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

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4 EXPLORING ADDITIONAL HIDDEN VALUES OF ROTAVIRUS VACCINES

I was able to identify at least two domains that could be of great interest to decision makers related to the introduction of rotavirus vaccines. The evidence of those values could only be measured if the vaccine was already introduced on a large scale for a few years in a country. I like to present here the domains of benefit/value I have fully explored in depth today.

4.1 QUALITY OF CARE IMPROVEMENT

One is about the benefit of improving Quality of Care in the hospital environment after introducing the vaccine, *B Standaert et al. accepted, 2015*. The point we want to make is that during every winter period the pediatric ward is overwhelmed by a huge patient influx because many infectious diseases in the very young children happen more or less during the same period. With the introduction of the rotavirus vaccine we have now a possibility to better regulate the patient inflow into the health care system and as a consequence improve the Quality of Care (QoC) in that environment. I was able to demonstrate that this hidden benefit generated by this vaccine was overwhelming not only at the level of gastro-enteritis suffering patients but for the whole pediatric department. To assess well the QoC I proposed a simple method of calculation based on existing data easily accessible in a hospital environment.

4.2 REDUCTION IN ABSENTEEISM

The other interesting benefit is about the observed reduction in absenteeism amongst working mothers with a first child during the epidemic season of rotavirus diarrhea. I observed a significant reduction amongst the administrative personnel in the City of Antwerp after the introduction of the vaccine in 2006 in Belgium, *B Standaert et al, submitted, 2014*. The latter is quite interesting as we often claim and simulate in our economic models that there is a high indirect cost among working parents when exposed to infectious diseases in children and that there is much benefit to be expected from introducing the vaccine for that domain. Here I was able to show the evidence and to quantify the benefit related to the introduction of the rotavirus vaccine with real life data.

IMPROVEMENT IN HOSPITAL QUALITY OF CARE (QOC) AFTER THE INTRODUCTION OF ROTAVIRUS VACCINATION: AN EVALUATION STUDY IN BELGIUM

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ABSTRACT

During each winter period hospital emergency rooms and paediatric wards are often overwhelmed by high patient influx with infectious diseases leading to chaotic conditions with poor quality of care (QoC) delivery as a consequence. The conditions could be improved if we were able to better control the influx by introducing for instance better prevention strategies against some of the most frequent infectious diseases. New prevention strategies using vaccination against rotavirus infection were introduced in Belgium in November 2006. We developed a measure of hospital QoC suitable for assessing the impact of paediatric rotavirus vaccination. The study is retrospective collecting routine data on bed and staff management in one paediatric hospital in Belgium. The data were divided in pre- and post-vaccination periods during rotavirus-epidemic and non-epidemic periods. The scores were constructed using Explanatory Factor Analysis (EFA). All patients enrolled were admitted to the paediatric ward over the period from 1 January 2004 to 31 December 2009. The results of the epidemic period indicated that bed-day occupancy, bed-day turnover and unplanned readmissions for acute gastroenteritis were lower in the post-vaccination compared with the pre-vaccination periods. The QoC scores were therefore significantly lower (indicating improved QoC) after the introduction of rotavirus vaccination, compared with pre-vaccination. The data suggests that the reduction in the winter peak of rotavirus-related hospitalisations after the introduction of the vaccine reduces pressure on hospital resources and improves the quality of hospital care. The findings should be further tested in similar settings.

INTRODUCTION

Rotavirus disease places a high demand on European healthcare systems, accounting for 56.2% of hospitalisations and 32.8% of emergency department visits for community-acquired gastroenteritis during the winter epidemic seasons in children aged <5 years [1]. The seasonal rotavirus peak coincides with other paediatric infections, such as respiratory syncytial virus (RSV), influenza, pneumococcal disease, and other causes of acute gastro-enteritis (AGE) [2;3]. Each winter, those infections cause a high influx of children with communicable diseases into paediatric hospital wards and emergency rooms.

These winter increases in hospitalisations for infectious diseases in young children place a heavy burden on the delivery of medical care [4;5]. Overcrowding and excess workload in hospital care is recognised as a serious problem for patients and staff [6;7]. High patient-to-nurse ratios are related to unfavourable patient outcomes and increased self-reports of staff burnout and job dissatisfaction [8]. In addition to staff stress, the influx of infectious disease cases may result in

wards crowded over capacity, facilitating pathogen transmission and increasing nosocomial infections [9]. This has been documented by epidemiological data, but the consequences have not been fully investigated [10;11]. Overcrowding leads to high turnovers, with consequent potential for premature discharge and high readmission rates [12-15]. Over-stressed conditions for staff may be associated with high sickness rates requiring recruitment of temporary personnel, which in turn may be associated with a risk of incorrect diagnosis and/or treatment. Thus, the seasonal influx of patients with communicable diseases during a short time risks a cascade of sequential problems each winter.

Rotavirus vaccination was introduced in 2006 and offers the potential for better control of the influx of infectious disease cases [16]. Rotavirus vaccination in countries with established vaccination programmes has consistently and significantly reduced the incidence of rotavirus gastroenteritis (RVGE) and associated hospitalisations, emergency department visits and outpatient/ physician office visits in the United States (US), Europe and Australia [17-20].

Belgium introduced rotavirus vaccination in November 2006, with an uptake of 85% in the first year [21] and 89% in the second year [22]. This high vaccine uptake is maintained throughout subsequent years where parents are asked for a co-payment of the vaccine of 11.6€ per dose [23]. We have previously investigated the change in winter paediatric hospitalisations from before to after the introduction of rotavirus vaccination [22]. By reducing the seasonal influx of urgent RVGE cases into paediatric hospitals, the vaccine could help to reduce the winter pressure on healthcare resources and staff, offering potential wider benefits beyond reduced healthcare costs and quality-of-life gains in improving hospital quality of care (QoC). Such benefits would accrue to patients and their families, staff and hospital managers. Patients, who at present may be exposed to overcrowded hospitals with staff operating under stressful conditions, could benefit from better care provided by a less pressured service. Staff could benefit from reduced work stress and thus better conditions for optimal delivery of care, and could be less prone to infections. Health authorities and management may benefit from more efficient overall operation of the healthcare system, and will be better able to maintain a high quality of hospital care throughout the year.

Can these additional potential benefits of rotavirus vaccination on QoC be measured, and could such a measure be used as a benchmark for assessing the value of a new vaccine to hospital care? The objective was to obtain a daily QoC score based on easily accessible variables that reflect the management of hospital beds and staff. The score should indicate when care management is at risk for a quality drop potentially affecting patients and caregivers, and should be able to measure the impact of a vaccine introduction. The following hypothesis was therefore tested. The average daily QoC score in hospital management during winter epidemic seasons is significantly/relevantly worse in pre-vaccination compared with post-vaccination periods with a large score difference amongst the AGE population, a moderate score difference in the infection-only population and a marginal difference score overall.

RESULTS

Descriptive results

Rotavirus infections

Testing for rotavirus started on 1 June 2005. The percentage of rotavirus-positive tests in the winter decreased from 56.9% (165/290) pre-vaccination to 23.0% (48/209) post-vaccination (Table 1).

Table 1 Number of rotavirus tests and rotavirus-positive tests by study period during the winter

RV tests	Pre-vaccination (2005–2006)	Post-vaccination (2007–2009)
Positive (%)	165 (56.9%)	48 (23.0%)
Total	290	209

RV, rotavirus; n: number

Bed management variables

Table 2 shows the results for bed-day occupancy (BDOR), bed-day turnover (BTOR) and unplanned readmissions (UnPln). During the observation period (1st of January 2004 to 31st of December 2009) the total number of bed-days occupied in the paediatric ward with 34 beds was 56,451 days (76%), of which 25,973 days (46%) were due to infectious diseases. Of these, 7,697 days (29.6%) were due to AGE. During the winter the mean number of occupied beds per day for AGE (BDOR) was much higher pre-vaccination than post-vaccination (7.52 bed-days vs. 4.47 bed-days, respectively). The AGE BTOR rate and AGE UnPln rate were also higher pre-vaccination than post-vaccination (0.048 versus 0.028 for BTOR and 0.56 versus 0.16 for UnPln, respectively).

Staff management variables

Surprisingly, the mean number of full-time equivalent staff per day (FTEs) and overtime hours (OTR) were higher in post- than pre-vaccination (Table 3, 14.468 FTEs versus 14.945 FTEs and 6.95 h versus 7.55 h OTR). However, the minimum numbers were much lower in post-vaccination periods (9.1 FTEs versus 6.9 FTEs and 3 h versus 0 h for OTR). It was not possible to split FTEs and OTR by patient group. Only a few days had overtime hours. Pre-vaccination, the number of days with overtime hours was 38/271 (14%), compared with 57/361 [16%] post-vaccination. Table 4 shows data on staff sick leave (SLT). The pre-vaccination period had higher average and maximum values for sick leave than the post-vaccination period (5.25 h versus 4.37 h).

Analytical results

Table 5 shows average Factor 1 (bed management score), Factor 2 (staff management score) and overall QoC scores (Factor 1 + Factor2) pre- and post-vaccination. QoC scores were significantly lower (improved QoC) post-vaccination than pre-vaccination in all three groups (AGE, Infection only, Overall). The largest difference was in the AGE group, as expected. It may be surprising that the QoC

Table 2 Bed management variables (2004-2009) for overall, infection-only, and AGE patient groups by study period during the winter

Study period	Value	Overall	Infection-only	AGE
Occupied beds per day (BDOR)				
Pre-vaccination	Mean	30.59	16.96	7.52
	N	271	271	271
	SD	7.05	4.29	3.51
	Sum	8,289	4,595	2,039
Post-vaccination	Mean	28.89	14.80	4.47
	N	361	361	361
	SD	7.25	3.95	2.19
	Sum	7,828	4,010	1,212
Bed turnover rate per day (BTOR)				
Pre-vaccination	Mean	0.253	0.079	0.048
	N	271	271	271
	SD	0.132	0.052	0.041
	Sum	69	21	13
Post-vaccination	Mean	0.284	0.065	0.028
	N	361	361	361
	SD	0.143	0.048	0.031
	Sum	77	18	8
Unplanned readmission rate per day (UnPln)				
Pre-vaccination	Mean	0.93	0.76	0.56
	N	271	271	271
	Cases	48	36	29
	SD	0.908	0.880	0.691
	Sum	253	207	152
Post-vaccination	Mean	0.38	0.29	0.16
	N	361	361	271
	Cases	25	19	9
	SD	0.685	0.529	0.404
	Sum	136	106	43

AGE, acute gastroenteritis; SD, standard deviation; N, Number of days

Table 3 Staff management variables (2004-2009) for overall study period during the winter

Study period	N	Sum	Mean	SD	Maximum	Minimum
Staff numbers per day (FTEs)						
Pre-vaccination	271	3920.9	14.468	3.064	21.3	9.1
Post-vaccination	361	5395.3	14.945	3.634	22.9	6.9
Overtime hours worked per day (OTR)						
Pre-vaccination	38	264	6.95	2.770	14	3
Post-vaccination	57	431	7.55	2.608	16	0

FTE, full-time equivalent; SD, standard deviation; N, Number of days

Table 4 Staff sick leave by season and study period

Study period	Value	Sick leave, hours	Sick leave, persons	Sick leave, FTE
Pre-vaccination	**N**	**271**	**271**	**271**
	Sum	1423.28	308	187.274
	Mean	5.252	1.14	0.691
	SD	5.990	0.95	0.788
	Maximum	25.47	4	3.351
	Minimum	0.00	0	0.000
Post-vaccination	N	361	361	361
	Sum	1579.33	311	207.807
	Mean	4.375	0.86	.575
	SD	5.148	0.858	.677
	Maximum	20.90	4	2.750
	Minimum	0.00	0	0.000

FTE, full-time equivalent; SD, standard deviation; N, Number of days

Table 5 Average QoC scores pre-and post-vaccination for each patient group in winter

Patient group	Factor	Pre-vaccination	Post-vaccination	Mean difference	t-test	p-value (2-tailed)
Overall	Factor 1	-0.061	0.065	-0.127	-1.034	0.30
	Factor 2	0.514	-0.554	1.069	10.332	0.000*
	QoC score	0.453	-0.488	0.941	5.767	0.000*
Infectious-only	Factor 1	0.506	-0.546	1.052	10.188	0.000*
	Factor 2	-0.100	0.108	0.209	-1.718	0.087
	QoC score	0.406	0.053	0.352	5.107	0.000*
AGE	Factor 1	0.501	-0.544	1.046	10.125	0.000*
	Factor 2	0.333	-0.361	0.695	6.152	0.000*
	QoC score	0.834	-0.906	1.741	11.153	0.000*

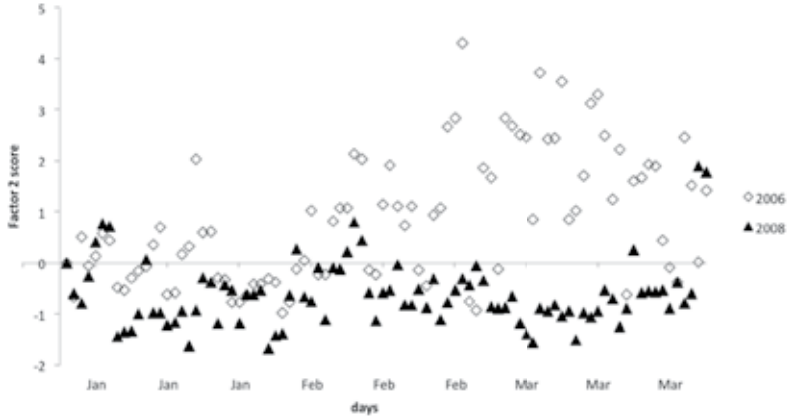
AGE, acute gastroenteritis; QoC, quality of care

*significant differences;

improvement post-vaccination in the infection-only group was not larger than in the overall group. This may be because the AGE group comprised a large proportion of the infection-only group, and there were relatively few non-AGE infections to benefit from improvements in time and bed-space. This is not the case when the overall paediatric ward is considered.

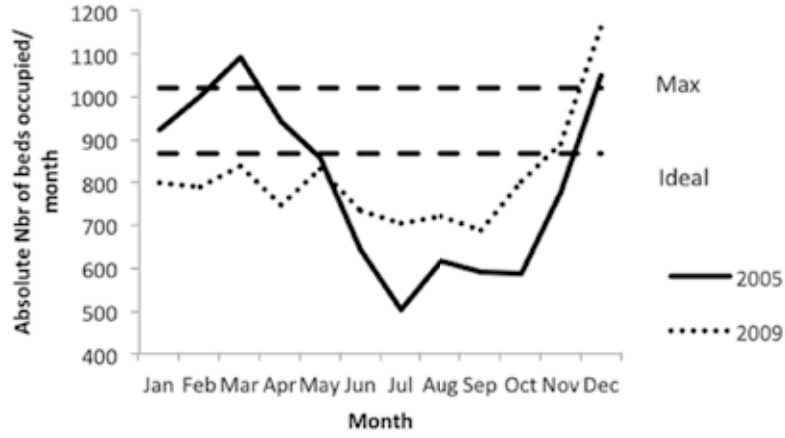
Figure 1 compares the daily Factor 2 (staff management) scores during the winter of 2006 and 2008 as an example. In 2006 (pre-vaccination) there was a period of stress, indicated by high Factor 2 scores, with no equivalent in 2008 (post-vaccination). Figure 2 shows as another example of the impact of the vaccine, the absolute number of bed-days occupied per month in 2005 (1 year pre-vaccination) and 2009 (2 years post-vaccination). Post-vaccination, BDOR stayed below the ideal threshold throughout the winter rotavirus season (January–March), whereas pre-vaccination the BDOR was above this threshold for several months. The increase in November–December in both years is partly explained by the hospitalisation of RSV cases.

Figure 1 Daily Factor 2 (staff management) scores in the winter of 2006 (pre-vaccination) and the winter of 2008 (post-vaccination)



Nbr: number; RV: rotavirus.

Figure 2 Bed occupancy number per month pre-vaccination and post-vaccination



Nbr: number; RV: rotavirus.

DISCUSSION

Introducing a new vaccine with an immediate high uptake (>85% coverage) and an explicit focus on reducing hospitalisations during epidemic seasons into an established healthcare system would be expected to affect hospital management [24;25]. Overcrowding as indicated by excess BDOR has been associated with increased hospital infections and patient mortality [26-28], and exposure to BDOR of >10% in excess of the recommended limit of ≤85% for >6 months has been associated with antidepressant treatment in hospital staff [29]. Overcrowding typically occurs in the winter, when influenza, RSV, pneumococcal disease and

rotavirus all circulate together, and can be exacerbated by rapid pathogen spread within the hospital causing high rates of nosocomial infection. However, although the problem of winter pressure is familiar to hospital staff, until now there has been no method to quantify that phenomenon into one single measure. The present study is a first attempt to develop a single QoC score that can quantify stress in healthcare services and can assess the impact of interventions, such as rotavirus vaccine introduction, on service stress.

As this was a retrospective analysis, we used data that were already available. This should allow replication of this analysis in other hospital settings collecting similar data which is the case for bed day management variables but could be more difficult for staff management variables that most often are not fully electronically available over a long enough period during pre-vaccination or before 2006 in Belgium. Overcrowding and its adverse effects on staff stress should be visible in measures of bed management and staff management, so we concentrated on variables in these areas. Some of these variables should be correlated, e.g. when BDOR is high, BTOR is also likely to be high, which in turn increases the risk of unplanned readmission. The technique of Explanatory Factor Analysis (EFA) allows identification of links between the variables and the integration of several variables into a new measure. In the present study, we pre-defined the number of Factors we wanted to work with, one on bed management and one on staff management, to facilitate the construction of an overall QoC score with the right weighting values for each variable in the EFA equation. As expected, the difference in winter QoC scores pre- and post-vaccination was highest among AGE patients. Notably, there was also a substantial difference for the overall group. This indicates that improved QoC after introduction of rotavirus vaccination benefited the paediatric ward as a unit, and not only patients with the specific infection targeted by the vaccine. We also explored an analysis of calculating QoC-scores in the non-winter periods expecting no much of a difference between the pre- and post-vaccination periods for the 3 patient groups considered and obtaining much lower scores than during the winter periods. Our hypothesis was confirmed and indicated a way to validate the construction of the score-composition. We report these particular data in the Appendix 1.

The analysis can also be used to identify periods of stress by plotting the daily scores. Our results showed that the daily Factor 2 (staff management) scores indicated an extended period of high stress in the winter of 2006, and bed occupancy indicated an extended period of overcrowding in the winter of 2005. Such information could be used to predict the development of problems and to implement remedial actions.

It should be emphasised that this analysis does not support reductions in personnel numbers in paediatric wards during the winter period now that rotavirus vaccination has been introduced. Instead, it demonstrates that there was considerable stress in paediatric wards prior to vaccine introduction. This stress could have detrimental effects on patients, staff and the efficient operation of the healthcare system. Introducing the rotavirus vaccine has reduced the seasonal

peak in rotavirus admissions, thus reducing the winter stress on healthcare services and improving QoC, which should benefit patients, staff and hospital management overall. But QoC scores are likely to be dynamic, since they are composed of several variables, and it is likely that they will continue to evolve over time.

The technique of EFA to build scores is not new and has especially been applied in the world of sociology [30]. In the medical world it has been used to help classifying patient-groups in function of disease severity levels based on scores constructed through the collection of data from questionnaires [31].

Currently, cost-effectiveness analyses of new vaccines have not been able to include any QoC benefits of vaccination. The present analysis offers a way to quantify the QoC benefit, which may allow its potential impact on hospital costs and quality-adjusted life-years (QALYs) to be incorporated in economic analyses. We are exploring this in future research. However we need to be sure to make links between the level of QoC-scores and the cost of disease management in hospital care or the impact on QALYs amongst the personnel. The latter should preferentially be investigated with prospective data collection. That process doesn't facilitate the implementation of such a study.

The present study has some limitations. First, it was conducted at a single centre, and the results should be confirmed in other settings. We are presently investigating the possibility of repeating the project in another hospital in Belgium with access to similar data. However, if we want to expand our research in other countries it will be difficult. As of today not many countries in Europe can confirm the analysis results we have as only a few of them have currently accepted the rotavirus vaccination as a universal mass vaccination program in children including the UK, Austria, and Finland. Moreover by limiting the study to one centre in Belgium it was also not possible to include all the variables we selected for the analysis. For instance we were unable to introduce nosocomial infection rates which are normally an appropriate indicator of stress situations in hospital management. That specific event underwent a dramatic observed reduction after the introduction of the vaccine. But because of too low numbers registered during the observation period in this centre, we could not include the variable in the analysis. Another option to circumvent the problem of too low observation units is to change the time unit of observation from day to week or months. This is an option we would like to further explore. Moreover, the EFA approach remains a subject of debate amongst experts [32]. One challenging item is about the fitting procedures to obtain the regression coefficients amongst the variables and the Factors in between, called the Factor loadings. Different approaches exist but there is no method that indicates the best or the worst approach in calculating these values. In this study here we have taken a conservative approach by selecting appropriate data and trying to make the analysis as uniform as possible. Full details are provided in the supplementary Appendix 1 to allow other researchers to replicate the analysis.

Introducing a new vaccine that affects a major public health problem could have many healthcare benefits beside the improvements of clinical benefits such as mortality and morbidity reduction. The new vaccine may also unexpectedly have an impact on other domains of the health care program if that program suffers as well about overcrowded hospital services during certain periods, stress in care delivery by health care professional, bad management of the beds to be used. These are conditions we often have difficulties to measure correctly about the deviations of normal practice. The analysis method here described as EFA has just the facility to be able to collect that new information quantitatively in an easy to applied way and it does not require the collection of additional data. It integrates several aspects of healthcare service stress by including both bed-day management and care of staff, which are linked and should therefore be evaluated together. The result of such an approach is that we are now in a position to measure the additional hidden benefit a vaccine can offer, showing an improved summary score in QoC with better patient care, more staff time, reduced spread of infectious disease in hospitals and more resources to apply on other disease areas. The QoC score can be used to predict periods of stress and identify problems to tackle during day to day management. Using the quantitative QoC score it may help to find more objective ways of analysing the issues of healthcare service stress and the benefit impact of new interventions.

METHODS

Hospital setting

The study was conducted at the Jessa Hospital in Hasselt, Belgium, which is also part of another rotavirus vaccine study [33]. Rotavirus vaccination was introduced in the region following the recommendation of the Flemish High Committee for Public Health Services (Hoge Gezondheidsraad). The hospital has 34 paediatric beds, and its database was electronically accessible. Its catchment area was uniform during the study period and there were no major management changes, allowing comparisons between pre- and post-vaccination periods. Ethical approval for the study was obtained in December 2012.

Variables

The hospital's existing database provided data on the following variables relating to management of patient beds and staff, measured per day that could be used for the construction of the QoC score:

- Bed-day occupancy number and rate (BDOR): Number of beds occupied/number of beds available per day;
- Bed-day turnover rate (BTOR): Number of patients discharged/number of beds available per day;
- Unplanned readmission rate (UnPln): Number of readmissions ≤7 days after discharge/total number of discharges per day;
- Rotavirus test rate and positive results (RVT): Number of tests performed per day and rate of positive test results;
- RVGE nosocomial infection rate (RVNR): number of RVGE nosocomial infections/total number of RVGE hospitalisations per day

- RVGE specific death rate (RVDR): number of RVGE specific deaths/total number of RVGE hospitalisations per day
- Hospitalisation rate (HR): number of hospitalisations/total number of children in the catchment area per day
- Full-time equivalent staff per day (FTE): Total number of hours worked by the personnel per day/7.6;
- Over-time work by the staff per day (OTW): Total number of extra hours taken by the personnel/total number of regular hours per day;
- Sickness leave by the staff per day (SLT): Total number of paid and unpaid sick days/total number of FTEs per day.
- Staff replacement per day (SR): number of replacement of staff/total number of staff present per day.

These variables were analysed descriptively and used to construct the QoC scores. First, the numbers per day were assembled to observe whether their distributions were normal. If not, the data were transformed using log-transformation, square-root or other methods until a normal or near-normal distribution was reached. Quintiles were then calculated in eight groups (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, $>95^{th}$) and each variable value per day was given a score of 1–8 according to its quintile category. We selected 8 categories in order to get enough granularity in the spread of the variable values. By not selecting too few or too many categories it may impact the analysis with too many empty cells or not enough sensitive correlation between variables. It should be noted that the end results (average daily QoC-scores) were analysed by grouping period of pre-vaccination and post-vaccination, pooling therefore the numbers of several years. We have also split the evaluation period within a year as rotavirus epidemic period or not. It is expected that the difference in QoC scores are enhanced if we consider those periods separately instead of a full year analysis that may dilute the impact with a period where no difference in results is expected when comparing pre-post vaccination in the non-epidemic seasons.

Meanwhile the following variables (RVNR; RVDR; HR; SR) were deleted from the first analysis. The event numbers were too small (no deaths and no replacement during the observation period) or showed no meaningful change over time, so these variables were not considered further. This was especially the case for RVNR that with 87 nosocomial infection observations over a 2557 day period was too low to obtain a meaningful result. Pooling results from different hospitals should enhance the analysis or considering a shorter time period for the assessment such as week observations instead of day observation could have been another approach to circumvent the obstacle of too few observations. Meanwhile changing the unit of observation may impact the calculation process when the data have been collected on a day to day basis. But it is certainly an option to consider when the analysing the data of only one center.

Study period

Data were collected for the period between 1 January 2004 and 31 December 2009, divided into a pre-vaccination period (before November 2006) and a post-

vaccination period (after November 2006). Winter epidemic months were defined as 1 January to 31 March.

Between 2004 and 2009, there were 2,557 days of which 632 (24.7%) days were during the winter. Of the winter days, 271 (42.9%) days were during the pre-vaccination period and 361 (57.1%) days were during the post-vaccination period. In the current analysis presented here we only demonstrate the results of the winter or the rotavirus epidemic period. We did an analysis of the non-epidemic period as well but that is reported in the supplement of Appendix 1.

Patients

The study included data on all patients admitted to the paediatric ward over the study period, stratified into three groups:

- Overall population (all admissions);
- Infection-only population (patients admitted for infectious disease of any kind);
- AGE population (patients in the infection-only group admitted specifically for AGE).

Data analysis

Descriptive

Summary descriptive statistics are reported for each variable selected for calculating the QOC scores with no statistical significance level reported per specific period evaluated for each variable. We did this on purpose as the focus of the study is on the measurement of the QoC scores and not on the individual variable results used to calculate the QoC scores.

Analytical

A summary QoC score for hospital care should integrate data from several variables to provide a useful overall measure. Explanatory Factor Analysis (EFA) [34] is a statistical method that assesses whether a number of observed variables are linearly related to a smaller number of unobservable Factors. We used EFA to derive two Factors from the observed variables. A scree plot indicated that only two Factors could be constructed from the data. These two Factors can be summed to produce a summary QoC score if the Factors are independent from each other. Before conducting the EFA, the observed data were standardised into eight quintiles as described above in order to be able to assemble them correctly together.

The EFA was conducted in several steps. First, the dataset was analysed with specific tests to assess whether EFA can be applied [35], constructing a correlation matrix for the pairwise correlation coefficients between the variables. The EFA should meet three objectives: it should be parsimonious (minimum number of new explanatory Factors created to explain the observed data); the new Factors should be independent of each other as far as possible; and the Factor scores should make sense (e.g. a Factor score about staff management should be driven

by variables such as overtime and sick leave). Second, the Principal Component Method (PCM) confirmed that two explanatory Factors could be derived. Third, each Factor was constructed with specific factor loadings using varimax rotation because of the independence of each Fatcor. Finally, the weighting coefficient of each variable in the equation that produces the Factor was adjusted after rotation.

Using the seven variables listed above, two new measures were constructed, Factor 1 (bed management) and Factor 2 (staff management). The daily score for each Factor was calculated with a regression equation of all selected variables. The sum of the two Factors is the summary QoC score. Higher scores indicate worse QoC. The Factor scores and QoC scores were compared between pre- and post-vaccination periods using the T-test, for each patient group in each season (winter and non-winter). All analyses were conducted using *IBM SPSS Statistics* v22.0.

Summary results for each Factor and QoC scores are presented in this paper. A full EFA analysis showing the calculation of the regression coefficients and Factors for one period (winter) and one patient group (overall) is provided in the supplementary Appendix 1.

REFERENCES

[1] Forster J, Guarino A, Parez N, Moraga F, Roman E, Mory O, et al. Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European children younger than 5 years of age. Pediatrics 2009 Mar;123(3):e393-e400.

[2] Giaquinto C, Van Damme P, Huet F, Gothefors L, Maxwell M, Todd P, et al. Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004-2005: the REVEAL study. J Infect Dis 2007;195 Suppl 1:S26-S35.

[3] Giaquinto C, Van DP. Age distribution of paediatric rotavirus gastroenteritis cases in Europe: the REVEAL study. Scand J Infect Dis 2010;42(2):142-7.

[4] Ducoffre G, Wuillaume F. Surveillance of Influenza A and Respiratory Syncytial Virus by the Belgian Sentinal Laboratory Network. Arch Public Health 2010;86(1):83-4.

[5] Eidelman AI, Megged O, Feldman R, Toker O. The burden of respiratory syncytial virus bronchiolitis on a pediatric inpatient service. Isr Med Assoc J 2009 Sep;11(9):533-6.

[6] Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA 2002 Oct 23;288(16):1987-93.

[7] Virtanen M, Pentti J, Vahtera J, Ferrie JE, Stansfeld SA, Helenius H, et al. Overcrowding in hospital wards as a predictor of antidepressant treatment among hospital staff. Am J Psychiatry 2008 Nov;165(11):1482-6.

[8] Richardson DB, Mountain D. Myths versus facts in emergency department overcrowding and hospital access block. Med J Aust 2009 Apr 6;190(7):369-74.

[9] Forster AJ, Stiell I, Wells G, Lee AJ, van WC. The effect of hospital occupancy on emergency department length of stay and patient disposition. Acad Emerg Med 2003 Feb;10(2):127-33.

[10] Van Damme P, Giaquinto C, Huet F, Gothefors L, Maxwell M, Van der WM. Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004-2005: the REVEAL study. J Infect Dis 2007 May 1;195 Suppl 1:S4-S16.
[11] Van der Wielen M., Giaquinto C, Gothefors L, Huelsse C, Huet F, Littmann M, et al. Impact of community-acquired paediatric rotavirus gastroenteritis on family life: data from the REVEAL study. BMC Fam Pract 2010;11:22.
[12] Keegan AD. Hospital bed occupancy: more than queuing for a bed. Med J Aust 2010 Sep 6;193(5):291-3.
[13] Miles TA, Lowe J. Are unplanned readmissions to hospital really preventable? J Qual Clin Pract 1999 Dec;19(4):211-4.
[14] Ashton CM, Kuykendall DH, Johnson ML, Wray NP, Wu L. The association between the quality of inpatient care and early readmission. Ann Intern Med 1995 Mar 15;122(6):415-21.
[15] Heggestad T, Lilleeng SE. Measuring readmissions: focus on the time factor. Int J Qual Health Care 2003 Apr;15(2):147-54.
[16] Giaquinto C, Dominiak-Felden G, Van DP, Myint TT, Maldonado YA, Spoulou V, et al. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. Hum Vaccin 2011 Jul;7(7):734-48.
[17] do Carmo GM, Yen C, Cortes J, Siqueira AA, de Oliveira WK, Cortez-Escalante JJ, et al. Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. PLoS Med 2011 Apr;8(4):e1001024.
[18] Parez N, Giaquinto C, Du RC, Martinon-Torres F, Spoulou V, Van DP, et al. Rotavirus vaccination in Europe: drivers and barriers. Lancet Infect Dis 2014 May;14(5):416-25.
[19] Van Damme P, Van der Wielen M, Ansaldi F, Desgrandchamps D, Domingo JD, Sanchez FG, et al. Rotavirus vaccines: considerations for successful implementation in Europe. Lancet Infect Dis 2006 Dec;6(12):805-12.
[20] Buttery JP, Lambert SB, Grimwood K, Nissen MD, Field EJ, Macartney KK, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. Pediatr Infect Dis J 2011 Jan;30(1 Suppl):S25-S29.
[21] Braeckman T, Van HK, Raes M, Vergison A, Sabbe M, Van DP. Rotavirus vaccines in Belgium: policy and impact. Pediatr Infect Dis J 2011 Jan;30(1 Suppl):S21-S24.
[22] Raes M, Strens D, Vergison A, Verghote M, Standaert B. Reduction in pediatric rotavirus-related hospitalizations after universal rotavirus vaccination in Belgium. Pediatr Infect Dis J 2011 Mar 23;30(7):120-5.
[23] Braeckman T, Theeten H, Lernout T, Hens N, Roelants M, Hoppenbrouwers K, et al. Rotavirus vaccination coverage and adherence to recommended age among infants in Flanders (Belgium) in 2012 1. Euro Surveill 2014;19(20).
[24] Anderson EJ, Rupp A, Shulman ST, Wang D, Zheng X, Noskin GA. Impact of rotavirus vaccination on hospital-acquired rotavirus gastroenteritis in children. Pediatrics 2011 Feb;127(2):e264-e270.

[25] Ogilvie I, Khoury H, Goetghebeur MM, El Khoury AC, Giaquinto C. Burden of community-acquired and nosocomial rotavirus gastroenteritis in the pediatric population of Western Europe: a scoping review. BMC Infect Dis 2012;12:62.
[26] Sprivulis PC, Da Silva JA, Jacobs IG, Frazer AR, Jelinek GA. The association between hospital overcrowding and mortality among patients admitted via Western Australian emergency departments. Med J Aust 2006 Mar 6;184(5):208-12.
[27] Tarnow-Mordi WO, Hau C, Warden A, Shearer AJ. Hospital mortality in relation to staff workload: a 4-year study in an adult intensive-care unit. Lancet 2000 Jul 15;356(9225):185-9.
[28] Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA 2002 Oct 23;288(16):1987-93.
[29] Virtanen M, Pentti J, Vahtera J, Ferrie JE, Stansfeld SA, Helenius H, et al. Overcrowding in hospital wards as a predictor of antidepressant treatment among hospital staff. Am J Psychiatry 2008 Nov;165(11):1482-6.
[30] James SA, Kleinbaum DG. Socioecologic Stress and Hypertension-related mortality rates in North Carolina. Amer J Public Health 1976;66(4):354-8.
[31] Logie CH, Earnshaw V. Adapting and Validating a Scale to Measure Sexual Stigma among Lesbian, Bisexual and Queer Women 1. PLoS One 2015;10(2):e0116198.
[32] Harman H. Modern Factor Analysis. 3rd edition ed. Chicago: University of Chicago Press; 1976.
[33] Standaert B, Gomez JA, Raes M, Debrus S, Velazquez FR, Postma MJ. Impact of rotavirus vaccination on hospitalisations in Belgium: comparing model predictions with observed data. PLoS One 2013;8(1):e53864.
[34] Kleinbaum D, Kupper L. Applied regression analysis and other multivariable methods. Boston, Massachusetts: Duxburt Press; 1978.
[35] Norusis M. SPSS Professional Statistics 6.1. Chicago, IL: SPSS Inc; 1994.

APPENDIX 1: EXTENDED REPORT ON EFA – ALL WINTER PERIODS (JAN TO MARCH), OVERALL (1) & COMPARISON OF WINTER & NON-WINTER PERIODS (2)

EXTENDED REPORT ON EFA

Variable selection

Two main groups of evaluation were considered: variables for bed management and variables for staff management.

- **Bed management** includes 7 variables: bed occupancy rate/day, bed turnover rate/day, unplanned readmission rate/day, RVGE infection rate/day, RVGE nosocomial infection rate/day, RVGE specific death rate/day, and hospitalization rate/day per 100,000 children.

- **Staff management** includes 4 variables: full-time equivalent/day, overtime work/day, sick-leave/day, staff replacement/day.

Four variables (death rates, hospitalization rates, RVGE nosocomial infection rate, staff replacement), were excluded due to the following reasons:

- No specific RVGE deaths were reported during the observation period
- Hospitalization rates per 100,000 people were calculated per age-group (i.e. age-specific rates) using the Flanders population as standard population. No much demographic variation was observed during the observation period. In the absence of any variation during the observation period this variable is therefore not suitable for the analysis. The variable could have been useful if important migration was observed or a high change in birth rate per year in the region.
- Too small number of RVGE nosocomial infection were reported (87 cases over the 6 year period)
- No staff replacement was reported during the observation period

Rates for bed-day occupancy (BDOR), bed turnover (BTOR), unplanned readmissions within 7 days after discharge (UnPln), and Full-time equivalent (FTE) were calculated using formulas given in Horton L.A. (2007) by the American Health Information Management Association (AHIMA).

Rates were calculated for 3 groups of patients: all hospitalizations (Overall), infection only (Infection Only), and Acute Gastro Enteritis (AGE). In this exercise here, we only present the calculation of the EFA for Overall and for the winter period only. Normally 6 EFA runs have been done to calculate for every season and every study period the scores.

For RVGE infection (RVGE -WM) the % of positive tests (Nr of positive tests divided by the Nr of RV tests) is calculated for all 775 days between 1/06/2005 through 31/12/2009.

For overtime work (OTR) (= overtime hours/regular hours) and sick-leaves (SLR) (= total paid and unpaid sick days/number of employees in the same period) were calculated per day.

Rates were checked for normality distribution and transformed to obtain normal distributions using log-normal transformation, square-roots transformation or other methods. Results were then subdivided into 8 groups using their percentiles ($\leq 5^{th}$, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, and $>95^{th}$).

Due to the nature of the data a significant number of days were event-free: no UnPln, no SLR, and no OTR.

- As a result 1,120 days (43.8%) for SLR, 2,187 days (85.5%) for OTR, and 1,435 days (56.1%) for UnPln were zeros.

- For RVGE tests 523 out of the 775 days (67.5%) have zero denominators.

Explanatory Factor Analysis

Factor analysis is a method for investigating whether a number of variables of interest Y_1, Y_2,..., Y_l, are linearly related to a smaller number of unobservable factors F_1, F_2, ..., F_k (i.e. latent variables).

Explanatory Factor Analysis (EFA) is used with principal component method (PCM) for the number of factor extractions and *direct oblimin* (oblique factors or correlated factors) or *varimax* (for orthogonal or independent factors) for factor rotation function that selects the variables most closely related to each factor extraction in order to obtain the right weights per variable selected.

Running EFA generates the following outputs:

- C*orrelation matrix* depicts correlation coefficients between each pair of variables. There are two potential problems:
  - Correlations are not high enough. If a variable seems to have very low correlations with many other variables, it is excluded from the analysis.
  - Highly correlated variables are another problem (extreme multi-collinearity and singularity (variables that are perfectly correlated)). They make it impossible to determine the unique contribution to a factor of the variables that are highly correlated.
    - *Bartlett's test of Sphericity* tests whether the correlation matrix resembles an identity matrix or is significantly different from an identity matrix. If the test is significant, it means that the correlations between variables are overall significantly different from zero (good news). Non-significant Bartlett's test is a concern.
    - Haitovsky (1969) proposed a significance test whether the determinant is zero (i.e. matrix is singular). If the test is significant it tells that the correlation matrix is significantly different from a singular matrix which implies that there is no severe multi-collinearity.
    - *Anti-image correlation* which gives Kaiser-Meyer-Olkin (KMO) values, is a measure of sampling adequacy (MSA). A value of 0.5 is the bare minimum. If a variable has a KMO <0.50, it must be dropped from the analysis.

- *Total variance explained* by each variable
- *Scree plot* (component on the x-axis versus their eigenvalues on the y-axis) to select the number of new extraction factors.
- *Communalities*- measures the proportion of variance explained by the extracted factors given per variable,
- *Reproduced correlation matrix* - gives correlation coefficients based on the factor model. To assess the fit of the model, we look at the residuals (differences between observed and fitted model). The smaller the residuals, the better the fit,

- *Component correlation matrix* - depicts the correlation coefficient between the extracted factors.
  - If the extracted factors are correlated (case one), then assumption of dependent factors is suggested and the oblique rotation (oblimin method) will be used to calculate the appropriate weighting values.
  - If the extracted factors are not correlated (case two), then we run factor analysis with the use of an orthogonal factor rotation (varimax method) for independent factors.
  - When factors are dependent (case one), we got the *Pattern Matrix* (contains the regression coefficients for each variable on each extracted factor), the *Structure Matrix* (contains correlation coefficients between each variable and factor), and the *Component Score Coefficients* per variable and per extracted Factor, for which *Factor scores* can be calculated per measurement day.
  - When factors are independent (case two), we got the *Rotated Component Matrix* which is the matrix of the factor loadings for each variable into each extracted factor, and the *Component Score Coefficients Matrix*, for which the Factor scores can be calculated.
  - Final output is the *Factor transformation matrix*. If the orthogonal (e.g. varimax) rotation were completely appropriate then we would expect a symmetrical matrix (i.e. same value above and below the diagonal).

Period score calculations

- The dataset has been subdivided by months (winter months: 1st of January to 31st of March & other months: 1st of April through 31st December) for defining the epidemic periods of rotavirus during the year which it is expected that the Factor scores will be different after the introduction of the vaccine, and by study period (pre- & post-vaccination).
- The rates for bed day management (bed-day occupancy, bed-turnover, and unplanned readmission ≤7 days after discharge) were calculated for Overall, Infection-Only, and AGE hospitalizations.
- The rates for staff management (FTE, Overtime and Average sick-leaves) were calculated for the Overall data only as it was impossible to define staff to infection only and to AGE only during the observation period.
- Factor Analysis of data was repeated 6 times. First three runs during winter months for Overall, Infectious-driven and AGE-driven hospitalizations. Second three runs were during other months for Overall, Infectious-driven and AGE-driven hospitalizations.
- We present here the EFA analysis for winter period only, Overall, as an example.

Factor scores

Following an exploratory factor analysis (EFA), factor scores are computed and used in subsequent analyses. Since both principal components and common factor extraction methods is used with EFA, a refined method is going to be used, namely the Anderson-Rubin (A-R) method. The A-R method is a variation of the Bartlett procedure, in which the least square formula is adjusted to produce factor scores that are not only uncorrelated with other factors, but also uncorrelated with each other.

Computation procedures consist of multiplying the vector of observed variables by the inverse of a diagonal matrix of the variances of the unique factor scores, and the factor pattern matrix of loadings for the observed variables. Results are then multiplied by the inversion of the symmetric square root of the matrix product obtained by multiplying the matrices of eigenvectors and eigenvalues (Formulae below). The resulting factor scores are orthogonal, with a mean of 0 and a standard deviation of 1. The A-R scores are automatically generated in SPSS by selecting the Anderson and Rubin option in the Factor Analysis.

$$\text{A-R} = F_{1xm} = Z_{1xn}\, U^{-2}{}_{nxn}\, A_{nxm}\, H^{-1/2}; \text{ and } G_{nxn} = X_{nxn}\, \Lambda_{Dnxn}\, X'_{nxn}$$

where n: is the number of observed variables, m: number of factors, F: the row vector of m estimated factor scores, Z: the row vector of n standardized observed variables, X and X': matrices of n x n eigenvectors, Λ_D: the n x n matrix of eigenvalues, G: the matrix product of eigenvalues and eigenvectors, and $G^{-1/2}$: the inverse of the symmetric square root of G.

The calculated A-R scores per Factor is then used to assess, using two-sided t-test for independent-samples, whether factor scores were statistically different between pre- and post-vaccination periods. Elevated A-R scores per extracted factor, indicates excessive burdens (i.e. higher: bed-day occupancy rates, bed turnover rates, unplanned readmission rates, overtime work, average sick-leaves and more FTE needed).

Levene's test was used to assess the equality of variances in the A-R scores. If the test was not significant, the two variances are assumed to be equal. Consequently, the t-test will be selected accordingly.

RESULTS

Factor Analysis – winter months

During the epidemic months (January 1st through March 31st) there were a total of 632 days of which 271 days (43%) were during the pre-vaccination period and 361 days (57%) during the post-vaccination period. As we include the data of testing for RVGE with only 268 days of observation during the winter months, the total analysis for the winter period relies on 268 days of observation.

Frequency distribution of data (percentiles) is shown below in **Table 1**.

For overall data (n= 268) during winter months, Factor Analysis was repeated 4 times and summary of the results is shown below in **Table 2**. In the final run (4th), UnPln and OTR were excluded from the analysis due to their individual KMO values being under the bare-minimum of 0.50.

Table 1 Frequency distribution of data for bed management and personnel management variables using their percentiles – Overall, winter

BDOR	Frequency	%	Cumulative %
≤ 44.12	1	0.4	0.4
>44.12 to 55.88	7	2.6	3.0
>55.88 to 73.53	31	11.6	14.6
>73.53 to 94.12	85	31.7	46.3
>94.12 to 108.82	70	26.1	72.4
>108.82 to 117.65	45	16.8	89.2
> 117.65 to highest	29	10.8	100.0
Total	268	100.0	
BTOR			
≤ 0.0294	5	1.9	1.9
>0.0294 - 0.0588	4	1.5	3.4
>0.0588 - 0.1471	32	11.9	15.3
>0.1471 - 0.2353	60	22.4	37.7
>0.2353 - 0.3529	87	32.5	70.1
>0.3529 - 0.4412	42	15.7	85.8
>0.4412 - 0.5294	22	8.2	94.0
>0.5294 to highest	16	6.0	100.0
Total	268	100.0	
UnPln			
0	129	48.1	48.1
>0 to 14.28	64	23.9	72.0
>14.28 to 25.00	50	18.7	90.7
>25.00 to 40.00	15	5.6	96.3
>40.00 to highest	10	3.7	100.0
Total	268	100.0	
SLR			
0	114	42.5	42.5
>0 - 0.044706	22	8.2	50.7
>0.044706 - 0.07694	65	24.3	75.0
>0.07694 - 0.11521	34	12.7	87.7
>0.11521 - 0.14193	13	4.9	92.5
> 0.14193 to highest	20	7.5	100.0
Total	268	100.0	
OTR			
0	230	85.8	85.8
>0 - 5.405405	15	5.6	91.4
>5.405405 - 7.69231	11	4.1	95.5
>7.69231 to highest	12	4.5	100.0
Total	268	100.0	
FTE			
≤8.29	1	0.4	0.4
>8.29 to 9.53	5	1.9	2.2
>9.53 to 11.05	45	16.8	19.0
>11.05 to 14.28	69	25.7	44.8
>14.28 to 16.91	90	33.6	78.4
>16.91 to 18.75	41	15.3	93.7
18.75 to 19.80	6	2.2	95.9
>19.80 to highest	11	4.1	100.0
Total	268	100.0	

Varimax rotation (independent factors) was used instead of the oblique rotation (related factors) since the extracted factors were not correlated. Excluding the two variables has improved the results significantly (see last row of **Table 2**).

Table 2 Summary of the results from running Factor Analysis (Overall data)

Run Nr	Rotation Method	Determinant (R)	KMO	Barttlet's test	df	% variance explained	Nr of extracted Factors	MSA* <0.50
1	oblique	0.297	0.576	320.6	21	67.04	3	UnPln-OTR
2	varimax	0.297	0.576	320.6	21	67.04	3	UnPln-OTR
3	varimax	0.347	0.595	279.9	15	57.70	2	OTR
4	**varimax**	**0.379**	**0.614**	**256.5**	**10**	**66.5**	**2**	**None**

*measure of sampling adequacy

Table 3 shows the R-matrix (correlation matrix). The first half contains Pearson's correlation coefficients between all pairs of variables whereas the bottom half contains the 1-tailed significance level of these coefficients. The correlation between SLR and FTE was statistically not significant. The correlation between RVGE-WM (Winter Months) and BTOR was weak (p= 0.059). The highest correlation coefficient was between BDOR and BTOR (r= 0.666). The Anti-image matrix has shown that the measure of sampling adequacy (MSA) for all remaining variables were above the bare minimum of 0.5 (Kaiser, 1974).[3]

Table 3 The correlation matrix[1]

Variables	BDOR	BTOR	FTE	SLR	RVGE-WM
BDOR	**1.000**	0.666	0.270	0.322	0.243
BTOR	0.666	**1.000**	0.312	0.224	0.096
FTE	0.270	0.312	**1.000**	0.006	-0.138
SLR	0.322	0.224	0.006	**1.000**	0.278
RVGE-WM	0.243	0.096	-0.138	0.278	**1.000**
Sig.(1-tailed)					
BDOR		0.000	0.000	0.000	0.000
BTOR	0.000		0.000	0.000	0.059
FTE	0.000	0.000		0.460	0.012
SLR	0.000	0.000	0.460		0.000
RVGE-WM	0.000	0.059	0.012	0.000	

[1]: Determinant (R) = 0.379

We re-run the factor analysis for this data without UnPln and we used orthogonal rotation (varimax) since the correlation coefficients between the extracted factors were very weak (Component correlation matrix). So, it is reasonable to assume independence between the extracted Factors.

As a result, the determinant of R-matrix has increased to 0.379. The value of this determinant is vital for testing for multicollinearity or singularity that must be > 0.00001.

3 Kaiser, Henry. An Index of Factorial Simplicity. F.Psychometrika, 39, 1, 31-6, Mar 74

With a sample of 268 (N), 5 variables (p) and a determinant of 0.379 gives Haitovsky's Chi-Square test score of 86.52 with 10 degrees of freedom (p*(p-1)/2). The observed value is greater than the critical value of 23.21 (for 1% level of significance). In addition, the KMO measure of sampling adequacy increased to 0.614, and total variance explained has increased to 66.5% (with two factors). Bartlett's test of Sphericity (approx. chi-square) of 256.592 (with 10 degrees of freedom) was highly significant indicating that Factor analysis is an appropriate method for analysing the data.

The KMO values for individual variables are given on the diagonal of the anti-image correlation matrix in **Table 4** below. KMO values (given along the diagonal) were all above the bare minimum of 0.50 (between 0.563 and 0.736). The partial correlations and covariance are given on the off-diagonal.

Table 4 Anti-image correlations for bed and staff management variables

Variables	BDOR	BTOR	FTE	SLR	RVGE-WM
Anti-image Covariance					
BDOR	0.496	-0.312	-0.093	-0.124	-0.136
BTOR	-0.312	0.535	-0.115	-0.029	0.041
FTE	-0.093	-0.115	0.856	0.042	0.163
SLR	-0.124	-0.029	0.042	0.851	-0.176
RVGE-WM	-0.138	0.041	0.163	-0.176	0.856
Anti-image Correlation					
BDOR	0.591[a]	-0.607	-0.143	-0.19	-0.212
BTOR	-0.607	0.598[a]	-0.171	-0.043	0.061
FTE	-0.143	-0.171	0.681[a]	0.050	0.191
Avg. SL	-0.190	-0.043	0.050	0.736[a]	-0.206
RVGE-WM	-0.212	0.061	0.191	-0.206	0.563[a]

Table 5 labelled as Total variance explained, gives initial eigenvalues (un-rotated) before extraction, after extraction (Extraction Sums of Squared loadings) and after rotation (Rotation Sums of Squared loading). The list of the eigenvalues associated with each factor before extraction equal nr of variables. The % of variance explained by Factor 1 is 41.1% of the total variance, followed by 25.38% by Factor 2 (i.e. Total variance explained is 66.5%).

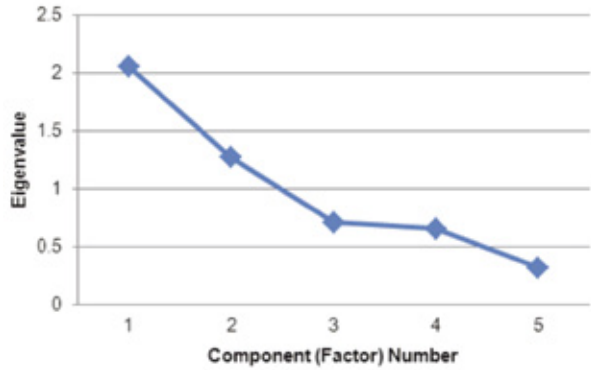
Table 5 Total Variance explained

	Initial Eigenvalues			Extraction SS Loadings			Rotation SS Loadings		
Nbr of Component	Total	% of variance	Cum. %	Total	% of variance	Cum. %	Total	% of variance	Cum. %
1	2.056	41.123	41.123	2.056	41.123	41.123	1.863	37.257	37.257
2	1.269	25.379	66.502	1.269	25.379	66.502	1.462	29.246	66.502
3	0.709	14.170	80.672						
4	0.652	13.036	93.708						
5	0.315	6.292	100.000						

SS: Sums of Squared; Extraction method: Principal Component Analysis

The scree plot (**Figure 1**) clearly indicates that the first two eigenvalues were >1.0 and therefore 2 factors have been selected. If >0.7 criteria was selected, then 3 factors would be extracted.

Figure 1 Scree Plot – Overall data – winter months (Jan to Mar)



Tables 6 and **7** depict the communalities and component matrix before rotation, respectively. The component matrix contains the loadings of each variable onto each Factor. We have two Factors based on Kaiser's criteria of selecting Eigenvalues >1.0. The communality, which is a measure of proportion of variance explained by the extracted factors, given in **Table 6** indicates that BDOR and BTOR have the highest values while average SLR has the lowest value.

Table 6 Communalities are given per variable

Variables	Initial	Extraction
BDOR	1.000	0.772
BTOR	1.000	0.739
FTE	1.000	0.640
SLR	1.000	0.523
RVGE WM	1.000	0.652

In Factor 1 (**Table 7**) high loadings are given for BDOR followed by BTOR (i.e. Bed management), while in Factor 2, high loadings are given to SLR, FTE and RVGE-VM. Notice that FTE and SLR are also important in Factor 1.

Table 7 Component Matrix (before rotation) [1]

Variables	Component	
	Factor 1	Factor 2
BDOR	0.877	-0.043
BTOR	0.826	-0.238
SLR	0.541	0.480
RVGE-WM	0.364	0.721
FTE	0.424	-0.678

In the top half of the matrix labelled Reproduced correlations given in **Table 8**, contains the correlation coefficients between all of the variables based on the Factor Model.

The diagonal of the Matrix contains the Communalities after extraction for each variable. Residuals are computed between observed and reproduced correlations.

Table 8 Reproduced Communalities – Overall – Winter

Variables	BDOR	BTOR-	FTE	SLR	RVGE-WM
Reproduced Correlation					
BDOR	0.772[a]	0.735	0.401	0.454	0.288
BTOR	0.735	0.739[a]	0.511	0.333	0.129
FTE	0.401	0.511	0.640[a]	-0.097	-0.335
SLR	0.454	0.333	-0.097	0.523[a]	0.543
RVGE -WM	0.288	0.129	-0.335	0.543	0.652[a]
Residual [b]					
BDOR		-0.069	-0.131	-0.092	-0.055
BTOR	-0.069		-0.199	-0.147	0.014
FTE	-0.131	-0.199		0.041	0.265
SLR	-0.132	-0.109	0.103		-0.312
RVGE -WM	-0.045	-0.033	0.197	-0.312	

[a]:Reproduced communalities

The rotated component matrix (**Table 9**) is a matrix of factor loadings for each variable onto each factor. This matrix contains the same information as the Component matrix except that it is calculated after rotation (using the varimax method).

Table 9 Rotated Component Matrix [a]

Variables	Component	
	Factor 1	Factor 2
BDOR	0.835	0.203
BTOR	0.784	0.397
FTE	0.704	-0.379
SLR	-0.042	0.806
RVGE WM	0.232	0.685

[a]: Rotation method: varimax with Kaiser normalization

Table 10 gives the component score coefficient matrix for each Factor from which Factor scores are calculated for each hospital day.

Table 10 Component score coefficients matrix

Variables	Component	
	Factor 1	Factor 2
BDOR	.388	.182
BTOR	.442	.036
FTE	.444	-.362
SLR	.0.041	.459
RVGE WM	-.128	.581

The final output is the Factor transformation matrix and if the orthogonal rotation was completely appropriate, we expect a symmetrical matrix (see below).

Component	Factor 1	Factor 2
Factor 1	0.869	0.496
Factor 2	- 0.496	0.869

ANDERSON-ROBIN (A-R) FACTOR SCORES & T-TEST FOR EQUALITY OF MEAN

Factor scores are calculated per extracted Factor using the A-R method. Independent sample t-test is used to assess whether factor scores were statistically different between pre- and post-vaccination for each Factor. Levene's test was used to assess whether or not the variances can be assumed to be equal. For Factor 1, Levene's test result of 4.228 was statistically significant, p= 0.041, equal variances cannot therefore be assumed. While for Factor 2, Levene's test of 0.341 was not significant (p= 0.560), equal variances can be assumed. The results of the t-test are therefore selected accordingly (**Table 12**). **Table 11** depicts descriptive statistics for factor scores per Factor and study period. For Factor 1, average A-R score were similar between Pre- and Post-vaccination (t-test= 1.034; p= 0.302), while for Factor 2, the average A-R scores were significantly higher during the pre-vaccination period compared with post-vaccination (t-test= 10.309; p<0.001).

Table 11 Descriptive statistics for A-R Factor scores per Factor & study period (Overall, Winter)

A-R Scores	Study Period	N	Mean	Std. Deviation	Std. Error Mean
Factor 1	Pre-vac	139	-0.0612	0.9088	0.0770
	Post-vac	129	0.0659	1.0894	0.0959
Factor 2	Pre-vac	139	0.5145	0.8213	0.0696
	Post-vac	129	-0.5544	0.7525	0.0768

Table 12 Independent sample t-test for A-R Factor 1 and 2 scores by study period (pre- versus post-vaccination)

Scores Group	Levene's test	Sig. Level	t-test	Sig. (2-tailed)	Mean Diff.	Std. Error Diff.	95% CI of the Diff.	
							Lower	Upper
A-R Factor 1	4.228	0.041	-1.034	0.302	-0.1272	0.1230	-0.3695	0.1151
A-R Factor 2	0.341	0.000	10.332	0.000	1.0690	0.1034	0.8653	1.2727

Comparing the epidemic winter data with the non-epidemic non-winter data

Table 1 Total number of rotavirus tests and rotavirus-positive tests by season and study period

	Pre-vaccination (2005–2006)			Post-vaccination (2007–2009)		
	RV tests, n	RV-positive tests, n	% RV-positive	RV tests, n	RV-positive tests, n	% RV-positive
January to March (winter season)	290	165	56.9%	209	48	23.0%
April to December (non-winter season)	196	41	20.9%	512	86	16.8%
Total	**486**	**216**	**44.4%**	**721**	**134**	**18.6%**

RV, rotavirus; n: number

Table 2 Bed management variables (2004-2009) for overall, infection-only, and AGE patient groups by season and by study period

Season	Study period	Value	Overall	Infection-only	AGE
Occupied beds per day (BDOR)					
January to March (winter season)	Pre-vaccination	Mean	30.59	16.96	7.52
		N	271	271	271
		SD	7.05	4.29	3.51
		Sum	8,289	4,595	2,039
	Post-vaccination	Mean	28.89	14.80	4.47
		N	361	361	361
		SD	7.25	3.95	2.19
		Sum	7,828	4,010	1,212
April to December (non-winter season)	Pre-vaccination	Mean	23.24	9.38	2.46
		N	611	611	611
		SD	7.54	4.82	2.11
		Sum	14,199	5,731	1,504
	Post-vaccination	Mean	25.15	11.20	2.83
		N	1039	1039	1039
		SD	9.10	6.59	2.27
		Sum	26,135	11,637	2,942
Bed turnover rate per day (BTOR)					
January to March (winter season)	Pre-vaccination	Mean	0.253	0.079	0.048
		N	271	271	271
		SD	0.132	0.052	0.041
		Sum	69	21	13
	Post-vaccination	Mean	0.284	0.065	0.028
		N	361	361	361
		SD	0.143	0.048	0.031
		Sum	77	18	8
April to December (non-winter season)	Pre-vaccination	Mean	0.208	0.043	0.016
		N	611	611	611
		SD	0.126	0.039	0.023
		Sum	127	26	10
	Post-vaccination	Mean	0.267	0.051	0.020
		N	1039	1039	1039
		SD	0.152	0.045	0.026
		Sum	278	54	21
Unplanned readmission rate per day (UnPln)					
January to March (winter season)	Pre-vaccination	Mean	0.93	0.76	0.56
		N	271	271	271
		Cases	48	36	29
		SD	0.908	0.880	0.691
		Sum	253	207	152
	Post-vaccination	Mean	0.38	0.29	0.16
		N	361	361	271
		Cases	25	19	9
		SD	0.685	0.529	0.404
		Sum	136	106	43
April to December (non-winter season)	Pre-vaccination	Mean	0.61	0.31	0.09
		N	611	611	611
		Cases	58	30	10
		SD	0.715	0.545	0.303
		Sum	370	190	55
	Post-vaccination	Mean	0.59	0.29	0.11
		N	1314	1314	1039
		Cases	130	64	26
		SD	0.789	0.547	0.344
		Sum	772	381	113

AGE, acute gastroenteritis; SD, standard deviation; N, Number of days

Table 3 Staff management variables (2004-2009) for overall by season and by study period

Season		N	% Total N	Sum	Mean	SD	Maximum	Minimum
Staff numbers per day (FTEs)								
January to March (winter season)	Pre-vaccination	271	10.6%	3920.9	14.468	3.064	21.3	9.1
	Post-vaccination	361	14.1%	5395.3	14.945	3.634	22.9	6.9
April to December (non-winter season)	Pre-vaccination	611	23.9%	8549.5	13.993	3.261	22.0	4.9
	Post-vaccination	1039	51.4%	18198.3	13.850	3.882	23.6	4.8
Overtime hours worked per day (OTR)								
January to March (winter season)	Pre-vaccination	38	10.2%	264	6.95	2.770	14	3
	Post-vaccination	57	15.3%	431	7.55	2.608	16	0
April to December (non-winter season)	Pre-vaccination	51	13.7%	346	6.78	2.436	14	4
	Post-vaccination	226	60.8%	1768	7.82	3.003	20	0

FTE, full-time equivalent; SD, standard deviation; N, Number of days

Table Staff sick leave by season and study period

Season	Study period	Value	Sick leave, hours	Sick leave, persons	Sick leave, FTE
January to March (winter season)	Pre-vaccination	N (days)	271	271	271
		Sum	1423.28	308	187.274
		Mean	5.252	1.14	0.691
		SD	5.990	0.95	0.788
		Maximum	25.47	4	3.351
		Minimum	0.00	0	0.000
	Post-vaccination	N (days)	361	361	361
		Sum	1579.33	311	207.807
		Mean	4.375	0.86	.575
		SD	5.148	0.858	.677
		Maximum	20.90	4	2.750
		Minimum	0.00	0	0.000
April to December (non-winter season)	Pre-vaccination	N (days)	611	611	611
		Sum	2613.82	578	343.923
		Mean	4.278	0.95	0.563
		SD	4.885	0.870	0.643
		Maximum	20.90	4	2.750
		Minimum	0.00	0	0.000
	Post-vaccination	N (days)	1314	1314	1314
		Sum	7657.50	1548	961.316
		Mean	5.83	1.18	0.732
		SD	5.823	0.929	0.763
		Maximum	28.50	5	3.750
		Minimum	0.00	0	0.000

FTE, full-time equivalent; SD, standard deviation; N, Number of days

Table 5 Average QoC scores per day pre- (2005-2006) and post-vaccination (2007-2009) for each patient group in winter and non-winter seasons

Patient group and season	Factor	Pre-vaccination	Post-vaccination	Mean difference	t-test	p-value (2-tailed)
Winter season (January to March)						
Overall	Factor 1	-0.061	0.065	-0.127	-1.034	0.30
	Factor 2	0.514	-0.554	1.069	10.332	0.000*
	QoC score	0.453	-0.488	0.941	5.767	0.000*
Infectious-only	Factor 1	0.506	-0.546	1.052	10.188	0.000*
	Factor 2	-0.100	0.108	0.209	-1.718	0.087
	QoC score	0.406	0.053	0.352	5.107	0.000*
AGE	Factor 1	0.501	-0.544	1.046	10.125	0.000*
	Factor 2	0.333	-0.361	0.695	6.152	0.000*
	QoC score	0.834	-0.906	1.741	11.153	0.000*
Non-winter season (April to December) [1]						
Overall	Factor 1	-0.073	0.027	-0.101	-1.088	0.28
	Factor 2	0.089	-0.032	0.122	1.219	0.22
	QoC score	0.015	-0.005	0.021	0.133	0.89
Infectious-only	Factor 1	-0.060	0.022	-0.082	-0.819	0.41
	Factor 2	-0.094	0.034	-0.128	-1.427	0.16
	QoC score	-0.154	0.056	-0.210	-1.490	0.14
AGE	Factor 1	0.011	-0.004	0.015	0.158	0.88
	Factor 2	0.035	-0.012	0.048	0.480	0.63
	QoC score	0.046	-0.017	0.064	0.451	0.65

AGE, acute gastroenteritis; QoC, quality of care

*significant differences; [1]all average QoC- scores differences were not statistically significant

EXPLORING THE POTENTIAL IMPACT OF ROTAVIRUS VACCINATION ON WORK ABSENTEEISM AMONGST FEMALE ADMINISTRATIVE PERSONNEL OF THE CITY OF ANTWERP THROUGH A RETROSPECTIVE DATA-BASE ANALYSIS.

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ABSTRACT

Objectives: Rotavirus vaccination has been reimbursed in Belgium since November 2006 with a high uptake (>85%). Cost-effectiveness analyses of the vaccine have been reported, including estimates of the indirect cost gain related to the reduction in work absenteeism. The objective of this study was to evaluate the latter parameter using real-life data.

Design & Settings: A simple model was built to estimate the reduction in absent work days per working mother with a firstborn baby after the introduction of the rotavirus vaccine. Next, data on work absences were retrospectively analysed (from 2003 to 2012) using a database of administrative employees (n =11,600 working women per year) in the city of Antwerp. Observed reductions in absenteeism after the introduction of the vaccine were compared with the results from the model. These reductions would most likely be observed during the rotavirus epidemic periods (from January to the end of May) for short-duration absences of ≤5 days. We compared data from outside epidemic periods (from June to December), expecting no changes over time pre- and post-vaccine introduction, as well as with a control group of women aged 30 to 35 years old with no 1st child.

Results: Model estimates were 0.73 working days gained per working mother. In the database of the city of Antwerp, we identified a gain of 0.88 working days during the epidemic period and an accumulated gain of 2.24 days over a 3-year follow-up period. In the control group no decrease in absenteeism was measured. Giving vaccine access to working mothers resulted in an accumulated net cost gain of €187 per mother.

Conclusions: Reduction in absenteeism among working mothers was observed during epidemic periods after the introduction of the rotavirus vaccine in Belgium. This reduction is in-line with estimates of indirect cost gains used in cost-effectiveness models of the rotavirus vaccine.

Key words: rotavirus, vaccination, work absence, absenteeism, workplace, herd effect, cost gain

Strengths and limitations

- Cost-effectiveness models of rotavirus vaccination simulate the absence from work due to rotavirus infection in children as well as the reduction in work absenteeism of mothers due to vaccine introduction, but nobody has evaluated these reductions with real-life data.
- The objective of this study was to evaluate the impact of introducing the rotavirus vaccine in Belgium on the reduction of work absenteeism over an observation period of 9 years (from 2003-2012), using real-life data from a database of the administrative personnel in the city of Antwerp. The vaccine was introduced with a high uptake in November 2006.
- The analysis suggests that rotavirus vaccination results in a reduction of absences from work among mothers with a 1st child during the first, second and third rotavirus epidemic periods after birth, with an accumulated 2.24 day gain/woman.
- This translated into a net cost gain for the employer of €187 per working mother.
- The main limitation of the study is that the results are based on retrospective data analysis with no causal relationship between the introduction of the vaccine and the reduction in absenteeism observed, but different indirect arguments have been brought forward.

INTRODUCTION

The rotavirus (RV) epidemic is an annual recurrent public health problem of severe diarrhoea in young children, with a peak incidence before the age of 2.[1;2] RV disease preferentially occurs during the winter months in the northern hemisphere and in countries with a more temperate climate. The viral spread occurs amongst young children but may manifest a higher rate of transmission around 10 months old, for it is at this age that being in a day-care centre the child is a conducive virus transmitter to younger and older children. [3]

RV vaccination was introduced in Belgium in November 2006 as a new management strategy against the illness.[4] Belgium was one of the first countries in Europe to integrate this vaccine into its routine childhood immunisation programme.[5] Vaccine uptake was high from the start (>85%) because it was recommended by the High Committee of Health Promotion. Moreover, the organisational structure for implementing immune protection in children and a good follow-up process are both well developed in the country.[6]

Several cost-effectiveness evaluations of the RV vaccine have been conducted and most of these analyses have included indirect cost estimates.[7-10] An analysis of the financial burden of RV disease in four European countries indicated that the indirect costs could be substantial: half of the total cost of the disease per child at-risk could be linked to these indirect costs.[11] However, until now these estimates have always been simulated and nobody has been able to evaluate the reduction of work absenteeism using real-life data subsequent to the introduction of the RV vaccine.[12] Obtaining that type of evidence is not an easy task as we need to have an environment where employment is stable among a large number of employees in order to follow enough working mothers with young children under the same working conditions and having the same exposure to the disease. In addition, we needed to obtain detailed information on each period of absenteeism with a start

and end date linked to the employee's family condition when a new child is born. The data should be available over a long enough period of time (at least 5 years) and in electronic format with easy access so that the time periods before and after vaccine introduction can be analysed and compared.

It was postulated that during epidemic RV disease periods working mothers with a 1st child would be absent from work for short durations (≤ 5 days) more often than during non-epidemic periods or after the introduction of the vaccine. In addition working women with no exposure anymore of children to the rotavirus disease should not experience any benefit of the vaccine expressed as a reduction in work absenteeism. We first constructed a simple, back-of-the-envelope model that could give us guidance in our search of parameters in real-life data sets.

DESIGN AND SETTING

Simple model construction

The simple model calculates the expected difference in worker absenteeism when comparing exposure versus non-exposure to the RV vaccine. It is expressed as the estimated number of days per year and per working mother with a 1st child. The value measured would then serve as a benchmark for analysing the observed data.

Observed data

We selected a database from the city of Antwerp which has a sufficient number of subjects from the target group (n≈11,600 women per year) over a long period of time (from 2003 to 2012). This database collects detailed information on absences from work for all its administrative personnel, including an overall reason with no particular details, duration, and time period of the absence (start and end date). It is also reasonably accurate because the personnel payment data is linked to that system. Moreover, through a unique subject number the database could be linked to other databases in the city which compile information on family composition and the birth dates of children born to each employee. The data were made available after decoding subjects to prevent identification of individuals and after approval of the project and its objectives by the administrative head of the city.

We performed the analysis in three steps. First, to increase the chances of observing a difference in absenteeism due to vaccination, we selected a target group of women with a 1st child approximately 10 months of age during the typical epidemic RV season (January through May) of each year. These children are known transmitters of the virus. In a second step, we conducted an annual analysis of the same working mothers but with a 1st child born any time during the year prior to the next epidemic period. We expected a larger difference (i.e., less absenteeism) from the first analysis than from the second one. In a third step we selected from the same data-base women aged 30 to 35y old with no 1st child, but working during the same observation period from 2004 to 2012, from January to May. It was hypothesized that these women, considered as a control group, should not benefit from the rotavirus vaccination and therefore we would not observe any decrease in work absenteeism over time.

Thus, in the first step we selected working women with a 1st child born during the months of April through July on a yearly basis from 2003 to 2011. That number was variable per year. We then recorded short absences from work (≤5 days) which were registered 10 months after the birth of their child. That specific period of 10 months postpartum was equal to the normal RV epidemic season. The sum of all work absences during that annual period of time in all years from 2004 to 2012 was then divided by the number of mothers considered the previous year in order to obtain an average value per working mother with a 1st child during the following epidemic period.

We compared the data by year to observe any marked difference in work absenteeism after 2006, which was the year RV vaccination was introduced. We also analysed absenteeism data from the same working mothers which was outside the epidemic period, expecting a much lower rate. To be able to compare the same values by time period, we analysed the average value by month for each period (epidemic and non-epidemic).

If an important difference was observed in the first step, we would then proceed to the second step of evaluating work absences during each epidemic period among mothers with a 1st child born anytime during the previous year (whole year birth cohort). We again reported the sum of all days absent from work in the postpartum year during epidemic and non-epidemic periods. We hypothesised that if the difference in absenteeism was large enough in the first step, it should still be present in the second step and that would facilitate the analysis of other time periods. In addition, we evaluated the same type of absences from work among mothers with a firstborn child in its 2nd and 3rd year of life (e.g. absences of mothers with a first child born during 2003 were evaluated in the epidemic periods of 2005 and 2006, respectively). Finally, we compared this observed data with the estimates we had obtained from the simple model. The control group was analysed the same way as the other groups. We report the same type of outcome measure over time which is the average number of days being absent from work per women during the epidemic period per year.

Based on the above results we could calculate the net cost gain per working mother through the average reduction in absenteeism post-vaccination. This was adjusted by the cost of the vaccine, which was considered at €60/dose [13]. The average gross salary for a working mother in the city of Antwerp was estimated at €135/day [14].

To observe a statistically significant difference between pre- and post-vaccination absenteeism per working mother, we compared the data by ranking mothers into 6 categories according to the number of days absent from work (0, 1, 2, 3, 4 and 5 days) during the epidemic period. We then applied a statistical ranking test (Mann Whitney U-test with $p<0.05$). Statistical analyses and the computation of 95% Confidence Intervals (CI) were done using IBM SPSS Statistics v22.0 and GraphPad v6.

RESULTS

Modelled data

As shown in Table 1, the simple model indicated that the introduction of the RV vaccine produced a gain range of 0.73 to 0.80 working days per mother with a 1st child in the vaccinated cohort. Because there was no maximum vaccine coverage in the vaccinated cohort, we needed to include a normal rate of infection among the unvaccinated in that cohort (="Rest"). A sensitivity analysis around that value was performed since high vaccination levels result a herd effect in the "Rest" group. Therefore, the difference between pre- and post-vaccination absenteeism could be higher.

Table 1 Model estimates

Parameter	Value	Absolute numbers	Difference
No Vaccination			
Working mothers with a 1st child	75		
% of mothers with a 1st child having diarrhea 1st year	20%	75*20%=15	
Average duration (days) for being absent for diarrhea in a child	5	15*5=75	
Average number of days absent/woman		75/75=1	1
Vaccination			
Working mothers with a 1st child	75		
% of mothers with a vaccinated child	85%	75*85%=64	
% of mothers no vaccinated child	(1-85%)=15%	75*15%=11	
vaccine efficacy against diarrhea	85%		
% of mothers with a vaccinated child still having diarrrhea	20%*(100%-85%)=3%	64*3%=2	
% of mothers with an unvaccinated child still having diarrhea (Rest)	20%	11*20%=2	
Average duration (days) for being absent for diarrhea in a child	5	4*5=20	
Average number of days absent/woman		20/75=0.27	0.27
Gain in working days avoided/woman after vaccination 1st year			(1-0.27)=0.73
Sensitivity analysis			
Proportion of children with diarrhoea is lower because of the vaccine's herd effect in the Rest group	10% instead 20%	11*10%=1	
Average duration (days) for being absent for diarrhea in a child		3*5=15	
Average number of days absent/woman		15/75=0.20	0.20
Gain in working days avoided/woman after vaccination 1st year			(1-0.20)=0.80

Observed data

First step analysis

Table 2 summarizes the annual number of days absent from work each epidemic season among the target group of working mothers with a 1st child born between April and July the previous year. It should be noted that a reduction in absenteeism is observed only after 2008 because the vaccine was introduced in November, 2006. In the non-epidemic period, large changes are not seen in any given month. We observed a substantial reduction in absenteeism (average days per woman (2003 to 2008) – average days per woman (2009-2012) = 0.821) noted from 2009 onwards, so that we proceeded with the second step.

Table 2 Average number of short work absences per targeted woman with a 1st child during the epidemic and non-epidemic seasons

Year	Women in target period	Epidemic period (Jan - May)					Non-epidemic period (June - Dec)				
		Cumulative days absent	Per woman	95% CI+	95% CI-	Per month	Cumulative days absent	Per woman	95% CI+	95% CI-	Per month
2003	56										
2004	57	98	1.750	2.252	1.247	0.350	76	1.357	1.764	0.950	0.194
2005	62	97	1.702	2.234	1.168	0.340	27	0.474	0.742	0.204	0.068
2006	66	98	1.581	2.048	1.113	0.316	58	0.935	1.309	0.561	0.134
2007	80	109	1.652	2.116	1.186	0.330	54	0.818	1.151	0.485	0.117
2008	65	148	1.850	2.285	1.414	0.370	67	0.838	1.136	0.538	0.120
2009	62	65	1.000	1.346	0.653	0.200	39	0.600	0.900	0.299	0.086
2010	96	63	1.016	1.354	0.677	0.203	66	1.065	1.484	0.644	0.152
2011	114	64	0.667	0.907	0.426	0.133	68	0.708	1.049	0.491	0.101
2012		98	0.860	1.113	0.588	0.172	84	0.737	0.972	0.501	0.105

Second and third step analysis

Table 3 reports the number of absent work days among mothers with a firstborn child during the epidemic period of the 1st postpartum year in 6 different categories (0, 1, 2, 3, 4, and 5 days) and the statistical test results obtained when comparing year 2004 with year 2009. From 2009 on, we observed a clear increase in the number of 0-day absences from work and a decline in the number 5-day absences. In the same table we report the data of the control group of women aged 30 to 35 years old with no marked change in absenteeism seen over time. The average values and the 95% CI are also reported. There is no much difference to be noted in the average values for the full cohort of women (Table 3) compared with the targeted cohort (Table 2) except for a narrower confidence interval in Table 3 because of the higher number of persons enrolled in the analysis. We further observed that during the non-epidemic period there was no big variation in the numbers noted year after year.

Table 3 Frequency distribution of days absent from work pre- and post-vaccination among mothers with a firstborn child in the 1st year of life during the epidemic period and non-epidemic period and amongst women with no firstborn child aged 30 to 35 years old during the epidemic period only

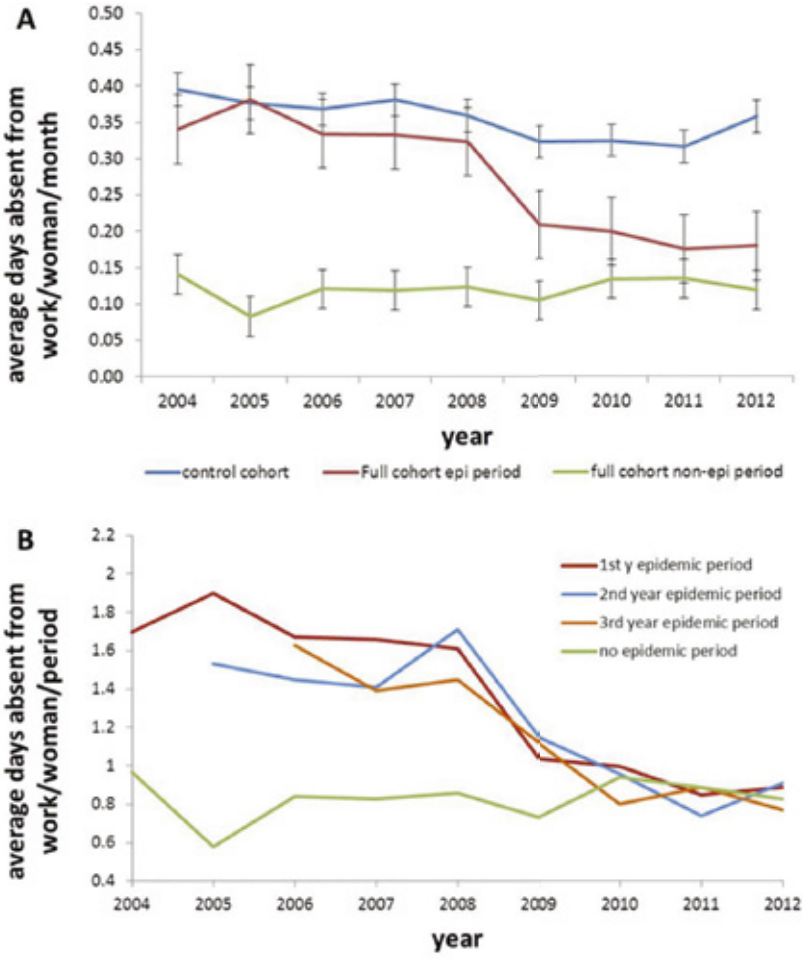
Days	2004*	2005	2006	2007	2008	2009*	2010	2011	2012
Full cohort of women with firstborn child, epidemic period									
0	70	85	78	94	101	116	131	159	167
1	34	26	32	22	39	54	37	32	41
2	10	17	14	33	16	22	13	30	19
3	8	8	14	15	13	14	16	16	10
4	12	13	11	10	19	8	10	10	11
5	31	48	31	35	35	13	14	9	17
Total N	165	197	180	209	223	227	221	256	265
Total N of absent days	281	376	301	348	361	237	221	225	238
Average	1.703	1.909	1.672	1.665	1.619	1.044	1.000	0.879	0.898
95% CI +	2.005	2.201	1.955	1.924	1.873	1.264	1.236	1.090	1.116
95% CI -	1.401	1.617	1.389	1.406	1.365	0.825	0.764	0.668	0.680
Cohort of women aged 30 to 35y, epidemic period									
0	248	303	365	399	435	242	440	500	464
1	179	176	168	191	257	372	167	206	230
2	106	104	123	109	128	162	109	126	195
3	63	60	76	79	79	72	101	139	111
4	61	77	93	81	97	77	65	71	89
5	157	155	160	215	203	81	144	144	200
Total N	814	875	985	1074	1199	1006	1026	1186	1289
Total N of absent days	1609	1647	1814	2045	2153	1625	1668	1879	2309
Average	1.977	1.882	1.842	1.904	1.796	1.615	1.626	1.584	1.791
95% CI +	2.106	2.008	1.960	2.021	1.903	1.711	1.740	1.688	1.892
95% CI -	1.847	1.757	1.724	1.787	1.689	1.519	1.512	1.481	1.691
Full cohort of women with firstborn child, non-epidemic period									
Total N	165	197	180	209	223	227	221	256	265
Total N of absent days	161	115	152	174	193	166	208	241	221
Average	0.976	0.584	0.844	0.833	0.865	0.731	0.941	0.941	0.834
95% CI +	1.203	0.801	1.070	1.026	1.063	0.931	1.156	1.136	1.023
95% CI -	0.749	0.367	0.618	0.639	0.668	0.532	0.727	0.746	0.645

N: working mothers; * Mann-Whitney-U test ($p<0.00$)

Figure 1A reports the results of Table 3 in a graphical presentation with the 95% CI included. The graph compares the average value per month and per time period because the epidemic and non-epidemic seasons have different durations (5 and 7 months, respectively). It is important to note that the full cohort of women with vaccinated children doesn't reach the same level of absenteeism of the non-epidemic period, but at the same time the control group does not manifest any substantial decline in absenteeism during the same observation period.

Figure 1B also shows the average number of absent work days during the epidemic period when the firstborn child is in its 1st, 2nd and 3rd year of life. It is interesting

Figure 1 (A) Average number of short work absences per woman per month for the control group (blue), the full cohort mothers during the epidemic period (red), and during the non-epidemic period (green) and (B) Average number of short work absences per woman in the full cohort in the 1st (red), 2nd (blue) and 3rd (yellow) year postpartum during the epidemic period, and the non-epidemic period (green)



Nbr: number; RV: rotavirus.

that the same type of decline in absenteeism is observed in subsequent years as for the 1st year postpartum analysis. As already mentioned, reductions in absenteeism started after 2008 following the introduction of the RV vaccine by the end of 2006. If we work with averages over the whole observation period, we can see that prior to the introduction of the vaccine the average number of days absent from work during the epidemic period was an estimated 1.71 days (average value from 2004 to 2008). The average number of days absent from work in the

non-epidemic period was 0.83 days (average value from 2004 to 2012). Thus, the estimated difference in absenteeism obtained from switching from no vaccination to vaccination is approximately 0.88 days per working mother with a 1st child in the 1st year of life (1.71 - 0.83); 0.70 days for 2-year old children (1.53 - 0.83); and 0.67 days for 3-year old children (1.50 - 0.83).

The accumulated gain per working mother with a 1st child during the epidemic period is 2.24 days (0.88+0.7+0.67). The absolute gain is difficult to measure from the database, which reports fluctuating numbers and different lengths of duration each year. Table 4 shows the calculated values, which is based on the average numbers we obtained.

Table 4 Estimated gain per working mother with a 1st child over a 3-year period

	Post-partum	Pre-vaccination: days absent from work*	Post-vaccination: days absent from work*	Difference (days)	Days gained (216 women)*
Average	1st year	1.71	0.83	0.88	190
	2nd year	1.53	0.83	0.70	150
	3rd year	1.50	0.83	0.67	144
	Sum	4.74	2.49	2.25	484

*Per working woman with a 1st child

The benefit of vaccination to an employer of an average annual work force of 216 working mothers with a 1st child is a gain of 484 working days over a 3-year period of time. At an average gross monthly salary of €3,000 or €135 per work day, the gross gain is €67,095 for the entire working mother cohort. The employer will spend a total of €26,640 for the vaccine if the cost is an estimated €120 per mother. The net gain is then quickly calculated, which is €40,455 for the cohort or €187 per working mother.

DISCUSSION

Many economic models evaluating the cost-effectiveness of paediatric vaccines report the indirect cost impact in sensitivity analyses.[10;15;16] These costs are estimated using the human capital cost evaluation method in which the estimated number of days in productivity loss are multiplied by an average cost per day for the target population under study.[17;18] The approach gives a first indication or exploration about the real value. We know, however, that these vaccination interventions can avoid a great amount of productivity loss, especially among working mothers whose children are at high risk of infection and who are receiving the paediatric vaccines. [19] In the current study, we conducted an investigation of the problem using real-life data and compared that to the results of a simple modelling exercise. The analysis confirms that there is a measurable reduction in work absenteeism among working mothers after the introduction of the rotavirus vaccine. When looking at the data in greater detail, we observed that this reduction was among cases with a high number of absentee working days (e.g. 5-day absences, see Table 3).

The initial intention of the project was focused primarily on increasing our chances of being successful in the selection of the right target group to show a difference in absenteeism which could be linked to the introduction of the rotavirus vaccine. Therefore, we opted for mothers with a 1st child since it is most likely in the Belgian culture that that person would be the first who takes time off work when the child suffers from an illness. Meanwhile, a critical question remained as to whether the observed reduction in work absenteeism was linked to the rotavirus vaccination introduction as many other reasons for short absences from work may cause a fluctuation in this parameter. The analysis here gives 5 reasons for the potential link. First, the reduction happened after the introduction of the vaccine in 2006 at the time we would expect to observe a major reduction during the epidemic rotavirus season. Secondly, mothers with a 1st child in their 2nd and 3rd year of life also manifested a reduction in absenteeism starting during the same year (2008), which can be explained by the known herd effect post-vaccination. If no herd effect was known for this vaccine, we would not observe these additional reductions in the other age groups. Thirdly, the observed reduction per working mother closely matches the modelled estimates (see Table 1), which was surprising. No reduction in work absenteeism was seen during the non-epidemic period, making it unlikely that new rules had been put in place by the employer to minimize short-term absences; otherwise we would have seen a reduction in absenteeism during all time periods after 2008. Finally, women with no exposure of their children to any rotavirus vaccination did not show any reduction in absenteeism during the same observation period. One additional point to mention here is that trying to link the reduction with the fluctuation of other childhood infections such as influenza is difficult to make as high epidemic infectious diseases during the pre-vaccine periods resulting in high rates of absenteeism should have been reported in the literature or in local disease reports which was not the case..

Specific conditions in retrospective data analyses must be fulfilled before it is possible to measure the changes observed. Those conditions are: 1) the demographic composition (gender and age) of the study population must remain stable in order to have the same denominator; 2) the rules and conditions for taking time off work must be maintained; 3) the disease must be causing a serious public health problem over a certain period so that a change in working patterns (e.g. absenteeism) can be observed; 4) the new intervention (e.g. the vaccine) must have an immediate high uptake as well as a large and rapid impact on the disease; 5) the data registry must be adequate, of high quality, consistent over time, and easily stored and accessible; 6) and finally, the target population must be a well-defined group. We cannot work with cultural changes over time (e.g. fathers instead of mothers suddenly becoming the main ones taking care of young children when the latter become sick). We obtained that unique combination of all these different factors in the database of the administrative personnel of the city of Antwerp. For instance, the fact that the data collected on absenteeism was linked to the payment condition of an employee makes the quality of the data very rich. If one of the conditional elements mentioned above is of poor quality, it automatically decreases the value of the whole investigation and the analysis. All the different elements are essential and none of them are more or less important

than the others. So it was highly critical that all the different elements were present at the same time in order to fit the analysis well.

Having a back-of-the-envelope estimate was a very helpful tool in understanding the potential gain to be observed in the real-life database. At the beginning of the study, we were looking at all the days of work absences and all mothers with children. That was not a viable option because the specific condition we were looking for was lost in the bigger numbers that were not related to a disease situation among children necessitating short absences from work (i.e., ≤ 5 days). It is also interesting that the observed data in the 1st year of a child's life was not so different from what we measured with the model. Surprisingly, it appeared that the benefit was even a little higher in real life than in the model, which could potentially be related to a higher incidence or distribution of the disease than what the model predicted or to a herd effect in the vaccinated age group itself. What is clear from the data, however, is that a herd effect was realized in other age groups who were unvaccinated when the vaccine was introduced, as reported in Figure 1B. The data confirmed what we observed in the RotaBIS study, in which we also observed the vaccine making a large impact as soon as it was introduced among unvaccinated age groups.[3] We know that the sample size of working mothers with a first child was small and could be considered as a limitation of the study. However, the analysis made was the best we could made in a country where the vaccine coverage rate for rotavirus vaccines was very high from start.

To our knowledge, this type of analysis is the first one to demonstrate that specific effect of the RV vaccine using real-life data. The conditions of RV infection provided the opportunity for this to happen: the disease is very contagious, preferentially hits very young children, is mainly incident during a short, epidemic season every year at the same time, and occurs among small children who need care by an adult. That conditional flow allows comparison of work absenteeism during epidemic and non-epidemic periods. It reinforces the circumstantial evidence showing a link between the observed reduction in absenteeism and the introduction of the vaccine, but we cannot claim or prove a clear causality from the data here. There are potentially other methods for collecting the same data prospectively, but it would be difficult to attain the same quality in the final results if one has to start from nowhere[20]. This is not a clinical trial. It is an analysis of an administrative database, in which the prospect of collecting that type of information in such a rigorous way is not obvious. It should also be clear that the overall benefit of the vaccine on a reduction in absenteeism in the workplace could be greater than what we measured here with a very specific sub-group of working mothers (those with a 1st child). It is likely that we could observe the same benefit among working mothers with a 2nd or 3rd child who was never previously exposed to RV.

Finally, will the results here discovered in this particular environment be easily transposable to other settings? Given the many conditions necessary to observe and measure the effect of a vaccine, it is likely that in other settings other amounts of benefit will be seen. For example, the facilities needed to be easily absent from work for childhood illness must be present in other places before we can observe the same result.

CONCLUSIONS

Working mothers with a 1st child benefit from RV vaccination through a reduction in work absenteeism. The model estimates and the observed data fit well for absences from work during the year following birth. The higher observed gain (0.88- versus 0.72-day gain) could be explained by a herd effect of the vaccine. There is possibly an underestimate of the total gain as only a selected group (mothers with a 1st child) was investigated. In the case of the city of Antwerp, the benefit can be expressed as a cost gain per woman as a cost-benefit ratio of 1.85 (working days gained/vaccine cost). Confirmation of these results with datasets from other public organisations in Belgium is expected in the near future.

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CONTRIBUTORSHIP STATEMENT

Baudouin Standaert has developed the protocol, made the analysis, and the reporting, and wrote the 1st draft of the manuscript. Els Van de Mieroop helped getting access to the data and reviewed the statistical analysis plan, give input into the review of the manuscript. Vera Nelen helped designing the study and reviewed the different drafts of the manuscripts.

DATA SHARING STATEMENT

All data were anonymized before sharing amongst the researchers. The method of analysis and the results were evaluated by all the researchers. Persons who are interested can get access to the data and the method of analysis on request.

REFERENCES

[1] Forster J, Guarino A, Parez N, Moraga F, Roman E, Mory O, et al. Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European children younger than 5 years of age. Pediatrics 2009 Mar;123(3):e393-e400.

[2] Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J 2006 Jan;25(1 Suppl):S7-S11.

[3] Standaert B, Gomez JA, Raes M, Debrus S, Velazquez FR, Postma MJ. Impact of rotavirus vaccination on hospitalisations in Belgium: comparing model predictions with observed data. PLoS One 2013;8(1):e53864.

[4] Plosker GL. Rotavirus vaccine RIX4414 (Rotarix): a pharmacoeconomic review of its use in the prevention of rotavirus gastroenteritis in developed countries. Pharmacoeconomics 2011 May;29(5):439-54.

[5] Parez N, Giaquinto C, Du RC, Martinon-Torres F, Spoulou V, Van DP, et al. Rotavirus vaccination in Europe: drivers and barriers. Lancet Infect Dis 2014 May;14(5):416-25.

[6] Raes M, Strens D, Vergison A, Verghote M, Standaert B. Reduction in pediatric rotavirus-related hospitalizations after universal rotavirus vaccination in Belgium. Pediatr Infect Dis J 2011 Mar 23;30(7):120-5.

[7] Bilcke J, Beutels P. Reviewing the cost effectiveness of rotavirus vaccination: the importance of uncertainty in the choice of data sources. Pharmacoeconomics 2009;27(4):281-97.
[8] Goossens LM, Standaert B, Hartwig N, Hovels AM, Al MJ. The cost-utility of rotavirus vaccination with Rotarix [trade mark] (RIX4414) in the Netherlands. Vaccine 2008;26:1118-27.
[9] Jit M, Bilcke J, Mangen MJ, Salo H, Melliez H, Edmunds WJ, et al. The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe. Vaccine 2009 Oct 19;27(44):6121-8.
[10] Standaert B, Parez N, Tehard B, Colin X, Detournay B. Cost-effectiveness analysis of vaccination against rotavirus with RIX4414 in France. Appl Health Econ Health Policy 2009;6(4):199-216.
[11] Standaert B, Harlin O, Desselberger U. The financial burden of rotavirus disease in four countries of the European Union. Pediatr Infect Dis J 2008;27(1):S20-S27.
[12] Giaquinto C, Van DP, Huet F, Gothefors L, Van der WM. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. J Infect Dis 2007 May 1;195 Suppl 1:S36-S44.
[13] Christiaens T, De Loof G, Maloteaux JM. Gecommentarieerd geneesmiddelenrepertorium 2014. 27th Edition ed. Ghent, Belgium: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG); 2014.
[14] Bevers T, Collard A, De Spiegeleire M, De Vos D, Gilbert V, Van Hove H. De loonkloof tussen vrouwen en mannen in België, 2010. 1st edition ed. Brussels, belgium: 2011.
[15] De WP, Black S, Borrow R, Pearce D. Modeling the impact of a new vaccine on pneumococcal and nontypable Haemophilus influenzae diseases: a new simulation model 1. Clin Ther 2009 Oct;31(10):2152-69.
[16] Farkouh RA, Klok RM, Postma MJ, Roberts CS, Strutton DR. Cost-effectiveness models of pneumococcal conjugate vaccines: variability and impact of modeling assumptions 1. Expert Rev Vaccines 2012 Oct;11(10):1235-47.
[17] Hutubessy RC, van Tulder MW, Vondeling H, Bouter LM. Indirect costs of back pain in the Netherlands: a comparison of the human capital method with the friction cost method 1. Pain 1999 Mar;80(1-2):201-7.
[18] Kotsopoulos N, Connolly MP. Is the gap between micro- and macroeconomic assessments in health care well understood? The case of vaccination and potential remedies. Journal of Market Access & health Policy 2014;2:23897.
[19] Alsarraf R, Jung CJ, Perkins J, Crowley C, Alsarraf NW, Gates GA. Measuring the indirect and direct costs of acute otitis media 6. Arch Otolaryngol Head Neck Surg 1999 Jan;125(1):12-8.
[20] Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research 2. J Clin Epidemiol 2000 Jul;53(7):688-95.