VA, Esteve PA, Arfella IL, Monrabal IS, Baveira LB, Lopez MG. Rotavirus gastroenteritis among children under five years of age in Valencia, Spain. Pediatr Infect Dis J. 2006, 25:455-7.

48. Asensi F, De Jose M, Lorente M, Moraga F, Clurya V, Arkanic S, Cescasino R, Vento M. A pharmacoeconomic evaluation of seven-valent pneumococcal conjugate vaccine in Spain, Value Health. 2004, 7:36-51.

49. Lenne X, Diez Domingo J, Gil A, Ríos M, Lluch JA, Dervaux B. Economic evaluation of varicella vaccination in Spain—results from a dynamic model. Vaccine. 2006, 24:6880-9.

50. Forster J, Frank HD, Henker H, Stehr K, Rieger C. Eine prospektive nationale Multizenterstudie zur Bewertung von Rotaviruserkrankungen in Deutschland. Monatschr Kinderheilk. 1999, Suppl 2: S148.

51. OECD: Selection of OECD Social Indicators: How does Italy compare? [http://www.oecd.org/dataoecd/35/2/34555477.xls], [homepage on the Internet]. Accessed June 2009.

52. BOT – Spanish General Council of the Official Colleges of Pharmacists. [CD-ROM]. 2006.

53. Gisbert R, Brosa M. Health Care Costs Database. SOIKOS Version 2.2. 2005.

54. Economical information System, regional health care ministry (Valencia).

55. INE (Spanish Statististic Institute), Índice de Costes Laborales (2002). [base de datos de Internet]. Madrid. [http://www.ine.es], Accessed June 2009.

56. Mitag HJ. Labour costs in Europe 1996-2002. Brussels: Eurostat; European Communities 2004.

57. BOE (Spanish Central Government Official Bulletin), 3/12/05, n° 289. Spanish Treasury, Orden EHA/3770/2005. Sec 1:39852

58. Gil de Miguel A, Carrasco P, Esteban J, San-Martín M, González A. Burden of hospitalizations attributable to rotavirus infection in children in the Autonomous Region of Madrid, Spain, period 1999-2000 [Spanish]. An Pediatr 2006, 64:510-5.

59. Kirkwood CD, Butterly J. Rotavirus vaccines—an update. Expert Opin Biol Ther 2003, 3:97-103. Review.

60. Giaquinto C, Diez Domingo J, Baldo Jose-Maria, Pazidora P, Forster J, Patrzalek M, et al. Primary care-based surveillance to estimate the burden of rotavirus gastroenteritis in European children aged <5 years. Excellence in Paediatrics, EIP Florence Italy 2009.

61. Gisbert R, Brosa M. Health Care Costs Database. SOIKOS Version 2.2. 2005.

62. Economical information System, regional health care ministry (Valencia).

63. INE (Spanish Statististic Institute), Índice de Costes Laborales (2002). [base de datos de Internet]. Madrid. [http://www.ine.es], Accessed June 2009.

64. Mitag HJ. Labour costs in Europe 1996-2002. Brussels: Eurostat; European Communities 2004.

65. BOE (Spanish Central Government Official Bulletin), 3/12/05, n° 289. Spanish Treasury, Orden EHA/3770/2005. Sec 1:39852

66. Gil de Miguel A, Carrasco P, Esteban J, San-Martín M, González A. Burden of hospitalizations attributable to rotavirus infection in children in the Autonomous Region of Madrid, Spain, period 1999-2000 [Spanish]. An Pediatr 2006, 64:510-5.

67. Kirkwood CD, Butterly J. Rotavirus vaccines—an update. Expert Opin Biol Ther 2003, 3:97-103. Review.

68. Giaquinto C, Diez Domingo J, Baldo Jose-Maria, Pazidora P, Forster J, Patrzalek M, et al. Primary care-based surveillance to estimate the burden of rotavirus gastroenteritis in European children aged <5 years. Excellence in Paediatrics, EIP Florence Italy 2009.

69. Gisbert R, Brosa M. Health Care Costs Database. SOIKOS Version 2.2. 2005.

70. Economical information System, regional health care ministry (Valencia).

Submit your next manuscript to BioMed Central and take full advantage of:
• Convenient online submission
• Thorough peer review
• No space constraints or color figure charges
• Immediate publication on acceptance
• Inclusion in PubMed, CAS, Scopus and Google Scholar
• Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit