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

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REDUCTION IN PAEDIATRIC ROTAVIRUS-RELATED HOSPITALIZATIONS AFTER UNIVERSAL ROTAVIRUS VACCINATION IN BELGIUM

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ABSTRACT

Background: This study investigated the impact of pediatric vaccination against rotavirus on the number of rotavirus-related hospitalizations of children in Belgium.

Methods: This retrospective database study was conducted at 12 pediatric hospitals in Belgium (546 pediatric beds, 30.6% of Belgian total). Children ≤5 years attending hospital for any reason were eligible if they had a rotavirus stool test at one of the study centers. The number of rotavirus-positive stool tests and hospitalizations for acute gastroenteritis (AGE) were compared for study periods pre-vaccination (June 2004 – May 2006) and post-vaccination (June 2007 – May 2009).

Results: The number of rotavirus-positive stool tests in children aged ≤5 years decreased from an average of 881 in the pre-vaccination period to 368 in the first year post-vaccination and 199 in the second. In children aged 2–24 months the percentage reductions were 65% (95% confidence interval [CI]: 62%, 69%) and 80% (95% CI: 77%, 83%) in the first and second years after vaccination, respectively, compared with pre-vaccination. In children aged <2 months the reductions were 50% (95% CI: 36%, 64%) and 64% (95% CI: 49%, 76%), respectively, and in children aged >24 months the corresponding values were 20% (95% CI: 14%, 28%) and 64% (95% CI: 56%, 72%). The number of AGE-driven hospital admissions and hospitalization days for AGE declined by 33% and 36%, respectively, from pre-vaccination to the second year post-vaccination in children aged ≤2 years.

Conclusions: Paediatric rotavirus vaccination in Belgium significantly reduced rotavirus-related hospitalizations in the first and second years after the introduction of the vaccine.

INTRODUCTION

Rotavirus infection is the leading cause of acute gastroenteritis (AGE) in young children worldwide,[1] and is associated with more severe symptoms and more hospital admissions than gastroenteritis due to other causes.[2] It is estimated to cause over 146,000 hospital admissions per year in children aged <5 years in the World Health Organization (WHO) European region,[3] and over 87,000 per year in the European Union countries.[4] In Belgium, the average number of hospital admissions due to rotavirus gastroenteritis in children aged <5 years was 6,790 per year between 2000 and 2005, and 12–21% of hospital days among children aged <2 years were associated with rotavirus.[5] In children aged <7 years, the incidence of hospitalization due to rotavirus has been estimated at 676 per 100,000 children

in Belgium (5,600 hospitalizations annually).[6] Estimates of the annual economic burden of rotavirus disease in Belgium range from €12.5 million (53% direct medical costs),[7] to €7.7 million in direct costs and a further €12.8 million in indirect costs.[6]

Vaccination against rotavirus is recommended in European guidelines[8;8] and by WHO.[9] Two rotavirus vaccines are currently available in Belgium, a two-dose monovalent human rotavirus vaccine (GSK Biologicals, Rixensart, Belgium)[10;11] and a three-dose pentavalent bovine-derived vaccine (Sanofi Pasteur MSD).[12] The two vaccines have been partially reimbursed (10.3 Euros/dose is charged to the patient) in Belgium since November 2006 and June 2007, respectively. Overall vaccine coverage in Belgium is estimated using sales data at approximately 85%[13] to 90%[14] in 2008–2009. The expected impact of vaccination on rotavirus hospitalizations and costs has been estimated by modeling studies in several countries.[15-18] Field data are important to demonstrate the impact of vaccination in routine practice.

The aim of the present study was to assess the real-world effect of vaccination on rotavirus-related hospitalizations in children aged ≤5 years, by comparing data collected before and after the introduction of generalized vaccination in Belgium.

MATERIALS AND METHODS

We conducted a retrospective database study at 12 hospitals in Belgium (9 general hospitals with a pediatric ward, 3 pediatric hospitals). Four were university hospitals. The centers were distributed across the three geographic regions of Belgium (Brussels, Flanders, and Wallonia). The 12 centers had 546 pediatric beds, representing 30.6% of the total of 1793 pediatric beds in Belgium.[19]

Eleven of the participating centers provided information on the laboratory assays used to detect rotavirus. Of these, one used immunofluorescence assay and the others used rapid immune-chromatographic tests. Two centers reported a change during the study period, using the same type of test but with a product from a different manufacturer. In Belgium a rotavirus antigen test is reimbursed for all children aged ≤2 years.

Data collection

All children aged ≤5 years who had a rotavirus detection test performed at one of the participating centers from 1 June 2004 to 31 May 2006 (pre-vaccination study period) or 1 June 2007 to 31 May 2009 (post-vaccination study period) were eligible for inclusion. The following information was recorded for each sample: patient's birth date and gender; sample date; rotavirus test result; date of admission and discharge. Only hospitalized patients were included in the primary analysis.

Multiple samples taken from the same patient in the same AGE episode, defined as the same hospitalization or a time lapse of <30 days between two samples, were considered duplicates. If all samples during the episode were all positive or all negative, the first sample was included. If some samples were positive and some negative during the episode, only the first positive sample was included.

Data analysis

The pre-vaccination study period was defined as 1 June 2004 to 31 May 2006. In analyses of the seasonal pattern of rotavirus tests, this was further divided into two study seasons, June 2004–May 2005 and June 2005–May 2006. The first post-vaccination study season was defined as 1 June 2007–31 May 2008, and the second post-vaccination study season was defined as 1 June 2008–31 May 2009. The number and proportion of rotavirus-positive tests was calculated per month for each study season.

Hospitalization was classed as AGE-driven if the stool sample was collected within 48 hours of hospitalization. The mean length of stay and total number of hospitalization days were calculated for hospitalized patients. Rotavirus infections were considered community-acquired if a stool sample taken within 48 hours of hospital admission was rotavirus-positive.

Owing to changes in data management systems, only nine of the participating centers could provide a complete dataset for all four study seasons. Three centers had incomplete or missing data during the June 2004–May 2005 season. To avoid potential bias introduced by missing data, our main analysis included only the nine centers with complete datasets. To test whether excluding the centers with incomplete data could have influenced the results, we conducted a separate analysis including data from all twelve centers.

Data were analyzed by age groups (<2 months, 2–24 months, and >24 months). A further sub-analysis was conducted in children aged ≥33 months, as this age group would have been too old for vaccination. Children aged <1 month on the date of hospital admission were excluded from the analysis of length-of-stay because the full date of birth was not collected in the first study year and this was the only way to exclude premature babies (who tend to have longer duration of hospitalization than other age groups).

We compared the absolute numbers of rotavirus-positive test results between the pre-vaccination study period and each of the two post-vaccination study seasons using the chi-square test assuming that the number of positive tests in the pre-vaccine period is the reference. The underlying assumption about the comparison of the periods pre- and post-vaccination is that the coverage area for each of the hospitals participating in the study is the same across the whole study period. Thus, the most relevant value to compare pre- and post-vaccination is the average absolute number of positive tests observed. The relative proportion of positive tests per season has less meaning if the number of tests taken per season has also decreased, because less pathology is observed overall. Hence, the denominator for comparison is not the number of tests conducted, but the number of positive tests observed in the pre-vaccination period.

For data on the length of stay, we compared the different study periods using the Mann-Whitney U-test. A p-value of <0.05 was considered statistically significant.

A separate analysis examined the number of rotavirus-positive tests in patients born in different birth cohorts. Birth date information was used to categorize patients into four birth cohorts: those born before 1 September 2006 (pre-vaccination); between September 2006 and August 2007 (cohort 1, early vaccination period, 65% estimated coverage); between September 2007 and August 2008 (cohort 2, 87% estimated coverage); and between September 2008 and the end of the study in May 2009 (cohort 3, 89% estimated coverage). Sales data showed that vaccine coverage was low prior to reimbursement, and we assumed that no children were vaccinated prior to reimbursement.

Ethical approval was not required because there was no medical file consultation, although ethics committee approval was obtained in four of the twelve centers. All ethics committees were informed about the study.

RESULTS

The number of rotavirus-positive stool tests in hospitalized children aged 2–24 months declined from 716 per year pre-vaccination to 249 per year in the first year after vaccination, a decrease of 65% (95% confidence interval [CI] 62%, 69%) (Table 1). The second year post-vaccination showed a further decline to 140 rotavirus-positive tests per year, a decrease of 80% (95% CI 77%, 83%) compared with the pre-vaccination period (Table 1). Children in the other age groups also showed a decrease in the number of rotavirus-positive tests post-vaccination (Table 1).

Table 1 Rotavirus-positive tests pre-vaccine and post-vaccine, hospitalized patients

Age group	Number of rotavirus-positive tests / all tests (%)		
	Pre-vaccination (June 2004–May 2006)	First year post-vaccination (June 2007–May 2008)	Second year post-vaccination (June 2008–May 2009)
<2 months	44/529 (8.3%)	22/547 (4.0%)	16/443 (3.6%)
2–24 months	716/2227 (32.1%)	249/1603 (15.5%)	140/1526 (9.2%)
>24 months	121/405 (29.9%)	97/356 (27.2%)	43/218 (19.7%)
Total (≤5 years)	881/3161 (27.9%)	368/2506 (14.7%)	199/2187 (9.1%)
	% decline in number of rotavirus-positive tests compared with pre-vaccination period (95% CI)		
<2 months		50%* (36%, 64%)	64%* (49%, 76%)
2–24 months		65%* (62%, 69%)	80%* (77%, 83%)
>24 months		20%* (14%, 28%)	64%* (56%, 72%)

*p<0.001

CI, confidence interval

The overall number of rotavirus tests performed in hospitalized children aged ≤5 years fell from an average of 3161 per year in the pre-vaccination period to 2187 in the second year post-vaccination (Table 1), a decrease of approximately 1,000 (30%) in the annual number of tests.

Figure 1 shows the seasonal pattern in the number of rotavirus-positive tests, with the pre-vaccination period divided into two study seasons (June 2004-May 2005 and June 2005-May 2006). The characteristic seasonal peak in rotavirus activity

Figure 1 Number of rotavirus-positive tests in the two years pre-vaccination and the two years post-vaccination in children aged ≤5 years, hospitalized patients

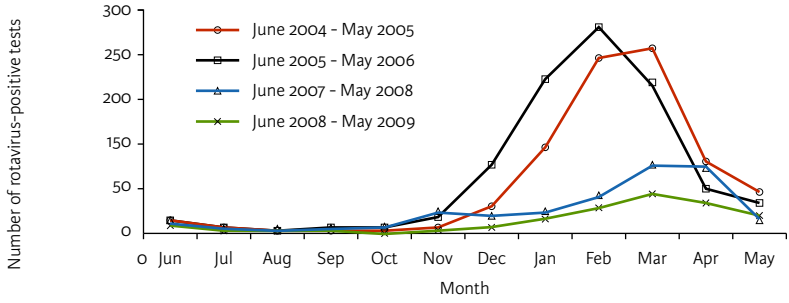
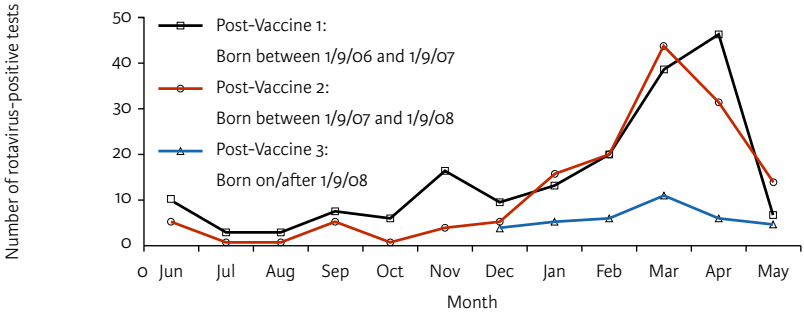


Figure 2 Number of rotavirus-positive tests in successive birth cohorts, hospitalized patients

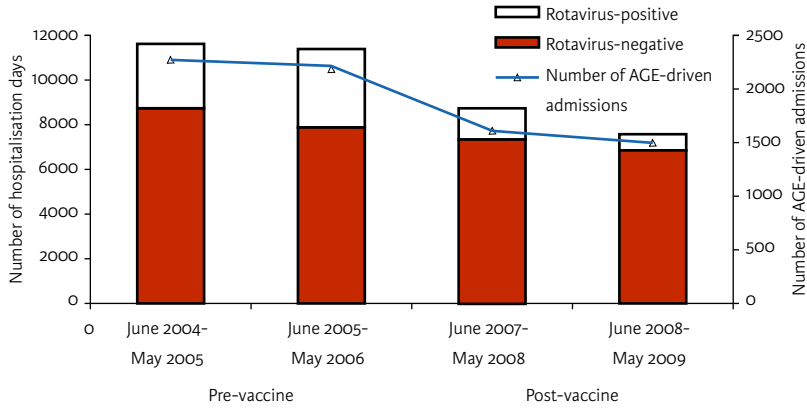


in the winter and early spring (January to March) was observed in both pre-vaccination seasons in children aged ≤5 years, and was delayed and attenuated in the two post-vaccination seasons (Figure 1). A similar pattern was observed in children aged ≤2 years (data not shown).

Figure 2 shows the absolute numbers of rotavirus-positive tests by month in the three birth cohorts born after vaccine introduction. By the latest birth cohort (cohort 3, born after 1 September 2008), the number of rotavirus-positive tests had fallen to a very low level and the seasonal peak had almost disappeared.

The maximum age of vaccinated children in the study was <33 months (born in or after September 2006, just in time to receive the vaccine after reimbursement of the first product in November 2006, and included in the last month of the study in May 2009). Children aged ≥33 months would have been too old for vaccination when reimbursement became available. The number of rotavirus-positive samples in this age group was 46/293 (15.7%) in the pre-vaccination period. In the 2008–2009 season, 138 tests were performed and the number of rotavirus-positive samples was 24. The decrease from 46 to 24 rotavirus-positive tests in this unvaccinated population is consistent with a modest herd protection effect,

Figure 3 Number of AGE-driven hospital admissions and hospitalization days in the two years pre-vaccination and the two years post-vaccination in children aged ≤2 years



although the numbers are small and a larger study with routine rotavirus testing would be needed to quantify the magnitude of the effect. The 24 positive tests in the 2008-2009 period represent 8.2% of the number of tests in the pre-vaccine period (24/293), a decrease of 7.5 percentage points.

Excluding newborn babies (aged <1 month), the number of community-acquired rotavirus infections was 722 in the pre-vaccination period in children aged ≤5 years, decreasing to 278 in the first year post-vaccination (61% decrease vs pre-vaccination) and 158 in the second (78% decrease vs pre-vaccination and a further 43% decrease vs first year post-vaccination). The number of nosocomial rotavirus infections in children aged ≤5 years (excluding newborn babies) decreased from 140 pre-vaccination to 75 in the first year post-vaccination (46% decrease vs pre-vaccination) and 33 in the second (76% decrease vs pre-vaccination and a further 56% decrease vs first-year post-vaccination).

The number of AGE-driven hospital admissions in children aged ≤2 years decreased in both the years post-vaccination compared with the pre-vaccination period (Figure 3), and the difference was statistically significant for the second year post-vaccination compared with pre-vaccination (p=0.016). The number of AGE-related hospitalization days also decreased in the two years post-vaccination compared with pre-vaccination, with a decrease in the proportion of days accounted for by rotavirus-positive cases (Figure 3). Mean length of stay in AGE admissions was not statistically significantly different between the study periods (pre-vaccination 5.1 days, first year post-vaccination 5.5 days, p=0.329, second year post-vaccination 5.1 days, p=0.192).

The proportion of rotavirus-positive samples in the study periods was similar in both the 9-centre and 12-centre analyses (Table 2). The same trend for a decrease from the pre-vaccination study periods to the post-vaccination study periods was observed in each of the study centers (data not shown).

Table 2 Comparison of results from the main analysis of 9 centers with complete data sets and the separate analysis including 3 additional centers with incomplete data (12 centers in total)

	9 centers (356 pediatric beds)	12 centers (546 pediatric beds)
Pre-vaccination		
Total number of samples per hospital per year	351	357
Number of rotavirus-positive samples per hospital per year	98	96
Percentage of samples rotavirus-positive	27.9%	26.9%
First year post-vaccination (2007–2008)		
Total number of samples per hospital per year	278	366
Number of rotavirus-positive samples per hospital per year	41	44
Percentage of samples rotavirus-positive	14.7%	12.1%
Second year post-vaccination (2008–2009)		
Total number of samples per hospital per year	243	297
Number of rotavirus-positive samples per hospital per year	22	27
Percentage of samples rotavirus-positive	9.1%	9.2%

DISCUSSION

Belgium was one of the earliest countries in Europe to include rotavirus vaccination in its pediatric immunization schedule, and coverage was estimated at approximately 90% in 2008.[14] This rapid uptake and high coverage means that Belgium offered one of the first opportunities in Europe for a study such as the present one to investigate the real-world effect of generalized rotavirus vaccination in routine practice at a national level.

Our results show that in Belgium the number and percentage of rotavirus-positive stool tests in children aged ≤5 years at the study hospitals dramatically decreased in the two years after introduction of generalized rotavirus vaccination. The seasonal peak in the winter and early spring that is characteristic of rotavirus in temperate countries,[1;20] was apparent in both the pre-vaccination years and was reduced and delayed in both the post-vaccination years. This is consistent with a reduction in rotavirus transmission, as observed in the US.[21;22] The effect was larger in successive birth cohorts, consistent with increasing vaccination uptake. The number of rotavirus-positive tests also fell in children aged ≥33 months, which would have been too old for vaccination when reimbursement became available.

The before-and-after design is a potential limitation of our study. Our data measure trends in rotavirus disease activity before and after the introduction of vaccination, and could therefore be influenced by natural fluctuations between rotavirus seasons or changes in practice. However, the sustained reduction in rotavirus-positive tests observed in our study is more likely to have been caused by the vaccine. Moreover, a similar reduction in positive tests was observed across all the participating centers. It would be interesting to compare our findings on rotavirus-positive tests with other similar practices, such as tests obtained for respiratory viral infections, and this would be a useful analysis to conduct in a subsequent follow-up study.

Another potential limitation is that we collected data from a sample of Belgian pediatric hospitals and wards. However, the 12 centers in the study (546 beds) accounted for 30.6% of all pediatric beds in Belgium, and the nine centers in the main analysis (356 beds) accounted for 20%. Furthermore, the study centers were drawn from all three of Belgium's geographic regions, and included a mix of general, pediatric, regional, and university hospitals in a range of socioeconomic environments, so they should be reasonably representative of the country as a whole.

Another potential limitation is that no clinical data were available because we did not access individual patient records, so severity may not be assessed. We assumed that AGE was likely to be the cause of hospital admission if a stool sample was taken within 48 hours of admission. The Belgian policy of reimbursing rotavirus tests only for children aged <2 years may alter the use of rotavirus testing in older children.

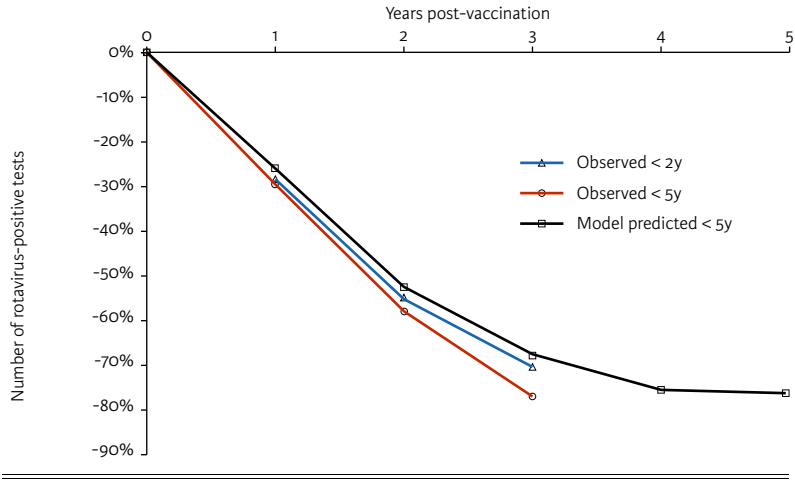
The analysis including the three centers with incomplete data showed a decline in the proportion of rotavirus-positive samples that was similar to that observed in the analysis only of centers with complete data (Table 2). Thus, the conclusions reached by the study would be the same regardless of whether the centers with incomplete data were included.

Our results are consistent with findings reported from other countries, which have reported a reduction in the number of rotavirus-positive tests from laboratory surveillance or a reduction in rotavirus hospitalizations. In a small study of hospital database records in Spain, the incidence of rotavirus AGE hospitalizations decreased by 75.6% in the 2008–2009 season compared with the pre-vaccination season.[23] An early (first season) analysis of data in children aged ≤15 years collected by a sentinel network in Austria including 11 pediatric hospital wards estimated a 74% decrease in hospitalization rate due to rotavirus gastroenteritis in the vaccine target population.[24] In our study, the number of rotavirus-positive tests in children aged 2–24 months decreased by 80% in the second year post-vaccination compared with pre-vaccination (Table 1).

In Australia, a retrospective analysis of routinely collected data investigated the impact of publicly funded rotavirus vaccination introduced in Queensland in July 2007.[25] Rotavirus notifications in children aged <2 years declined by 53% in the first year after vaccination and by 65% in the second year, and the proportion of rotavirus-positive tests decreased by 45% and 43%, respectively, compared with pre-vaccination.[25] There was evidence for a herd protection effect, as notifications and the proportion of rotavirus-positive tests declined post-vaccination in older children.[25] A study in New South Wales reported substantial decreases in the seasonal increase in laboratory-confirmed rotavirus infections in children aged <15 months (young enough to be vaccinated) and in children aged 15 months to 5 years who were too old for vaccination.[26]

Data from the US National Respiratory and Enteric Viruses Surveillance System (NRVESS) showed a substantial reduction in the number of rotavirus-positive test results, with a shorter and later rotavirus activity peak, in the seasons after

Figure 4 Comparison of model predictions with real-world observations



introduction of rotavirus vaccination (2007–2008 and 2008–2009) compared with the seasons before vaccine introduction (2000–2006).[22] This is consistent with our observation of an attenuated and delayed seasonal rotavirus peak after vaccination in Belgium (Figure 1). However, the US surveillance system does not allow evaluation of the impact on hospitalization.

Few other countries had as high and rapid an uptake of rotavirus vaccination as experienced in Belgium. In the present study, we show that rotavirus vaccination had an impact both on the number of rotavirus-positive tests and on AGE-driven hospitalizations, with a sustained effect over two seasons. Continued disease surveillance will be needed to assess the long-term impact of rotavirus vaccination on the disease, for example to monitor any changes in virus genotype distribution.[27]

We have compared our observed results with the expected decrease in rotavirus-related hospitalizations predicted by a previously published model[17;18] developed by one of the authors (BS) and colleagues (Figure 4). The model-predicted effects match the observed data well, although the model estimates were slightly lower than the observed effect. This is because vaccination can reduce infections in the unvaccinated population by herd protection,[28] which a static model cannot take into account. The absolute difference in hospitalization reduction in children aged ≤5 years was 3% in the first year post-vaccination and 6% in the second.[29] The difference was smaller in children aged ≤2 years, because vaccine coverage is high in this age group whereas the age group of children ≤5 years includes children who were too old to receive vaccination. Thus, there is more potential for a possible herd protection effect in children aged ≤5 years, resulting in a larger difference between the model and observed data. Since rotavirus infection occurs mainly in children aged <5 years, after which natural immunity typically develops, the herd protection effect is expected to be transient during the introduction of vaccination.

When the whole population of children <5 years has been vaccinated, the effect of herd protection should decline towards zero, assuming that vaccine coverage in the target population remains high. The close match between our observed findings and model-predicted results supports the validity of our model in Belgium, and shows that modeling can be an effective method for estimating the expected effect of preventive interventions such as vaccination.

In conclusion, this study showed that rotavirus vaccination in Belgium significantly reduced rotavirus-related hospitalizations in children aged ≤5 years in the first and second years after the introduction of the vaccine. This supports the results of randomized controlled trials and is an example of the substantial reduction in the burden of pediatric hospitalizations that can occur shortly after rotavirus vaccine uptake in a population. Further monitoring of the number of rotavirus infections and rotavirus-related hospitalizations over subsequent years will provide valuable data on the long-term impact of rotavirus vaccination.

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IMPACT OF ROTAVIRUS VACCINATION ON HOSPITALISATIONS IN BELGIUM: COMPARING MODEL PREDICTIONS WITH OBSERVED DATA

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ABSTRACT

Background: Published economic assessments of rotavirus vaccination typically use modelling, mainly static Markov cohort models with birth cohorts followed up to the age of 5 years. Rotavirus vaccination has now been available for several years in some countries, and data have been collected to evaluate the real-world impact of vaccination on rotavirus hospitalisations. This study compared the economic impact of vaccination between model estimates and observed data on disease-specific hospitalisation reductions in a country for which both modelled and observed datasets exist (Belgium).

Methods: A previously published Markov cohort model estimated the impact of rotavirus vaccination on the number of rotavirus hospitalisations in children aged <5 years in Belgium using vaccine efficacy data from clinical development trials. Data on the number of rotavirus-positive gastroenteritis hospitalisations in children aged <5 years between 1 June 2004 and 31 May 2006 (pre-vaccination study period) or 1 June 2007 to 31 May 2010 (post-vaccination study period) were analysed from nine hospitals in Belgium and compared with the modelled estimates.

Results: The model predicted a smaller decrease in hospitalisations over time, mainly explained by two factors. First, the observed data indicated indirect vaccine protection in children too old or too young for vaccination. This herd effect is difficult to capture in static Markov cohort models and therefore was not included in the model. Second, the model included a 'waning' effect, i.e. reduced vaccine effectiveness over time. The observed data suggested this waning effect did not occur during that period, and so the model systematically underestimated vaccine effectiveness during the first 4 years after vaccine implementation.

Conclusions: Model predictions underestimated the direct medical economic value of rotavirus vaccination during the first 4 years of vaccination by approximately 10% when assessing hospitalisation rates as compared with observed data in Belgium.

INTRODUCTION

The economic assessment of the newer rotavirus vaccines (Rotarix® [Rotarix is a registered trade mark of the GlaxoSmithKline group of companies] and Rotateq™ [Rotateq is a trademark of Merck & Co. Inc.]) at the time of their first introduction in 2006 was largely model-based, in the absence of long-term data on vaccine effects [1-3]. Most assessments at that time used static Markov cohort models instead of dynamic models [4], which simplified the model construction, the number of

assumptions introduced, and the data requirements [5]. Cohort models analyse the vaccine situation at epidemiological steady-state [6] when vaccination is already well established in the population at risk, children less than 5 years old in the case of rotavirus. More recently, there has been a shift towards developing more complex models for estimating the total benefit of rotavirus vaccines because a herd effect after vaccination has been reported from observational data [7-10].

Observational studies have shown that rotavirus infection produces partial immunity after each exposure [11;12], with complete immunity acquired after three to four infections. This partly explains the peculiar distribution of rotavirus disease as a function of age, which forms a bell-shaped curve during the first two years of the birth cohort. A Markov cohort model can replicate the natural history of rotavirus disease in a birth cohort over time, with the highest disease burden occurring in children aged between 6 months and 2 years, followed by a sharp decline up to the age of 5 years, after which natural immunity across the cohort is maintained.

The early economic models of rotavirus vaccination included much uncertainty due to the many unknowns in the data available at the time, such as the impact of rotavirus disease on quality-adjusted life-years (QALY), waning of vaccine efficacy over time (presumed from clinical trials), and the proportion of rotavirus gastroenteritis cases who do not seek medical care [13]. Such unknowns were modelled using 'best-guess' baseline assumptions, tested in sensitivity analyses to evaluate their impact on the incremental cost-effectiveness ratio (ICER).

Among these unknowns, vaccine waning is of particular interest. Vaccine efficacy in the cohort models was derived from clinical trial results for the rotavirus vaccines. The trials indicated higher vaccine efficacy against rotavirus diarrhoea during the first year than in subsequent years [14]. However, it should be noted that the decrease in vaccine efficacy measured over time in the European trial was mainly due to a large reduction in rotavirus diarrhoea events reported in the non-vaccinated arm (-42%), rather than due to an increase in the numbers of events in the vaccinated arm as one would expect from vaccine waning over time. This indicated that the vaccine waning assumption in the early models should be re-examined.

The two rotavirus vaccines have now been in use for several years, and real-life data are becoming available. A few follow-up studies after vaccine introduction provide information on real-life vaccine effectiveness on specific mortality reduction in Mexico and hospitalisation rates in Brazil, US, Australia and some European countries [15-22]. It is now possible to test whether the model-predicted results presented at the time of the product launch were accurate enough to report reliable cost-effectiveness data. Clearly, should substantial discrepancies occur between prediction and observation, understanding the possible causes would be valuable to improve the next generation of vaccine models. Few attempts have yet been made in the published literature to compare results predicted by models at vaccine introduction with real-life data observed over time.

Belgium provides a good opportunity to conduct such a comparison for rotavirus vaccination, as modelled estimates and observed data from a follow-up study of four years post-vaccination and two years pre-vaccination are available [18;23]. In a previous paper on the impact of rotavirus vaccination on hospitalisation in Belgium, we reported that the observed reductions in rotavirus hospitalisations after vaccine introduction were greater than those predicted by modelling [18]. In the present analysis, we have explored this discrepancy further using the most recent data from the observational study (up to four years post-vaccination) to identify potential reasons for the differences, and have adjusted the modelled ICER for differences between predicted and observed data.

METHODS

Model construction

When rotavirus vaccination was introduced in Belgium in 2006, a Markov cohort model, mainly based on the model published by Melliez et al. [23;24], assessed at vaccine steady-state the rate of rotavirus acute gastroenteritis (AGE) in a birth cohort by month up to the age of 5 years. The model included different management options typical for the Belgian context such as staying at home, seeking medical advice from a primary care physician or a specialist, visiting the emergency room, or admission to hospital. The distribution of rotavirus AGE cases by age was constructed following a Weibull function [25]. A Weibull distribution with its shape ($k = 1.5$) and scale ($\lambda = 24.2$) parameters allows replication of the distribution of rotavirus disease as a function of age, influenced by the gradual disappearance of maternal antibodies after birth and by new rotavirus infections appearing over time that stimulate the development of natural immunity. The two parameters should be adjusted for country-specific data using calibration techniques specifying breastfeeding behaviour and the frequency of infection exposure over time.

Vaccine efficacy data used in the model were taken from a European trial, which showed a decrease in effect over time that differed between mild (staying at home), moderate (seeking medical advice), and severe (hospitalised) cases [14].

For each level of disease severity, specific costs and utility scores were applied [23]. The model compared vaccinated and unvaccinated cohorts and allowed for changes in vaccine coverage. Herd protection was not included. The model estimated the vaccine effect on the number of AGE events, medical visits, emergency visits, hospitalisations and deaths in a birth cohort of children up to the age of 5 years. It also reported the overall cost, QALY impact, and ICER for vaccination compared with no vaccination.

Observational study

A vaccine impact study was set up one year after the introduction of the rotavirus vaccine in Belgium [18;21]. Full details and the results for the first two years post-vaccination (up to May 2009) have been published elsewhere [18]. Data were collected retrospectively after each rotavirus season from a sample of 12 Belgian

hospitals. All children aged ≤5 years who had a rotavirus detection test performed at a participating hospital from 1 June 2004 to 31 May 2006 (pre-vaccination study period) or 1 June 2007 to 31 May 2010 (post-vaccination study period) were eligible. Only hospitalised children were included, and data were analysed for the nine centres with a complete dataset. Ethical approval was not required because there was no medical file consultation.

The post-vaccination study period was divided into successive years, each running from June to May (June 2007–May 2008, June 2008–May 2009 and June 2009–May 2010) to cover the winter rotavirus season. The period between 1 June 2006 and 31 May 2007 was not included in our study, because reimbursement for rotavirus vaccination was not available for the whole of this period (partial reimbursement was introduced in Belgium in November 2006 for Rotarix® and in June 2007 for RotaTeq™ [18]). Thus, although June 2006–May 2007 could be considered as the first year post-vaccination, the date of reimbursement meant that it was neither fully pre-vaccination nor fully post-vaccination. In this study we therefore analysed data from the second post-vaccination year (June 2007–May 2008) onwards. For each year the number and the proportion of rotavirus-positive episodes were calculated per week. Hospitalisation was classified as AGE-driven if the stool sample was collected within 48 hours of hospitalisation. The most relevant variable to compare in the pre- and post-vaccination periods is the absolute number of rotavirus-positive episodes observed, assuming no change in catchment area between the study periods for each participating hospital.

Comparison between observed and modelled data

From the raw observed data we first calculated the frequency of hospitalisation per week for each of five age groups (0-1 year; 1-2 years; 2-3 years; 3-4 years; 4-5 years) over a period of one year for the pre-vaccination period and for the second (June 2007–May 2008) and fourth (June 2009–May 2010) years post-vaccination. As the data are from a small sample, it is likely that data from a larger sample would follow a smoother distribution. This is represented by adjusting the raw frequencies to smoothed parametric curves using @RISK 5.7 software (Palisade Corporation, US). The software is an add-in program in Microsoft Excel® that uses the collected data as input variables, for which it creates a distribution expressed as a probability density function from a list of around 20 continuous parameterised distributions. Since all probability distribution functions must have a unit area, the software automatically scales the probability values so that the density curve has an area of one. The method of least squares is used to minimize the Root-Mean Square Error between the curve points and the theoretical distribution function selected (RMS Error value < 0.05 or the best Chi-squared statistics noted between the observed data and selected parametric distribution). The figures obtained are referred to in this paper as smoothed curves, or adjusted observational data. Because the smoothed curves are parameterised distributions, they are easier to work with when calculating values for the areas under curves.

The original modelled data were derived from a hypothetical birth cohort followed over time from birth to age 5 years, whereas the observed data were derived from

multiple one-year cross-sectional observations in a population of children aged up to 5 years. To allow a transparent comparison between the two, it was necessary to transform the results from the cohort model to a population approach, which could be compared with the population data from the observational study.

This transformation includes as a first step elaborating the original single cohort model into a multiple cohort model with five birth cohorts, sequencing the start by delaying each subsequent year. This construction allows the vaccine coverage rate and the vaccine efficacy to be varied by month, year, and age group. Vaccine efficacy and coverage values are shown in Table 1. The baseline age distribution for rotavirus AGE events in each cohort model followed a Weibull function as described above. The age distribution for hospitalised events used a modified distribution to take into account the higher hospitalisation rate in infants and young children. The parameter values used in each Weibull distribution are shown in Table 1. The net hospital age-distribution result in each cohort model was the combination of the two distributions, multiplying the density probability function of the AGE distribution by the hospitalisation distribution, leading to a combined distribution (Figure 1).

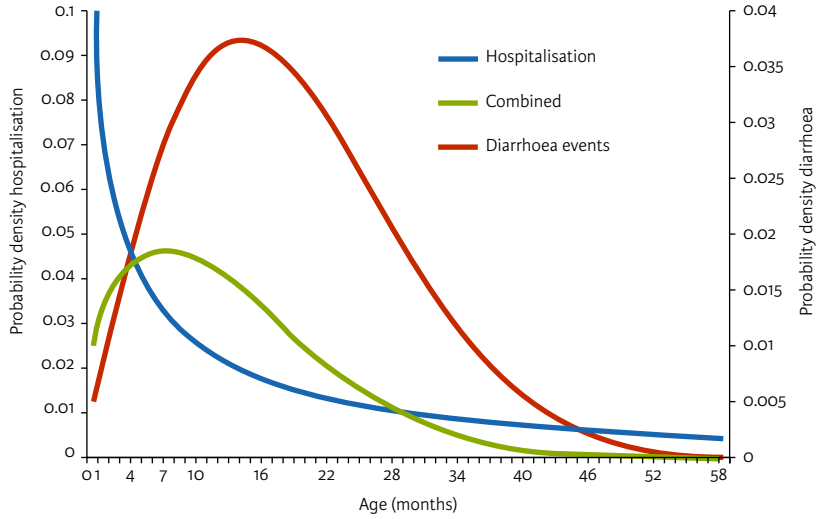
Table 1 Model-specific adaptations to fit pre-vaccination observed data

Parameter	Value
Disease distribution as a function of age from birth to month 60	Weibull 1 with parametric distribution of $k = 1.5$ and $\lambda = 24.2$
Hospitalisation distribution as function of age from birth to month 60	Weibull 2 with parametric distribution of $k = 0.6$ and $\lambda = 29.3$
1st year vaccine coverage	60%*
2nd year vaccine coverage	80%*
3rd year vaccine coverage	85%*
4th year vaccine coverage	85%*
Estimated vaccine efficacy 1st year	95%
Estimated vaccine efficacy adjustment every subsequent year post-vaccination (reduction in efficacy to represent vaccine waning)	15% per year

*reported from Intercontinental Medical Statistics (IMS) data

The next step was to introduce two assumptions in the analysis that could be checked against the observed data. First, we assumed that the annual epidemic rotavirus spread of hospitalised disease in children aged up to 5 years followed a normal distribution. Registry data on the annual spread of rotavirus indicate that this assumption is acceptable [26]. We therefore constructed a normal distribution over a 52-week period with a standard deviation of 0.16 for a mean value of 1, by which the spread of the disease is absent over a period of 16 weeks per year. The second assumption was that the age distribution per week in the normal distribution followed the combined distribution of the age cohort, as defined in Table 1. As a consequence, the disease spread each year appeared first and disappeared last in infants and young children, compared with older children, reflecting the distribution with a higher hospitalisation rate in infants and young children.

Figure 1 Probability density functions for defining hospitalisation rate as a function of age (pre-vaccination)



This approach allowed precise measurement of differences between the impact of vaccination in the model construct and the observational data. Any differences identified between the observation and the modelled results were explored to see if potential explanations could be found. Once potential explanations were identified, we adjusted the model input values to be equivalent to the observed data to estimate adjusted ICERs.

RESULTS

Figure 2 shows the pre-vaccination curves for adjusted observed data on the number of hospitalisation events by week and age group (Figure 2A) that were similar to the modelled results from the multiple age-cohort model (Figure 2B). As expected, the pre-vaccination peak in rotavirus hospitalisations was highest in children aged <1 year. In the observed data the peak appeared at approximately the same time of the year (Week 8) in all age groups, consistent with seasonal rotavirus spread and indicating a dependency in rotavirus transmission between age groups. The two assumptions introduced into the multiple cohort model to construct a population approach appeared to hold when comparing the distribution results of the model and the observation data. Moreover, there was close agreement between the observed and modelled numbers of rotavirus hospitalisations by age group per year for the pre-vaccination scenario (Table 2).

In the post-vaccination period, the observed data showed that the seasonal peak in rotavirus hospitalisations was reduced in magnitude and delayed (shifted to the right) in the second year after vaccine introduction for the first two age groups, with further reduction and delay in the fourth year across all age groups (Figure 3A-D).

Figure 2 Observed and modelled numbers of hospitalised rotavirus events (pre-vaccination)

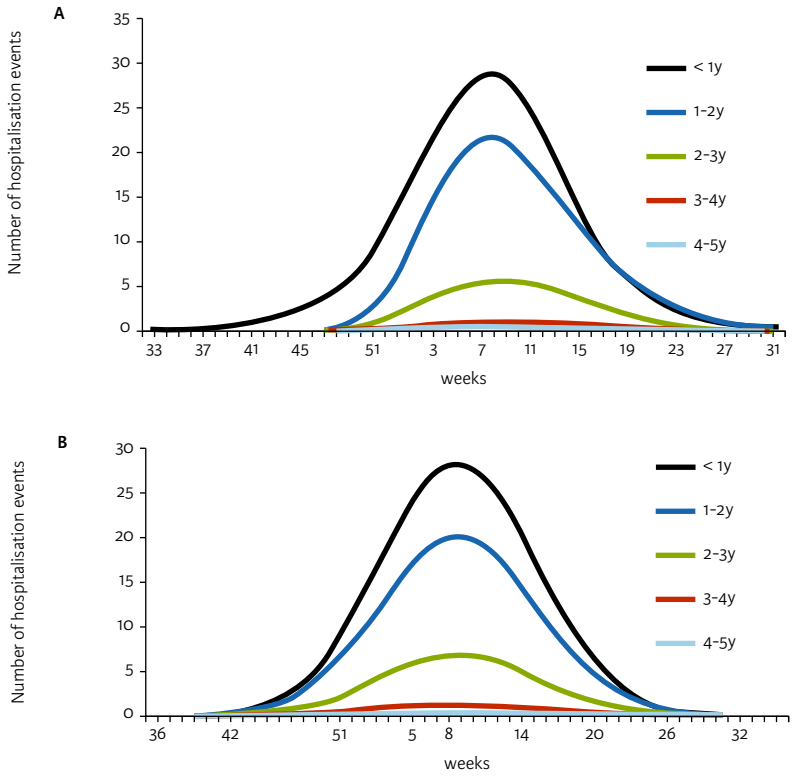
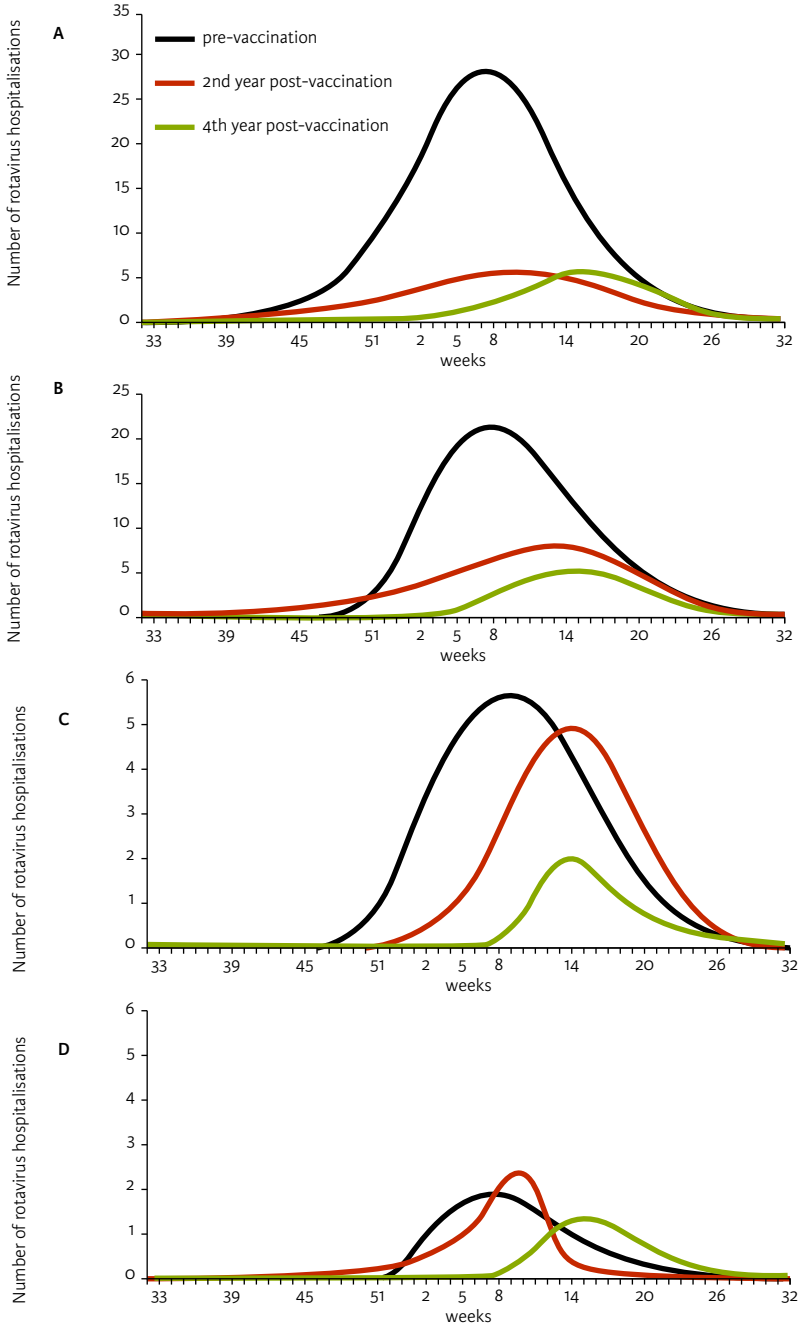


Table 2 Reported hospitalisation events over one year by age group pre-vaccination, for observed and modelled data

	Number (%) of rotavirus hospitalisations	
Age group (years)	**Observed**	**Modelled**
< 1	454 (51.8%)	439 (49.8%)
1–2	319 (36.2%)	312 (35.4%)
2–3	86 (9.7%)	106 (12.0%)
3–4	15 (1.7%)	21 (2.4%)
4–5	7 (0.8%)	3 (0.3%)
Total	**880**	**881**

As the observational study included children aged up to 5 years, some of the children enrolled in the post-vaccination period were too old for vaccination when the vaccine was introduced, and thus were unvaccinated. The age threshold increased in successive years post-vaccination. In the second year post-vaccination (June 2007–May 2008), the maximum age of vaccinated children was 21 months (born in or after September 2006, just in time to receive vaccination

Figure 3 Impact of rotavirus vaccination after 2 and 4 years of vaccination by age group (observed data). Aged ,1 year (A); Aged 1–2 years (B); Aged 2–3 years (C); Aged .3 years (D). Weeks are numbered according to seasonal distribution



after reimbursement of the first rotavirus vaccine product in November 2006, and included in the last month of that study year in May 2008), and in the fourth year post-vaccination (June 2009–May 2010) the maximum age of vaccinated children was 45 months (born in or after September 2006 and included in the last month of that study year in May 2010). The reduction in hospitalisations post-vaccination compared with pre-vaccination observed in the age groups who were too old to be vaccinated (Table 3), indicated that the vaccine had an indirect protective effect.

Table 3 Observed and modelled data pre- and post-vaccination by year and age group

		Post-vaccination			% reduction from pre-vaccination		
Age group (years)	**Pre-vaccination**	**Year 2**	**Year 4**	**Adjusted**	**Year 2**	**Year 4**	**Adjusted**
Observed							
<1	454	125	77		72%	83%	
1-2	319	164	72		49%	77%	
2-3	86	61	17		29%	80%	
3-4	15	9	10		40%	33%	
4-5	7	9	3		-29%	57%	
Total	**880**	**368**	**179**		**58%**	**80%**	
Modelled							
<1	439	146	127	127	67%	71%	71%
1-2	312	161	111	73	48%	64%	77%
2-3	106	106	48	29	0%	55%	73%
3-4	21	21	11	7	0%	48%	67%
4-5	3	3	3	3	0%	0%	0%
Total	**881**	**437**	**300**	**239**	**50%**	**66%**	**73%**

Number of rotavirus hospitalisations from observed and modelled data. Adjusted data refer to modelled data with vaccine waning removed from the model (i.e. assuming that vaccine efficacy is the same in subsequent years as in the first year)

There is a second group of children ineligible for vaccination, those too young to receive the vaccine (aged up to 2 months). The number of observed rotavirus gastroenteritis events in this age group also declined in the years after vaccine introduction (Table 4) (Chi-square-test for trend, $p < 0.01$). The results indicated that a herd protection effect may also occur in children too young for vaccination, due to reduced transmission of natural rotavirus infection after vaccine introduction.

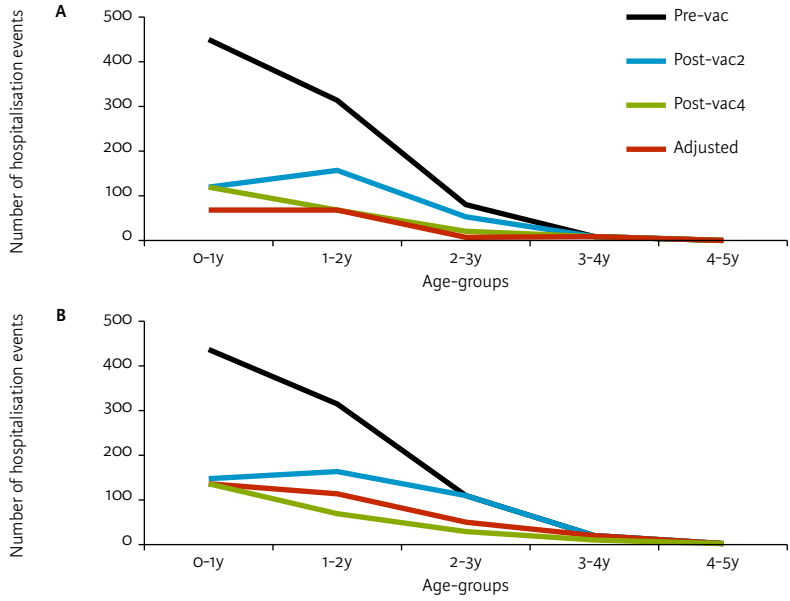
Table 4 Rotavirus hospitalisations pre- and post-vaccination in infants < 3 months old

	Number of rotavirus hospitalisations			
Age group	**Pre-vaccination**	**Post-vaccination 2nd year**	**Post-vaccination 3rd year**	**Post-vaccination 4th year**
0-1 month	18	12	4	6
1-2 month	46	8	13	11
2-3 month	38	23	14	6

(Chi-square for trend: $p < 0.001$).

The overall herd effect that occurred in real life was not included in the model. But the more rapid decrease in hospitalisations in the observed data, compared with the model, is also noteworthy because the model assumed a decrease in vaccine efficacy year on year (Table 1), which was not apparent in the observed data. In

Figure 4 Pre- and post-vaccination data by year and age group



Observed data (A); Modelled data (B). Pre-vac, pre-vaccination; Post-vac2, second year post-vaccination; Post-vac4, fourth year post-vaccination; Adjusted, modelled results assuming no vaccine waning, included for comparison purposes

sensitivity analysis, the model was run with no decrease in vaccine efficacy (i.e. assuming that vaccine efficacy was the same in subsequent years as in the first year). These data are shown in Table 3 and Figure 4 as 'Adjusted' data. They closely followed the observed data for the fourth year post-vaccination.

The estimated ICER for rotavirus vaccination was based on the modelled data at the time of vaccine introduction. Our earlier results [18] indicated that the model underestimated the reduction in hospitalisation rates. Our present results show that herd effect on the one hand, and lack of waning on the other, were the main differences between the original static model and real-life data (Figure 3, Tables 3 and 4). Adjusting the model for these factors produced an estimated ICER slightly more favourable to rotavirus vaccination than the estimated ICER without these adjustments (Table 5). The change in the ICER was small (approximately a 10% improvement), because the major impact of change was mainly measured two years after vaccine introduction when the hospitalisation rate was already reduced. The ICER was calculated from the perspective of the healthcare system (direct medical costs only), and so did not capture some categories of cost such as lost productivity from parents taking time off work to look after a sick child. Such costs were not included because we were unable to collect data on them in a real-life setting. A further reduction in the ICER would be expected with an analysis performed from a societal perspective capturing a wider range of costs.

Table 5 Cost-effectiveness of rotavirus vaccination pre- and post-adjustment

	Cost	Difference	QALY	Difference	ICER
Pre-adjustment					
No vaccination	70 €		-0.002		
Vaccination	139 €	69 €	-0.00063	0.00138	51 000 € [23]
Post-adjustment					
No vaccination	70 €		-0.002		
Vaccination	135 €	65 €	-0.00055	0.00145	44 828 € (-10%)

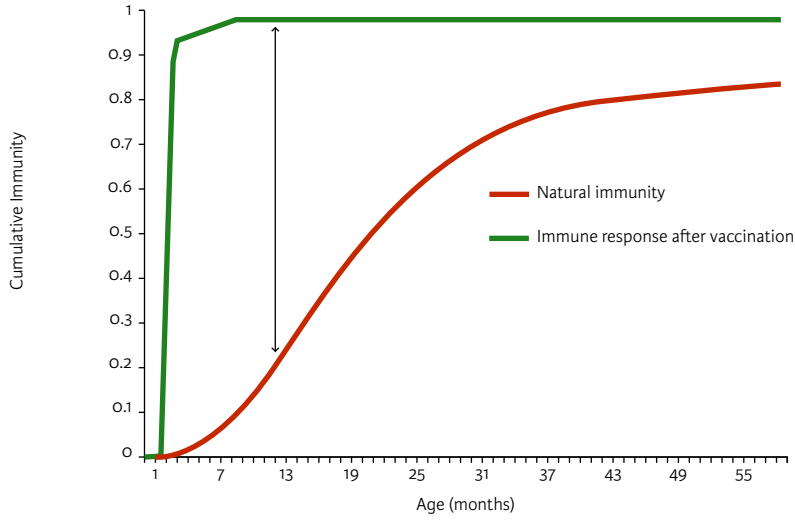
ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

DISCUSSION

This analysis compared observed data on rotavirus-related hospitalisations collected in routine clinical practice for four years post-vaccination in Belgium with previously modelled estimates of the effect of vaccination in the same country. The observed reduction in hospitalisations with data from two years post-vaccination has previously been shown to exceed the reduction predicted by the static model [18]. Two differences between the modelled and the observed data were identified that could explain this discrepancy. First, the observed data indicated an indirect herd effect in infants too young (aged <2 months) and too old for vaccination when the vaccine was introduced, which was not included in the model. Second, the model assumed a waning of vaccine efficacy over time based on clinical trial data, which did not appear to be reflected in the observed data from a real-life situation over time frames of three or four years.

Regarding waning of vaccine efficacy, analysis of the vaccine efficacy results of the European trial may offer an explanation that better helps in understanding the difference between the modelled and the observed data. Vaccine efficacy is normally measured as the proportion of one minus the ratio of events that appear in the study arm that received the vaccine divided by the number of events that occur during the same time interval in the non-interventional arm. When analysing the vaccine efficacy in the first and subsequent years of the trial, researchers assume that if a dramatic decrease in events occurs in the non-interventional arm in the second year compared with the first year, as seen in the European trial (the decrease observed in the first versus subsequent year is > 40%), a similar decrease should also be observed in the vaccinated arm on top of the measured vaccine benefit of the first year. Any deviation from this result is explained as a reduction in vaccine efficacy called vaccine waning. This assumption is hard to accept as the explanation. The absolute number of events in the vaccinated group during the second year amounted to about the same values as in the first year. So, most of the decrease in vaccine efficacy in the second year in the trial was due to a sharp decrease in the number of events in the denominator, rather than to a sharp increase of the numbers in the vaccinated arm. We hypothesise that the results in the non-interventional arm could have been influenced by a herd effect in the trial, because the randomisation process included 2 vaccinated children for 1 non-vaccinated child. This 2:1 randomisation may have further decreased the number of events in the non-vaccinated arm in the second year of the trial. As a result of

Figure 5 Natural immunity and immune response after vaccination, showing the net effect of vaccination (arrow line)



this observed evidence – a large imbalance in the number of events observed over time in the non-vaccinated arm – the true vaccine efficacy measured in the trial may be an underestimate compared with vaccine effectiveness observed in real life, as seen here in the impact study results. It is of interest that the decrease in the subsequent year seen in the 2:1 randomised trial (>40%) was greater than that observed in a 1:1 randomised trial of rotavirus vaccination conducted in the US, where the reduction from the first year to the second was approximately 15% [27].

Even if we introduce a correction into the model by excluding the waning scenario (adjusted results in Table 3), the model still underestimates the total vaccine benefit, mainly because of the indirect protection in infants too young to be vaccinated (aged <2 months). This can be seen in Figure 4, where the change in number of hospitalisations between pre-vaccination and the second and fourth years post-vaccination in children aged <1 year was considerably larger in the observed data (Figure 4A) than in the modelled data (Figure 4B). The indirect vaccine efficacy seen in these very young infants is likely to remain at steady-state level. This analysis also provides indirect information about rotavirus transmission in children. Since rotavirus vaccination appeared to have an indirect protective effect on young infants, our results suggest that children in the age range eligible for vaccination can infect younger children.

If vaccination alters the natural transmission of rotavirus in the population outside the at-risk group, it is possible that an age-shift of rotavirus disease could occur, as predicted by dynamic models [7]. However, if the wild-type rotavirus still circulates in the whole population, allowing reinfection and boosting of natural immunity, age-shifts of rotavirus disease may be less likely to happen after introducing vaccination.

It is not yet known how rotavirus vaccination will affect rotavirus transmission. It is, however, likely that reported observations over longer time periods will see less important herd effects per year than observed here as soon as the whole at-risk population (children aged <5 years) has been vaccinated.

Our analysis of the observed data suggests that no reduction in vaccine efficacy (vaccine waning) occurred in real life during the first 4 years. It is known that subjects repeatedly exposed to rotavirus gradually build up natural immunity over time. This has been well illustrated by Velazquez and colleagues [28] and others [29]. The observed age-related disease pattern (more cases in young children than in older ones) reflects this immunity build-up, together with other factors that could affect exposure such as behaviour changes. Therefore the effect measured in a clinical trial is not only the vaccination effect, but is a difference between vaccinated and unvaccinated groups (which can be called a net effect) (Figure 5). As natural immunity develops over time in the non-vaccinated group, the net effect would change over time, and that could be mistakenly interpreted as vaccine waning. Herd protection effects could influence the change in net effect as natural immunity would be larger in its absence (because exposure to the virus would be larger).

The results presented in this paper indicate that the ICER estimated from the model for vaccination versus no vaccination, using vaccine efficacy results from randomised controlled trials, may have underestimated the benefit of rotavirus vaccination. Adjusting for that difference would result in a model outcome more closely related to the observed data. The effect is marginal from a healthcare system perspective, as the benefit is mainly seen after two years of vaccine exposure when hospitalisation rates are already low. However, it may have a larger impact on the ICER considered from a societal perspective. We conducted a simulation exercise to explore the potential effect if the reduction in hospitalisations observed in this study were also to occur across the whole disease management area of non-hospital medical visits and indirect costs. If non-hospital medical visits and indirect costs are reduced by the same amount as observed for hospitalisations, the ICER results estimated by the model would improve by >30%. Collecting real-life data on non-hospital medical visits and indirect costs to test this prediction would be a valuable area for future research. This finding will of course be country-specific, depending on the specific disease management programmes in place and whether the economic assessment is conducted after reaching the steady-state level.

In conclusion, it is likely that previously published economic models underestimated the total benefit of rotavirus vaccination, by not including an estimate of herd protection and by including a vaccine waning effect that was not reflected in real-life conditions during the first 4 years of vaccine introduction. These findings could be applicable in other disease areas in which natural immunity develops over time as a result of regular exposure to the infectious agent, although this is not often observed. Static cohort models have major difficulties in capturing such effects and may therefore underestimate the total benefit of vaccines when introduced in children.

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MEDIUM- TO LONG-TERM IMPACT OF ROTAVIRUS VACCINATION ON HOSPITAL CARE IN BELGIUM: 7-YEAR FOLLOW-UP PERIOD OF ROTABIS (ROTAVIRUS BELGIUM IMPACT STUDY) WITH PROJECTIONS.

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ABSTRACT

Background: Rotavirus vaccination has been introduced in Belgium since 2006. A sharp decline in hospitalisations was observed during the first years after vaccine introduction with the high uptake it had (>85%). Our study objective is to investigate whether this hospital decline is maintained and to simulate projections.

Methods: The Rotavirus Belgium Impact Study (RotaBIS) allows an analysis of rotavirus vaccine impact amongst children in 11 hospitals in Belgium over a 9 year period (2005-2013) with 2 years pre- and 7 years post-vaccine introduction. Results are compared by year and by subsequent birth cohort aging up to 5 years. The 2 different analysis methods help dismantling the different (direct and indirect) effects of vaccine protection to simulate future hospitalisation trends.

Results: During the whole observation period 40,552 rotavirus detection tests were performed of which 5,832 were positive (14.4%). After rotavirus vaccine introduction a significant reduction in number of tests performed (-35%) was combined with a dramatic drop in numbers of positive test results (-76%). The decreases were spectacular during the first two years of vaccine introduction but after that the decrease flattens. Comparing cross-sectional with cohort data it shows that the initial drop was heavily influenced by the herd effect of the vaccine. Cohort analysis demonstrates a low rate of residual disease over time suggesting another infection source than the child population.

Conclusions: Residual disease will be maintained in the community when a same vaccination strategy is continued over time starting vaccination of children only at 6 weeks' time.

Keywords: rotavirus, vaccination, gastroenteritis, hospitalization, children

INTRODUCTION

Rotavirus (RV) infection is the most common cause of diarrhea in young children less than 5 years old across the world [1;2]. The infection has a seasonal epidemic spread in temperate climates with a much higher frequency during the winter [3-5]. Severe consequences of RV gastroenteritis (RVGE) are more often observed in children under the age of 2 years, after which a dramatic drop in the number of diarrhea events is noticed [6]. After the age of 5 years, children have normally acquired a natural immunity so that RV diarrhea is seldom reported [7-9].

RVGE is very contagious and therefore its spread remains difficult to control even with rigorous application of primary hygienic measures [10]. As a result, the RVGE epidemic is a well-known annually recurring public health problem. In Belgium for instance, before the introduction of the vaccine, it was causing a disease burden of around 70,000-75,000 diarrhea events per year in children under the age of 7 years [11;12]. But the RV infection has some interesting features that make the contagion quite unique. RV immunity is built up by successive infection exposures of which the first one is the most severe leading to acute symptoms but the following ones are progressively less severe [9;13].

To reduce this public health burden a radical change in disease management should be considered such as the early stimulation of infants' immunity between the ages of 6 and 10 weeks, thus providing protection while still being regularly exposed to the virus. This new management strategy uses RV vaccines, which have been available in Europe since 2006 for a two-dose vaccine, *Rotarix*™ (GlaxoSmithKline Vaccines, Rixensart, Belgium), and since 2007 for a three-dose vaccine, *Rotateq*® (Merck and Co. Inc, Whitehouse Station, New Jersey, United States). The first dose of the vaccine can be administered from 6 weeks of age, with a minimum interval of 4 weeks between subsequent doses [14;15]. To date, only a few countries in Europe have taken the advantage of the vaccine availability to start reimbursement or to make the vaccine accessible through tenders. Four countries in Western Europe introduced the RV vaccine into their routine immunization schedules soon after the vaccine became available: Austria, Belgium, Finland and Luxemburg [16]. By February 2014, national universal RV vaccination recommendation had been implemented in a few additional countries, including Estonia, Germany, Norway, and the United Kingdom (UK) [17].

Studies from Austria [18;19], Finland [20] and Belgium [21-23] have reported quite impressive reductions in hospitalizations 2-3 years after vaccine introduction combined with a vaccine herd effect. The medium- to long-term effect of the vaccine within the same at-risk group has not often been reported [24;25]. In the study presented here we report about results of Belgium where the vaccine uptake was very high from start (>85% first year) and where cohorts of children ≤5 years of age were followed from 2005 through 2013 (2 pre-vaccination and 7 post-vaccination years) [26]. Such a long follow-up period should help in better understanding how the vaccine is working in real life conditions. For instance we hypothesize that if there is only one infection source (the children themselves) and the vaccine effectiveness remains the same together with a well-maintained high vaccine uptake (>85%), the reduction in RVGE hospitalization rate should continuously decrease year after year leading to an elimination of the disease very soon. This suggestion can now be tested by analyzing the number of hospitalizations seen and expected by year and in each birth cohort over time, and by comparing the differences. If there are major deviations between expected and observed results, the shape of the curve could help identifying a likely reason for the difference. Sources of curve deviation could include another source of infection not affected by the vaccine, vaccine waning, variable vaccine coverage rate, selection bias among some of the participating centers, or a combination of the different reasons.

MATERIAL AND METHODS

Data source

Retrospective hospital database analyses were conducted at the same 11 hospitals in Belgium over an observation period of 9 years (2005-2013). Nine were general hospitals with a pediatric ward and two were pediatric only hospitals. In addition 4 of the 11 centers were university hospitals. The centers were distributed across the country and covered the three regions of Brussels, Flanders and Wallonia. All the centers had combined around 500 pediatric beds, representing 17% of the total of 2,750 pediatric beds in Belgium.

Each participating center provided information on the laboratory assays used to detect RV. We collected in each center the following information: center code; children's date of birth; children's age; gender; date of sampling; RV test results (negative, positive); outcome (ambulant or hospitalized); date of hospital admission and discharge; and length of hospital stay in days. The data were pooled anonymously before any analysis occurred. Ethical approval for the study was obtained from each participating hospital, each year we collected the data.

All children aged ≤5 years old who had a RV detection test performed at one of the participating centers from January 1, 2005 to May 31, 2013 were eligible for inclusion in the current analysis. The pre-vaccination study period was defined as from January 1, 2005 to December 31, 2006. The period from January 1, 2007 to May 31, 2013 was considered as the post-vaccination period (reimbursement of the vaccine was introduced in November 2006). The number of tests performed and the proportion of RV-positive test results were calculated for each participating center, per month, per year and for 7 different age groups (≤2 months, >2–12 months, >12 months–2 years, >2–3 years, >3–4 years, >4–5 years, >5 years). Children aged <12 months were subdivided into two groups (≤2 months and >2–12 months) because the former group was too young for vaccination but could experience a herd protection effect once the vaccine is introduced.

Data analysis

The data are analysed in two different ways:

- cross-sectional by year: the number of hospitalizations during the epidemic period of each year (January until the end of May) for the 7 age-groups during the period 2005–2013 is summed up and reported annually. The data are compared by age-group and overall per year: pre-vaccination versus post-vaccination (1st year, 2nd year, nnd year… 7th year post-vaccination).

- by birth cohort followed over time: the number of hospitalizations during the epidemic period is noted in the birth cohort for the first and for each subsequent year of that cohort until the children are getting 5 years old. The results are summed up by year for each birth cohort and for the total follow-up period. The results are compared by subsequent birth cohorts. Using this approach, we could report 3 vaccinated subsequent birth cohorts getting 5 years old and 5

vaccinated subsequent birth cohorts getting 3 years old. We also compare those results with the pre-vaccination period but cross-sectional only as those data were not under the influence of RV vaccination.

Two important assumptions underlying the comparison of the annual number of RV-positive test results are that the catchment area for each of the participating centers remained the same across the whole observation period of 9 years and that no change in disease management behavior for testing the children ≤5 years old on RV disease occurred during that period. It means that if fewer tests were performed once the vaccine has been introduced, this has mainly to do with less suspected cases presenting themselves to the hospital unit and not with a change in behavior of the physician who was less likely to perform RV test once the vaccine was introduced. Therefore, the most relevant value to compare between the years is the accumulated number of RV-positive test results and not the proportion of RV-positive test results.

Model simulation

To well-understand the real impact the vaccine has, this can best be achieved by comparing observed results with a model simulation in which we separately control the different aspects that could impact the outcome (hospital reduction) such as changing the vaccine efficacy over time, initiating a second source of infection not being under the influence of the vaccine, changing the vaccine waning rate, or changing the vaccine uptake per year. For doing that comparison we selected from the observed data the birth cohort follow-up data up to the age of 3 years in order to obtain enough data-points over time.

We developed a time difference equation model based on the initial data collection of the first years of observation. An analysis is then simulated in which the decrease in hospital numbers for the first few years fits the observed data with fixed parameters over time, a calibration process:

$$X_{n+1} = X_n * cov_n * 1 - r + X_n * 1 - cov_n + X_m$$

in which:

- r is the fixed decreasing value equivalent to the vaccine efficacy (VE),
- cov is the vaccine coverage rate,
- x_o is the starting hospital numbers at t_o,
- x_m is the residual disease hospitalization ($X_m = X_o * f$),
- f is the fraction of hospitalization caused by another source of infection
- n indicates number of years

With the model we may easily adjust the shape of the simulated curve changing separately the vaccine uptake (cov) at specific n time points, the vaccine waning by decreasing r, the residual disease caused by another source of infection by changing f. The simulated shape can then be compared with the observed data and the best fit is selected for the most plausible scenario of projected future hospitalizations related to the disease.

Outcomes

An annual comparison of cross-sectional data will identify the importance of the herd effect generated by the vaccine. Analyzing and comparing successively vaccinated birth cohorts over time will indicate whether the vaccine wanes. Comparison of the summary measures of vaccinated birth cohorts per year with simulated predictions will test the hypothesis about different sources of infection. Finally, the proportional difference in RV-positive test results between pre- versus the most recent post-vaccination period analyzed (2012-2013) across the 11 participating centers will identify any selection bias in participating centers that may explain why residual disease could be observed over time. Results are tested for statistical significance using Chi-square tests for trend of proportional data, with a statistical significance level of $p<0.05$ [27].

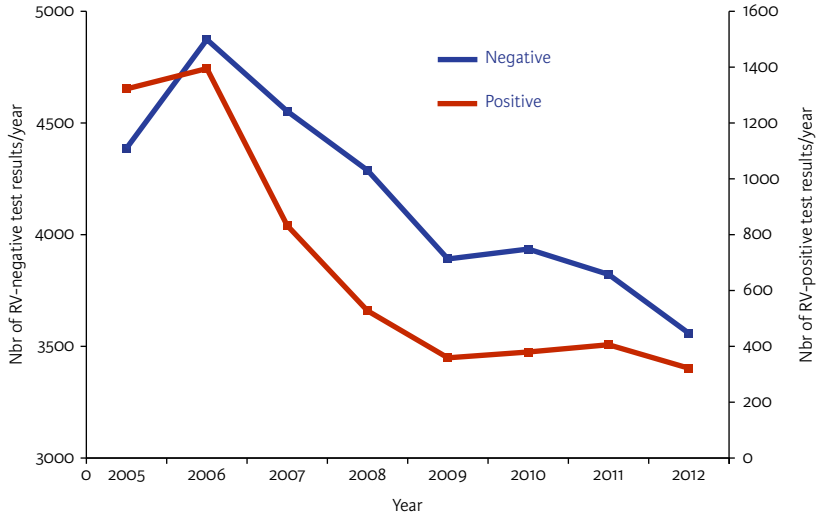
RESULTS

Cross-sectional analysis

Among the 11 participating centers 40,552 RV tests were conducted over the observation period of 9 years, with a much higher frequency during the epidemic months. The overall number of RV-positive test results recorded during that period was 5,832 (14.4%). Over the years, the overall number of tests performed significantly decreased from 6,278 tests in 2006 during the pre-vaccination period to 3,893 tests in 2012 during the post-vaccination period, representing a reduction of 38%. Moreover, the absolute number of RV-positive test results decreased from 1,399 tests in 2006 during the pre-vaccination period to 327 tests in 2012 during the post-vaccination period, representing a reduction of 76.6%. The decrease in RV-positive test results was extremely sharp during the first 2-3 years after the introduction of the vaccine and then flattened over time, compared with the more linear decrease in the number of RV-negative tests over time (Figure 1). The non-linear reduction in the number of RV-positive test results over time was statistically significant ($\chi^2=215.95$; $p<0.0001$).

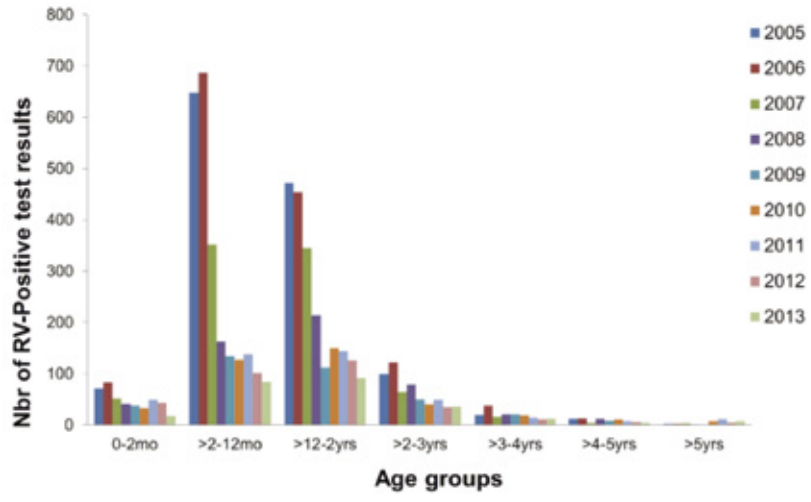
The number of RV-positive test results is shown by age group and year in Figure 2. There was a sharp drop in the number of RV-positive cases in the first year after the introduction of RV vaccination, especially in the vaccinated age groups (>2–12 months and >12 months–2 years) which represent nearly 78% of the entire study population. There was also a drop in the number of positive cases in children who were either too young (≤2 months) or too old (>2 years) to be immunized.

Figure 1 Number of RV-negative and RV-positive test results performed per year in the 11 participating centers



Nbr: number; RV: rotavirus.

Figure 2 Distribution of RV-positive tests results by age group and year.



Nbr: number; RV: rotavirus; mo: months; yrs: years.

Birth cohort analysis

Table 1 shows the numbers of RV-positive test results by age group and by year for each epidemic period (January until end of May). The accumulated data represent 85% of the total RV-positive test results, with the remaining 15% observed in the other months of the year, especially November and December.

In 2007, the cross-sectional results indicated a total of 710 RV-positive test results, which was 44% lower than the year before when no vaccine was provided (there were 1271 RV-positive test results in 2006). Following the birth cohort from 2007 to 2012, and summing the values year-by-year with increasing age in the table (69+305+199+44+16+5+2), reached 640 RV-positive test results. As expected, this is lower than the cross-sectional result of 2007. The difference between the two values (710 versus 640) is explained by the difference between age groups subject to the herd effect only (marked as yellow cells in the table for the cross-sectional calculation) versus the age groups subject to direct vaccine effect plus the herd effect (marked as light brown cohort cells).

Table 1 Cross-sectional analysis by age and year and analysis by birth cohort for the RV-positive test results during the epidemic period

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
≤2 mo	**84**	100	69	45	41	32	44	31	28	474
>2-12 mo	**551**	634	305	127	108	101	95	80	82	2083
>12 mo-2 yrs	367	**381**	266	199	88	116	107	88	89	1701
>2-3 yrs	82	111	**51**	59	44	23	38	29	31	468
>3-4 yrs	16	34	14	**18**	16	16	7	9	13	143
>4-5 yrs	9	10	3	12	**7**	7	5	5	3	61
>5 yrs	2	1	2	1	0	**6**	10	2	7	31
Total CS	**1111**	**1271**	**710**	**461**	**304**	**301**	**306**	**244**	**253**	**4961**
Total BC						**1098**	**1092**	**640**	**302**	

Footnote: BC: Birth Cohort; CS: Cross-sectional; Light brown cells: birth cohort analysis; Yellow cells are the herd effect cells; Red bold numbers indicate how the birth cohort totals were calculated.

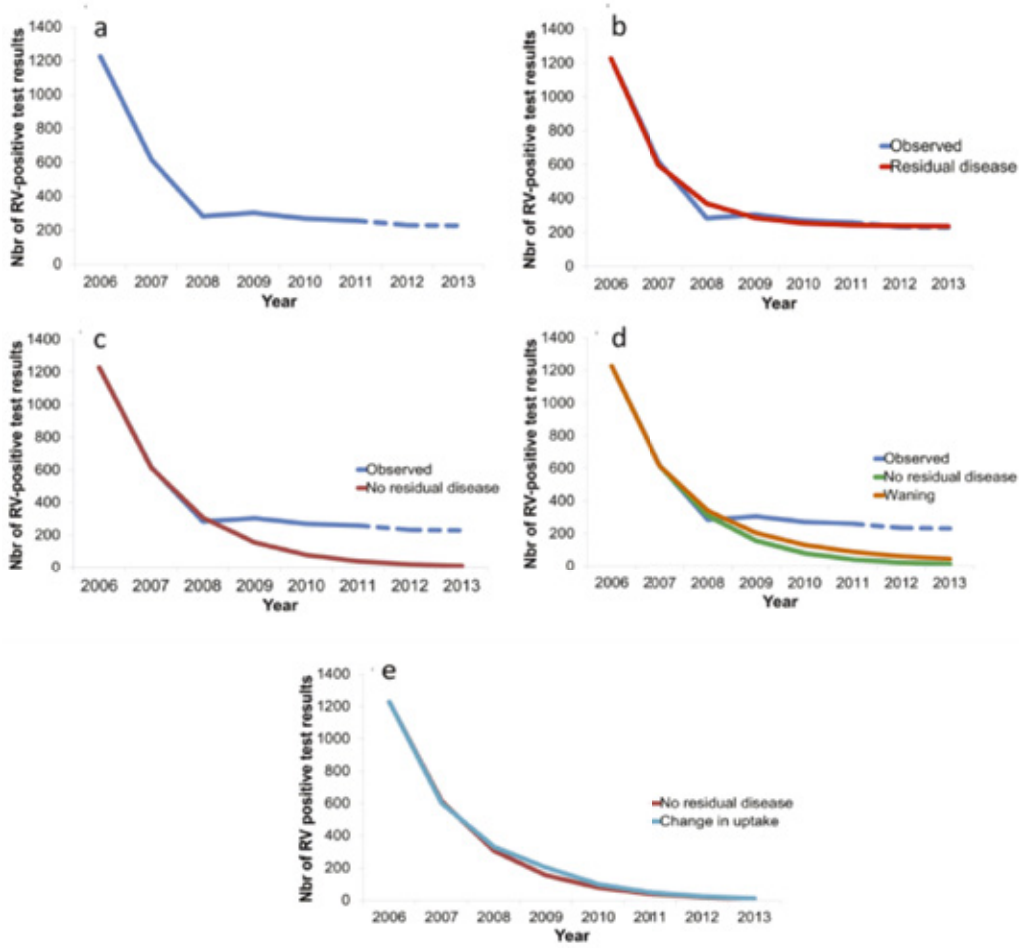
A herd effect was maintained after the first 5 years of the vaccination programme, as shown by the continued reduction in RV-positive test results seen in children <2 months of age who are too young for vaccination (first row, yellow cells).

A particularly interesting finding in the cohort analysis is that the data do not show any additional drop in the early age groups (>2–12 mo and 12 mo–2 yrs) after the large decrease of the first 2 years. This indicates that the rate of decrease in hospitalization changes over time, which indirectly reveals that another factor must influence the process of RV infection in this child population.

Model simulations

Figure 3 compares first-year observed results (a) with simulations of having another source of infection in the population (b), having no other source of infection in the population (c), vaccine waning (d), and having a different vaccine uptake scenario (e).

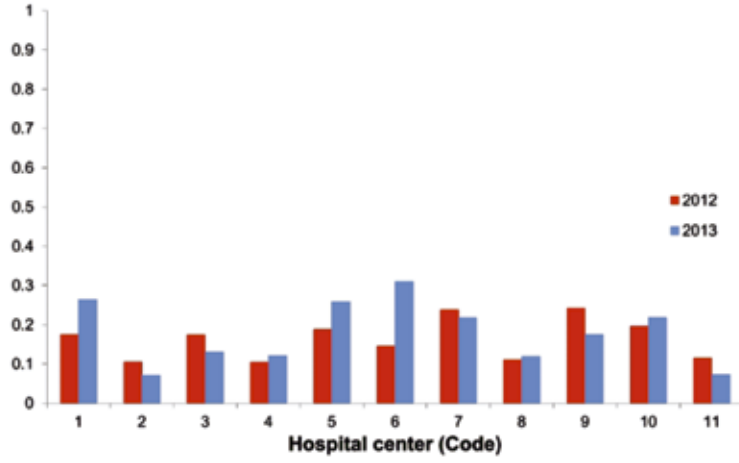
Figure 3 Comparing observed data (a) with simulations of adding residual disease (residual disease) over time (b); with fixed reduction in RV-positive test results without residual disease (c); vaccine waning (-10% per year) (d); changing vaccine coverage rate (85% to 65%) (e)



Footnote: Nbr: number; RV: rotavirus.

There was a good fit between the observed data and the simulations for the first 3 years when the r-factor in the simulation equation equals 0.5 and no other source of infection was present (c). Under such scenario we could normally foresee an elimination of the disease over a few years as we initially hypothesized. However, a much better overall good fit of the whole observed curve shape (b) was obtained if the additional source of infection with residual disease (f-factor) was introduced in addition to the r-factor (slightly adjusted to 0.4 first year and 0.6 in subsequent years). The f-factor was estimated at 12% of the hospitalizations in the equation.

Figure 4 Difference in proportion of RV-positive test results during the post-vaccination period (2012 and 2013) compared with the pre-vaccination period (2006) in each hospital center (code)



Nbr: number; RV: rotavirus.

For vaccine waning (d), we first simulated a decrease of 10% of r per year. To obtain a perfect fit with the observed data the annual waning would have to reach 35%, starting in the second year of vaccination.

Varying the vaccine uptake from 85% to 65% in 3rd year doesn't affect the curve (e) so much as the biggest drop in hospitalization occurs in the first years and what happens thereafter appears having a marginal effect. The point to make here is that any decrease in vaccine uptake later on, cannot explain the observed curve as it is now.

Finally the proportion of RV-positive test results across all the participating hospital centers was higher during the pre-vaccination period (2005-2006) than during the post-vaccination period (2012-2013) as expected. The average difference between 2005-2006 and each of 2012 and 2013 was 0.163 (minimum 0.10 to maximum 0.24) and 0.178 (minimum 0.07 to maximum 0.30), respectively. No center was noticeably an outlier (see Figure 4).

DISCUSSION

This analysis of medium- to long-term impact of RV vaccination on specific test results measured annually in the same 11 hospital centers in Belgium has identified several interesting features.

First, there was a large reduction in frequency of RV disease during the normal seasonal epidemic period after vaccination of the first birth cohort had started. The decrease of 70–80% in RV-positive test results, compared with the period of no vaccination, was achieved within two years after vaccine introduction. After that large initial drop, subsequent annual decreases were more modest (around

10–15% per age group). A similar early vaccine effect (the sharp drop in the first year) was seen in the UK during the first year after the vaccine introduction [28]. The decline was more spectacular during the first year than in the present study. This could be due to the start date of the vaccination campaign in the UK, which was planned by the end of the second quarter the year before the start of the next epidemic season. In Belgium, vaccination began much closer to the next epidemic season, namely in the fourth quarter of the year [29].

Second, in addition to the important direct vaccine effect seen in the first vaccinated birth cohort, we also observed during the same period a substantial drop in the unvaccinated age groups (i.e. children too young or too old to be vaccinated, as shown in Table 1). This phenomenon clearly indicates the high transmission rate of the virus between the different age groups, resulting in a high indirect herd effect of the vaccine during the first years of the vaccination programme until the whole at-risk group (aged up to 5 years old) is covered.

The overall drop in disease events was spectacular during the first 2 years, because the younger age groups targeted by the vaccine programme are the groups most affected by RV disease (peak incidence rates) and are the highest receivers and transmitters of the virus to other age groups. Virus transmission within these age groups and to other age groups was directly and indirectly reduced by the vaccine. Once the at-risk group has been vaccinated, herd effects in the older age-groups would be expected to disappear, as children in this group would have been vaccinated when they were younger. This would leave herd effects only in children ≤2 months of age (who are too young for vaccination) as an additional benefit sustained over time.

With 7 years of real-world observations after vaccine introduction, this study provides information about the likely source of infection of RV disease in the child population. The results split by age group in Figure 2 indicate that the role of the vaccine is primarily to stop the spread of the infection within the child population. The vaccine fulfills that task very well, as it induces a high herd effect across the different unvaccinated age groups during the same period. To obtain such a high vaccine impact, the main source of infection must be within the children themselves as such a high vaccine effect can only be obtained if it blocks the root cause of infection transmission. However, the amount of indirect herd effect depends heavily on how children are normally nurtured during that period. For example, do they attend day-care centers and at what starting age, do they have regular contact with other children elsewhere, and are different disease patterns observed between different age groups if child management or behavior changes? These questions affect the likely sources of infection and patterns of disease transmission between and within age groups, and would be valuable areas for further research. Finally, the different observed rates of disease reduction in subsequent years across different age groups are a signal that different infection forces operate within the child population. The most plausible explanation, simulated in Figure 3, is that there is an additional source of infection that can be clearly seen once most of the herd effect has faded away after the vaccine

programme has been in place for a few years and all the at-risk children have been vaccinated. This scenario appears much more likely than a vaccine waning scenario, because an annual decrease of 35% in vaccine effect starting one year after its introduction must occur to fit the observed data. Another possibility could be that the vaccination coverage rate fluctuated over time, but it is unlikely that that potential disturbance may impact so heavily the outcome results. In addition in Belgium the vaccine coverage rate remained stable and quite high during the whole observation period (>86%, IMS data).

These indications of additional sources of infection suggest that the disease and the virus will not be easily eliminated unless the other sources of infection can be targeted by different vaccination strategies.

A cohort analysis illustrates effects within the child population over time, including the dynamics of indirect vaccine impact. This type of investigation is more sensitive and better able to identify the real-world benefit of the vaccine than using vaccine efficacy data obtained through randomized clinical trials, where the control group may be influenced by the herd effect. This may reduce the measured vaccine efficacy, as seen in the European trial [30]. Following a first birth cohort over time should normally demonstrate a larger reduction of RV-positive test results than a first-year cross-sectional evaluation, because the vaccinated birth cohort includes a mixture of direct and indirect vaccine effects in each subsequent year if the coverage rate is not 100%. In contrast, the cross-sectional analysis only includes the measured herd effect in addition to the first-year direct effect of vaccination of a small age group. Thus, we would expect to observe a larger effect in the birth cohort analysis than the cross-sectional analysis when comparing the two datasets, which is consistent with the results observed in this study. However, cross-sectional and cohort data would be expected to reach the same end result for the sum of the different at-risk age groups as soon as all the children from all the different at risk age-groups have been vaccinated, approximately 9 years from the start [31;32]. Comparing birth cohort and cross-sectional analyses can also estimate the magnitude of the pure herd effect that can be generated by the vaccine in this disease.

Finally, all centers responded to the vaccine in a similar way over time. The observation of a residual disease burden could have been linked to specific centers that did not apply the same vaccination strategy in their catchment area, or to potential insourcing in some specific areas of unvaccinated children from outside Belgium where vaccination is not yet routinely performed. These possibilities were not measured in the present study.

A limitation of the current study is that we do not fully control the denominator of the study, and thus we assume that the target population has not significantly changed over the 9 years of the study period. For a small country as Belgium with a stable population, this assumption is reasonable. Another assumption is that no change behavior in testing the children for RV infection appeared over time after the introduction of the vaccine.

This analysis may provide the first evidence of another source of RV infection that exists outside the child population. This source appears to be less spectacular in spreading the disease in the child population than transmission within the age group, and may also be less likely to be significantly influenced by vaccination because the current vaccination strategy may not directly touch this reservoir.

In conclusion, the results of this study help to fill a gap of important information about the impact of RV vaccination over the medium- to long-term. The main features reported are the sustained reduction in hospitalization. A new finding that could potentially be important is that there may be different sources of infection in the child population, which may make it difficult to reduce the disease to very low levels. A residual disease presence observed over time means that we need to continue to monitor events each year in order to detect any new developments.

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