Cost-effectiveness analysis of rotavirus vaccination of Belgian infants

KCE reports 54C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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SUMMARY

INTRODUCTION

A mathematical simulation model, by definition, is not reality. It is a tool, which helps to understand complex issues, and project a range of scenarios that cannot be tested in the real world, because of time, ethical and practical constraints. In this case, it may help understand the implications of deciding on the use of the currently available oral rotavirus vaccines (Rotarix® and RotaTeq®) to our greatest advantage. In health economic evaluation, as applied in this report, what is to our society's greatest advantage is defined as the combination of interventions leading to the greatest possible health gains, for as many people as possible (i.e. maximization of health gains (expressed here mainly as life-years and Quality-Adjusted Life-Years (QALYs gained)), under a given budget constraint.

We have reviewed the international published and unpublished literature, and collected and analyzed a wide range of Belgian epidemiological and cost data. A simulation model was developed, parameterized and fitted by using scientifically validated data, as much as possible from Belgian sources. Simulations were performed to estimate how effective and cost-effective universal rotavirus vaccination of Belgian children would be.

The results of these simulations were highly dependent on the decision maker's perspective (that of the health care payer or society), and can be summarised as follows.

RESULTS

Health Care Payer Perspective

- The results are influenced considerably by the number of caregivers assumed to experience an impact on their health related quality of life (HRQOL), and the valuation of care for which no health care resources are used (non-medical costs and HRQOL impact for the child and caregiver(s)).
- According to the most plausible and in our opinion most relevant scenario, fully funded universal rotavirus vaccination would cost €50,024 (95% range: €25,374 - €99,730) per QALY gained with Rotarix®, and €68,321 (95% range: €35,982 - €132,635) per QALY gained with RotaTeq® (health care payer perspective).
- Multivariate sensitivity analysis showed the cost-effectiveness of a universal vaccination program versus no vaccination to depend mainly on the uncertainty of the estimates for waning of efficacy and number of RV related deaths.
- At an average of €80,709 per QALY gained, the current situation (private rotavirus vaccination with Rotarix® or Rotateq™ at intermediate levels of uptake, partially reimbursed by the National Health Insurance (RIZIV/INAMI)) is less cost-effective than fully funded universal vaccination. This is a very robust result given that per vaccinated child, the effects are equal (at best) and vaccination costs are higher for private versus universal vaccination (with universal vaccination a reduction can be obtained on the purchase price).
- Considering all the currently available information for both vaccines, fully funded universal vaccination is more cost-effective with Rotarix® than with RotaTeq®. The same probably applies for private vaccination.

Societal Perspective

- On average, fully funded universal rotavirus vaccination is more cost-effective for society than for the health care payer, but the impact of parameter uncertainty on the results is also greater for society than for the health care payer. Fully funded universal rotavirus vaccination would be slightly cost-saving with Rotarix® (95% range: cost-saving to €128,662), and would cost €29,618 (95% range: cost-saving to €183,164) per QALY gained with RotaTeq®.
- Multivariate sensitivity analysis showed the cost-effectiveness of a universal vaccination program versus no vaccination to depend mainly on the uncertainty around the number of days away from work in order to care for a child with clinical symptoms of rotavirus infection.
- In line with the health care payer perspective, fully funded universal vaccination is more cost-effective with Rotarix® than with RotaTeq®, and universal vaccination is more cost-effective than private vaccination.

We discuss these results for both perspectives in more detail below.

DISCUSSION

Health Care Payer Perspective

Within the health care payer perspective, the results are substantially influenced by the analytical choice of whether or not to consider the HRQOL impact of rotavirus illness on one or more caregivers in addition to the child's HRQOL itself (Table I). Currently there exists no consensus on how this choice should be made. The cost-effectiveness analysis for Australia included loss in quality of life for one caregiver (baseline), whereas the England&Wales study included QALY losses for two caregivers. As rotavirus disease in a child is likely to impact on the parents, but is not likely to impact to the same extent on both parents (and as not all families are two-parent families), we chose to consider only one affected caregiver per child in our model. Note that in health economic evaluation in general, the HRQOL impact on other people than the patient is usually ignored.

Not so much an analytical choice, but a problem of missing information, the cost and QALY burden for rotavirus infected children, experiencing clinical disease, but for whom no medical care is sought, has often been ignored in cost-effectiveness analyses. Indeed, the Australian and England&Wales cost-utility studies do not include this group of children in their model, whereas the US and UK cost-effectiveness analyses do. Although estimation of this burden requires some assumptions to be made, it seems realistic to assume this burden to be non-negligible. Therefore we chose to consider in our model to some extent the burden (consisting of a small impact on HRQOL and a small personal direct cost per episode for many children) associated with children experiencing rotavirus clinical disease but for whom no medical care is sought. Moreover, the estimation of the loss in quality-of-life in children and their caregivers when children are sick, but no medical care is sought, is difficult. In our analysis, we varied the latter QALY loss between zero (no QALY loss) and the 'full' QALY loss for cases for whom medical care is sought (based on a study that was set up especially for this purpose), hence taking into account the uncertainty of this estimate.

Note that even in an optimistic scenario (i.e. including burden for sick children for whom no medical care is sought, and the QALY loss for two caregivers of the child), the willingness to pay for a QALY gained needs to be €55,700 and €75,800 for Rotarix® and RotaTeq®, respectively in order to take the right decision with at least 90% certainty by fully funding these vaccination programs.

Table I. Proportion of acceptable incremental cost-effectiveness simulations, at a willingness to pay of €50,000 for an additional Quality Adjusted Life-Year gained (based on 1,000 simulations), for Rotarix® and RotaTeq® vaccination (health care payer's perspective). Scenarios considering no, one or two caregivers per child, with and without including plausible estimates of the burden of children (and their caregivers) for whom no medical care is sought.

	ROTARIX®		ROTATEQ®	
	'no medical care' not considered	'no medical care' considered	'no medical care' not considered	'no medical care' considered
no caregiver	2%	8%	1%	2%
1 caregiver	6%	46%	1%	13%
2 caregivers	26%	81%	6%	46%

On average, based on the most plausible input parameter distributions, fully funded universal rotavirus vaccination with Rotarix® would cost €50,024 per QALY gained, and with RotaTeq®, €68,321 per QALY gained (health care payer perspective). For Rotarix®, it would cost €166 to prevent a case, €2084 to prevent a hospitalization, €371,298 to gain a life-year and €16,980,510 to avert a death. For RotaTeq® these costs are €231, €2516, €471,673 and €21,576,809, respectively.

These results lie in between the results obtained for universal rotavirus vaccination in other countries (Table II). For Australia, Newall et al. (*forthcoming*) considered both vaccines to be possibly cost-effective, depending largely on the application of QOL utilities and the perspective used (health care provider or society). Although this study did not consider burden for children for whom no medical care is sought, costs for RVGE-related hospitalizations are higher than in Belgium, and a substantial part of the children went to an emergency department for their rotavirus infection. Moreover, no waning was assumed in their analysis. In France and England&Wales universal rotavirus vaccination was considered to be cost-**in**effective. Details on the French study are not yet available, but in England&Wales universal vaccination is less cost-effective than in Belgium and Australia, mainly because (1) the incidence rate of RVGE-related hospitalizations is estimated much lower; (2) only illness in children for whom medical care was sought, was considered preventable; (3) Rotarix® efficacy estimates were based on the Latin American, and not the European study (which showed higher efficacy estimates).

Table II. Cost per QALY gained for universal vaccination with Rotarix® or RotaTeq™ versus no vaccination in different Western countries.

		HEALTH CARE PAYER	SOCIETY
Belgium (current study)	Rotarix®	€ 50,024	cost-saving
	RotaTeq®	€ 68,321	€ 29,618
Australia (Newall et al, *forthcoming*)	Rotarix®	€ 30,051	cost-saving
	RotaTeq®	€ 46,699	cost-saving
France (Institut de Veille Sanitaire, 2006)		€ 138,000	
England&Wales* (Jit & Edmunds, 2007)	Rotarix®	€ 89,251	€ 79,741
	RotaTeq®	€ 116,904	€ 108,272

*An additional study set in the UK (Lorgelly et al, 2007), did not use QALYs as an outcome measure and hence cannot be compared here.

In the current analysis for Belgium, depending on the analytical choices made, cost-effectiveness ratios (cost/QALY) vary between €4979 and €201,945 (minimum and maximum Rotarix®) and between €13,508 and €250,823 (minimum and maximum

RotaTeq®). Multivariate sensitivity analysis showed that the higher cost/QALY estimates are mainly due to high values for waning (of efficacy against outpatient, GP and pediatrician visits, and RV episodes left without medical care) and low values for number of RV related deaths. As for many vaccines at the time of introduction, there are no data on the long-term effects of these new rotavirus vaccines. In the analyses for Australia and England&Wales, no waning of efficacy was assumed. However, for both vaccines estimates are available on efficacy for the first and the 2nd season for some endpoints, and this information is used to estimate waning from one season to the next in our model. In the England&Wales study, cost-effectiveness was particularly sensitive to the number of deaths attributable to rotavirus. In our analysis too, the number of deaths has a large impact on the QALY loss, and the uncertainty around this parameter is large, because we were unable to obtain Belgian death certificates for the purpose of our study.

The current situation in Belgium whereby parents and their insurers pay private market prices for the 2-dose Rotarix® vaccine is less cost-effective than fully funded universal vaccination (with Rotarix® as well as RotaTeq®). Private vaccination is more expensive (as the cost per dose is higher), less effective (as uptake is lower) and less equitable (as still a substantial amount is copaid) than fully funded universal vaccination. Indeed at a coverage of the current program of 60% to 80% (based on personal communications from Kind & Gezin and GSK) the costs of the program can be estimated at €11,694,633 to €15,592,844 per vaccinated cohort (implying these are annual costs). For universal vaccination, the costs of the program (based on the uptake of other vaccines at the same ages and ex-factory prices reduced by 10%), would be €14,052,390 (Rotarix®) to €14,604,690 (RotaTeq®) per year. As shown in the analyses the negociated price of the vaccine impacts the cost-effectiveness ratio to a large extent.

Fully funded universal vaccination is more cost-effective with Rotarix® than with RotaTeq® mainly due to the higher efficacy against rotavirus of any severity of Rotarix® compared to RotaTeq®. Similar results were found in other countries (Table II).

Although higher efficacy against rotavirus of any severity is the main reason why vaccination with Rotarix® is more attractive, the following considerations can be made regarding the advantages and disadvantages of the two vaccines. One could think optimistically that RotaTeq® is effective against a broader range of rotavirus serotypes than Rotarix®, because it contains 5 different reassortant rotavirus strains (whereas Rotarix® contains only one). However, at present there is no empirical evidence to support this. Another consideration can be made in relation to vaccine shedding: after Rotarix® vaccination, a substantial shedding of the vaccine is observed whereas almost no vaccine shedding is observed after RotaTeq® vaccination. Vaccine shedding could give rise to herd immunity, which for this vaccine would be a positive effect. However, vaccine shedding can also lead to gene reassortments of vaccine strain with wild strains, and hence to changes in rotavirus genotypic distribution. Therefore the genotypic distribution should be followed up after widespread use of rotavirus vaccines. Additional elements that may plead for the use of the 2-dose schedule of Rotarix® (compared to the 3-dose schedule of RotaTeq®) are related to overcrowding of the schedule, and the knowledge that more new vaccines are expected to become available for introduction soon.

Societal Perspective

For the societal perspective, fully funded universal rotavirus vaccination would be cost-saving with Rotarix® (95% range: cost-saving to €128,662), and €29,618 (95% range: cost-saving to €183,164) per QALY gained with RotaTeq®. Hence, on average fully funded universal rotavirus vaccination is more cost-effective for society, than for the health care payer, but uncertainty is larger than for the health care payer perspective. This uncertainty is mainly due to the wide range for the number of days parents are away from work to care for their sick child. Some parents will not miss work, whereas other parents stay home from work for up to 7 days to care for their child. This heavy impact of work loss on the cost-effectiveness of vaccination also explains the large

difference in cost-effectiveness between Rotarix® and RotaTeq® vaccination. Because it offers greater efficacy against rotavirus of any severity, Rotarix® vaccination would prevent more mild RVGE episodes than RotaTeq®, and consequently would reduce the work loss due to RVGE infections more. This results in substantially lower (i.e. better) cost-effectiveness ratios of Rotarix® versus RotaTeq®, making the difference between the two vaccines more pronounced under a societal perspective.

CONCLUSIONS

- In Belgium rotavirus vaccination would reap by far most of its benefits from preventing short lived mild disease in virtually all young children (expressed mainly through QALY losses and indirect costs). The effectiveness and cost-effectiveness of rotavirus vaccination is considerably determined by the value a policy maker wishes to give to the prevention of mild disease, and his/her willingness to pay for a QALY.
- When the burden of illness is taken into account for all children (including those not seeking health care) and two of their caregivers in a best case scenario, the willingness to pay for a QALY gained needs to be €55,700 and €75,800 for Rotarix® and RotaTeq®, respectively, in order to take the right decision with at least 90% certainty by fully funding a universal rotavirus vaccination program instead of having no rotavirus vaccination at all.
- The current situation in Belgium whereby parents and their insurers pay private market prices for the 2-dose Rotarix® vaccine (and recently also the 3-dose Rotateq vaccine) is clearly less preferable than fully funded universal vaccination, because it is more expensive and –at best- equally efficacious per vaccinated person, less effective (as uptake is lower) and less equitable (as still a substantial amount is copaid by the parents). The program of universal vaccination (at >97% uptake) is estimated to cost €14.0 million (Rotarix®) to €14.6 million (RotaTeq®) per vaccinated cohort, whereas private vaccination at 60% to 80% uptake is currently estimated to cost €11.7 to €15.6 million (Rotarix®).
- On average, based on the most justified analytical choices and the most plausible input parameter distributions, fully funded universal rotavirus vaccination would cost €50,024 (95% range: €25,374 - €99,730) per QALY gained with RotaRIX®, and €68,321 (95% range: €35,982 - €132,635) per QALY gained with RotaTeq® (health care payer perspective). In Belgium there is currently no publicly available value for the societal willingness to pay for a gain of one QALY.

Research Agenda

- Sub-analyses of data from recent clinical trials indicated that the instantaneous efficacy of a reduced schedule (i.e. one dose of Rotarix® or two doses of RotaTeq®) would be very high. Unfortunately none of these trials were designed to study the longer term efficacy of using fewer doses than currently recommended for either vaccine nor the immediate comparison with the currently recommended schedules, and therefore do not offer a sufficient basis to make a model-based analysis of reduced schedule options. It is in the best interest of developed and developing countries around the world that clinical efficacy trials be set up urgently to specifically compare the current schedules of rotavirus vaccines with reduced ones.

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1 BACKGROUND AND LITERATURE REVIEW

1.1 GENERAL BACKGROUND

Rotavirus (RV) is the leading cause of acute gastroenteritis (AGE) worldwide. [2] It affects nearly all children, even in developed countries, by the age of five years. Mortality resulting from RV infection is low in developed countries but AGE due to RV (RVGE) has a great impact on the health of infants, and it is the main cause of hospitalization for AGE in children. Hospitalization for RVGE and the large number of AGE cases treated in ambulatory settings have a significant economic impact due to both direct medical costs involved (e.g. hospital costs, practitioners' fees, and medication) and also substantial indirect costs as parents are often required missing work to take care of their sick children.

The substantial disease burden and the availability of rotavirus vaccines (oral vaccines Rotarix® and RotaTeq® (hereafter denoted as RotaRIX respectively RotaTEQ, detailed information on both vaccines can be found in Appendix G) give the potential introduction of a universal childhood rotavirus vaccination program a prominent place on the health agenda in many countries. Rotavirus vaccination is currently recommended and free in the US, Austria and Luxembourg; in Belgium rotavirus vaccination (both with RotaRIX and RotaTEQ) is recommended and partially reimbursed. Given the investment costs associated with this program, countries considering its implementation would prefer to do so on the basis of sound assessments of its population effectiveness, budget-impact and cost-effectiveness. Given the country-specific nature of the prevalence of circulating rotavirus serotypes, and the costs of treatment for associated clinical disease, such assessments are likely to differ from one country to the next. Furthermore, value judgements on the willingness to pay to avoid morbidity and mortality are also typically somewhat different between different societies.

1.2 LITERATURE REVIEW METHODS

A literature search was done through PubMed (includes the Cochrane library), EconLit (the world's economic literature), NHS EED (quality assessed economic evaluations), and Current Contents. The first search was done on 18th December 2006, the second search on 10th April 2007. The search was focused on publication dates starting from the year 2000, because only then the first relevant publications appeared on rotavirus vaccines other than Rotashield. The search term 'rotavirus' AND 'vaccin*' NOT 'review' was used. The first PubMed search resulted in 518 hits. After removing 52 duplicates, a total of 466 references remained. The second search resulted in another 95 references. The Current Contents search resulted in 155 extra references; the EconLit and NHS EED searches in another two references.

The 718 studies were categorised based on abstracts (and full content if needed) in the following categories:

Experimental clinical research

Nine randomized, double-blinded, placebo controlled clinical trials for the safety, efficacy and immunogenicity of RV vaccines are published (6 for RotaRIX and 3 for RotaTEQ). For RotaTEQ, only clinical studies evaluating the pentavalent vaccine were included (i.e. clinical studies on quadrivalent versions were excluded). These studies are summarized in the next paragraph (1.3) and described in detail in Appendix A.

Model- and economic studies in developed countries

Up until April 10, 2007, three cost-effectiveness studies for plausible RV vaccine candidates in developed countries were published. Two for the UK[3, 4] and another for the US[5]. We know of one other (yet unpublished) cost-utility analysis (i.e. accounts also for the effect on quality of life of preventing episodes of RVGE) in a developed country, i.e. a

study performed in Australia (Newall et al, forthcoming). These studies are summarized in paragraph 1.4 and described in detail in Appendix B.

Other

Five cost-effectiveness studies in developing countries (and countries in transition) were found (Chile, Nigeria,Vietnam, Asia and Uzbekistan). Furthermore, 22 studies concerned Rotashield, a vaccine that was withdrawn from the US market in October 1999 due to its association with intussusceptions. A total of 190 studies described the epidemiology of rotavirus infections and the associated disease burden. Another 168 references were reviews, short reports and opinions, and the remaining 321 articles included biochemical, plant and animal trials, studies on intussusceptions, and others.

1.3 EFFICACY, SAFETY AND IMMUNOGENICITY OF ROTAVIRUS VACCINES

A detailed overview of the efficacy, safety and immunogenicity of the RV vaccines RotaRIX and RotaTEQ can be found in the Appendix A.

This overview can be summarized very shortly as follows:

SUMMARY EFFICACY

The efficacy of RotaRIX and RotaTEQ vaccines in reducing rotavirus-related health outcomes depends on country, severity of AGE, and vaccine formulation. The estimates of most importance for the cost-effectiveness study in Belgium are the ones resulting from the large trials in developed countries (RotaRIX: Europe (n=3994), RotaTEQ: Finland and USA (n=5673)):

Efficacy against RVGE of any severity

RotaRIX: 87%

RotaTEQ: 72.7%

Efficacy against severe RVGE

RotaRIX: 95.8%

RotaTEQ: 98.0%

Efficacy against hospitalizations

RotaRIX: 100%

RotaTEQ: 95.8%

Efficacy against different serotypes: RVGE cases in the trials were predominantly G1, so efficacy estimates against other serotypes are based on a small number of observations. Serotype-specific efficacy estimates are therefore used in univariate sensitivity analysis.

Efficacy after 2nd and 3rd epidemic season is lower than after 1st epidemic season

SUMMARY SAFETY

Intussusception and serious adverse events: no increased risk in vaccine compared to placebo group;

Deaths: for both vaccines, a larger number of deaths was reported in the vaccine compared to the placebo group; however, this difference was not statistically significant.

Adverse effects (vomiting, diarrhoea, fever, irritability):

RotaRIX: no difference between vaccine and placebo group

RotaTEQ: largest study showed no difference, but combined with 2 other studies: higher risk of vomiting and diarrhoea in vaccine group compared to placebo group;

Faecal shedding: RotaRIX vaccination results in substantial shedding of vaccine strain, whereas no such shedding is expected or observed with RotaTEQ.

Post-marketing in the US: The number of intussusception cases reported to date after RotaTEQ administration does not exceed the number expected based on background rates of 18-43 per 100,000 per year for an unvaccinated population of children ages 6 to 35 weeks [1].

SUMMARY IMMUNOGENICITY

Immunogenicity of the RotaRIX and RotaTEQ is not directly taken into account in our cost-effectiveness analysis, because:

No clear relationship between immunogenicity and efficacy of the vaccines is shown.

Comparison between induced immunity by RotaRIX and RotaTEQ is difficult, because seroconversion rates were defined differently and were measured at different time points.

Immonogenicity was assessed as seroconversion of antirotavirus antibody IgA and serospecific neutralizing antibodies.

1.4 ECONOMIC EVALUATIONS OF ROTAVIRUS VACCINATION PROGRAM OPTIONS

At the time of writing, we are aware of three cost-effectiveness analyses in developed countries [3-5]. We know of one other (yet unpublished) cost-utility analysis in a developed country, i.e. a study performed in Australia (Newall et al, *forthcoming*). A detailed overview of these economic evaluations of rotavirus vaccination program options can be found in the Appendix B.

2 DATA AND METHODS

2.1 METHODS

2.1.1 General

Data analyses and simulations were performed using MS Excel XP, @Risk 4.5, SAS 9.1 and R 2.4.1.

The baseline costing perspective is that of the Belgian health care payer, which includes collective payments by the Belgian health care system, as well as co-payments for health care by patients. All cost data are expressed in Euro 2006. Our primary measure of relative efficiency is direct medical costs per Quality-Adjusted Life-Year (QALY), though a wider range of health outcomes is presented in incremental cost-effectiveness analyses. Time preference is accounted for by discounting costs at an annual constant rate of 3%, and effects at 1.5%. These analytical choices are in line with Belgian guidelines for economic evaluation in health care. More detailed discussion of each of the parameter estimates, and the theoretical foundation for these, given an analytical option to choose, is given in further subsections below. More basic discussions on methodological issues for the economic evaluation of vaccination programs were described previously.[6-9].

We consider the following options in our analysis:

Option 1: no vaccination.

Option 2: private vaccination (current situation with partial reimbursement), i.e. RotaRIX vaccination using a 2-dose schedule with vaccine administration at 2 and 3 months of age. (On 31 May 2007, at the moment of finishing this report, RotaTEQ came on the market in Belgium.)

Option 3: fully funded universal vaccination

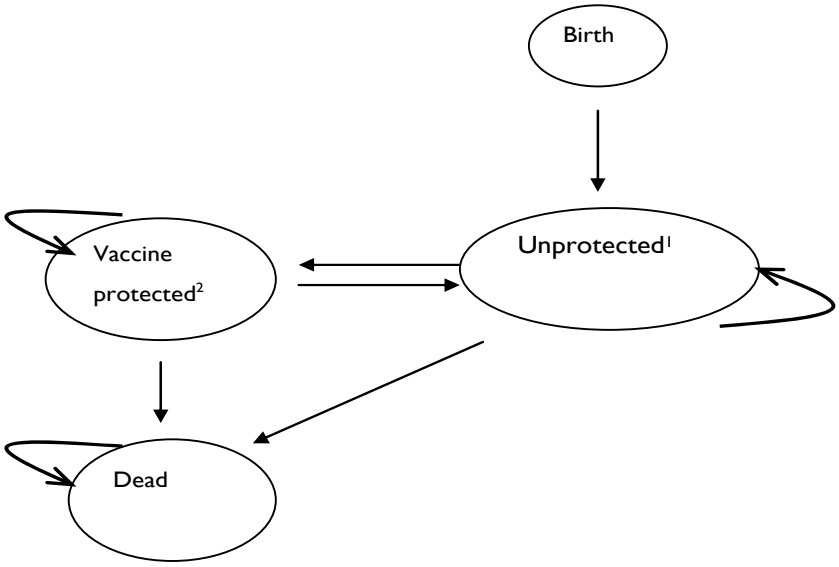
RotaRIX vaccination using a 2-dose schedule with vaccine administration at 2 and 3 months of age.

RotaTEQ vaccination using a 3-dose schedule with vaccine administration at 2, 3 and 4 months of age.

2.1.2 Mathematical model structure

The simulation model is a deterministic compartmental static model. Individuals are modelled to seek health care (GP and pediatrician (Ped) consultations and hospitalizations) according to their age in months over a seven year period. A seven year period is used, because incidence data on rotavirus infection are available for children between zero and 6 years of age. The vaccines are estimated to impact to varying degrees (see paragraph 1.3) on consultations, hospitalizations (both community and hospital-acquired) and deaths.

Figure 2.1: Basic structure of the static cohort model



1 not vaccinated, or vaccinated but not (or no longer) protected in varying degrees against consultations, hospitalizations and death

2 Vaccinated and still protected, despite waning against consultations, hospitalizations and death separately

Individuals are modelled to transition between the depicted states (Fig. 2.1) in monthly cycles.

Health care resource utilisation is estimated under the three options listed in the previous paragraph, based on pre-vaccination age-specific population rates of consultation, hospitalization and mortality. With the assumption of a static population, the annual number of any one outcome among all children <7 years of age equals the cumulative number of that outcome the birth cohort experiences from 0 to 83 months.

This choice of model and structure is justified by the properties of RV infection and disease, as well as the properties of current RV vaccines using the following argument: there is currently no convincing evidence that RV vaccines would induce herd immunity, particularly if vaccination coverage is immediately high (and faecal shedding of vaccine strains by vaccinated children is likely to only exceptionally indirectly immunise susceptible people in their physical vicinity (i.e. with a vaccination program, unvaccinated, and previously uninfected babies of similar age would be very rarely exposed)).

2.2 EPIDEMIOLOGY AND CLINICAL DATA

2.2.1 Databases used

Data were derived from a variety of existing databases in Belgium as well as from surveys, one of them set up specifically for the purpose of this analysis (CM survey).

2.2.1.1 MKG

The registration of MKG ('Minimale Klinische Gegevens/ Résumé Clinique Minimum', i.e. Minimal Clinical Data) is mandatory for every hospital in Belgium since 1991. This means that for each hospitalized patient, information such as birth date, address and sex, and other information such as length of stay (LOS) in the hospital, diagnosis, techniques used and treatments have to be recorded and sent to the FOD (Federal Government). Data are stripped from patient-identifying information. These data are coupled with the MFG ('Minimale Financiële Gegevens/ Résumé Financier Minimum', i.e. Minimal Financial Data), which records the costs of each hospital stay. This means that the relationship between treated pathology and the costs to the health care system can be studied. Data are obtained for years 2000-2005. More detailed information about which data were available can be found in Appendix C (Request of MKG-MFG data).

A separate MKG database contains records of outpatients (i.e. patients not staying overnight in the hospital).

The advantage of the coupled MKG-MFG data is that it is obligatory for all hospitals. However, one should keep in mind that we do not know how accurate each hospital reports the obligatory MKG data, nor how reliably the data are gathered. For instance in the delivered dataset for this analysis, an inconsistency was found, likely due to a problem in (re)coding data (see paragraph 2.2.2.1.1, also for how this problem was handled). Hence, interpretation of the data should be done with care.

Moreover, MKG database contains hospitalizations of children with RVGE as main and as secondary diagnosis, but it is not clear from the data if those infections are community- or hospital-acquired. This is further discussed below.

2.2.1.2 CARENET

The concept of Carenet is designed for the exchange of information about hospital admission, extension, end of hospitalisation and costs of hospitalisations between hospitals and health insurance companies through an electronic system (internet platform). All insurance companies participate in the project in a national intermutualistic context. (Information (names, location) of hospitals currently joined to Carenet is available: http://www.carenet.be/nl/, accessed 26/02/2007).

We obtained access to data on hospitalized patients who were CM (see further) members and were younger than 7 years (anonymous data, no identification possible). A search for the text string 'rota' was performed on all diagnostic descriptions. Next, only the patients for which 'rota' in the diagnosis referred to RVGE were manually selected.

Two datasets were thus compiled:

patients with RVGE as diagnosis for years 2004 and 2005

patients with RVGE as diagnosis for year 2006

Both datasets contain for each patient length of stay in the hospital, age, costs to the National Health System (NHS, i.e. direct health care costs for RIZIV/INAMI) and co-payments by patients and their private insurance (mainly "remgeld" and "supplementen"). If a patient died, the date of death was recorded. Moreover, based on the complete diagnosis description, a medical clinician was asked to categorise patients in RVGE main and secondary diagnosis.

The dataset of 2006 lacked hospitalizations from December (last date of leaving the hospital reported, was 25 November for RVGE as main diagnosis, and 28th November for RVGE as secondary diagnosis).

Note that, besides our dataset only including CM members, the representativeness of the data is very different over the different years. On January 1st 2004, data from only 15 hospitals (7% of all hospitals) were included in Carenet. One year later (January 1st 2005) 73 hospitals (34%) participated, and on January 1st 2006, this number had arisen to 133 (62%), and on January 1st 2007 the number was 180 (84%). In the analysis adjustments were made to accommodate this, and as input data for the simulation model, we concentrated on the most recent data from this database (see Methods).

2.2.1.3 WIV

The division Epidemiology of the WIV ('Wetenschappelijk Instituut Volksgezondheid/ Institut Scientifique de Santé Publique', i.e. Scientific Institute of Public Health) has a network of microbiology labs ("sentinel labs") for the surveillance of infectious diseases in Belgium. Each sentinel lab sends weekly reports to the WIV of the number of positive stool tests for a selection of germs. Participation of labs is voluntary. In 2001, 128 labs participated (representativeness of the data in 2001 are reported, because these data will be used in analysis (see below)). This is about half (54%) of all microbiology labs in Belgium at that time, and 1.5% of the Belgian population covered. In 2001, 70% of the sentinel labs were linked to a hospital, whereas from all microbiology labs in Belgium at that time, 54% were linked to a hospital and 46% were private.[10] Hence, WIV data contain positive lab tests of hospitalized as well as non-hospitalized patients.

Individual data of positive lab tests were asked for the years 1999-2005, for a range of germs which are possible causes for acute gastro enteritis (AGE), i.e. Rotavirus, Adenovirus, Campylobacter, Cryptosporidium, E. coli, Y. enterolitica, Giardia, Listeria, Shigella and E. histolytica. Positive rotavirus tests were only reported in 2000, 2001 and 2005. However, from October 2005, no data were received from CHU St Pierre due to technical reasons. This lab represented in 2000 and 2001 6.7% of reported rotavirus in the network. Positive E.coli tests were reported in 1999-2002 and 2004-2005. Data on Salmonella for years 2000-2006 were obtained from the National Reference Centre for Salmonella and Shigella, Scientific Institute of Public Health. Other germs that cause AGE, but for which no data on lab tests were available are Astrovirus, Brucella, Vibrio cholerae, Enterovirus, Enterococcus and Norovirus. For each patient with a positive test, the identified germs, week of the tests and birth date of patient are available. Additionally, postcode + region (Flanders, Brussels or Wallonia), technique (culture, serology, microscopy, molecular) and information on sample (blood, CSF or stools) are usually available.

A consideration to be made for this dataset is a possible overestimation of severe RVGE cases and young cases, because 1) RV tests are not systematically prescribed and performed, 2) there is only re-imbursement for children under 2 years of age.

2.2.1.4 REVEAL

The REVEAL study[11-14] was set up to estimate the burden of gastroenteritis due to rotavirus and related health care costs in children less than 5 years of age in specific catchment areas of 7 European countries between 1st October 2004 and 30 September 2005. Thus, the burden of RVGE in three different health care settings was assessed: hospitals, emergency rooms and primary care health units. For Belgium, the catchment area was defined in the city of Antwerp. This catchment area included 2 hospitals, 2 emergency departments and 22 primary care practices. Children were screened for eligibility (i.e. <5 years, living in the defined study area during the study period, seeking medical intervention, with symptoms corresponding to the clinical case definition of AGE, and with signed parental consent form). Children included in the study were followed-up by means of questionnaires: (1) a baseline questionnaire completed by the investigator, (2) a baseline questionnaire completed by the parents and (3) a follow-up questionnaire completed by the parents. Additionally, for those children who were admitted to hospital, a follow-up questionnaire was completed by the treating nurse (or by the parents with

assistance from the treating nurse if required). Moreover, from each child included in the study, a sample was obtained for rotavirus testing. The results described estimated incidence rates of AGE and RVGE by setting (hospital, emergency room, primary care participant), age and season; proportion of RVGE among AGE, duration of hospitalization, distribution of RVGE types, comparison of clinical characteristics and hospitalization rates among RV+ and RV- cases and working days lost. Additionally, cost data were obtained.

However, some considerations on representativeness of these data should be made. It is likely that not all children in the catchment area went to one of the 2 hospitals included in the study, which could result in an underestimation of the AGE burden. Moreover, only 127 of the 1007 eligible children were included in the study (i.e. participation rate of hospitalized children: 32.78%, emergency room: 1.78% and primary-care: 20.67%). 695 children were not included because no written consent was obtained, 184 children were not included because they were not native Dutch speakers, and another child was not included because there was no phone access. This leads to the following selection and information biases (which were also mentioned as such in the REVEAL report):

Selection biases:

- It cannot be excluded that in case of severe AGE parents might be reluctant to participate in an epidemiological study, and this may have led to an underestimation of the incidence of children with severe AGE
- The activity and work (over)load in the various settings, the time of the day when inclusions occurred, may also have played a role in the inclusion of children.
- GPs were not randomly selected, but included based on a convenience sample.
- Some characteristics of the respondents may differ from the study population.
- Participation rates could have been affected by the fact that consent was required from both parents. It might be exceptional that both parents take their child to the GPs office or to the emergency service, whereas they could be more likely to be both present if the child required hospitalization.

Information biases:

- Parents may have been likely to overestimate severity of signs and symptoms.
- In a primary care setting, denominators were calculated using the list of patients routinely attending the participating GP in his catchment area. This denominator may however not include all children less than 5 years of age in the catchment area.

The results of this study are used as an additional source of information for comparison with other datasets (e.g. MKG dataset).

2.2.1.5 CM survey

The database from the National Christian Sickness Fund ('Christelijke Mutualiteiten/ Mutualité Chrétienne', CM hereafter) contains all resource use information of members of the largest sickness fund in Belgium. The membership population of CM corresponds to 43.7% of the total Belgian population. There is a slight bias in favour of the older age groups, but this should not grossly distort the estimates based on this sickness funds. In terms of socio-economic characteristics, the unemployed are slightly underrepresented (40.6% of the unemployed are members), but, again, the overall difference is relatively limited (i.e. 43.7% versus 40.6%) [15].

A survey was set up to obtain detailed information on the following aspects of RV positive tested patients and his/her caregiver(s): medical costs and non-medical or personal costs, social background and LOS in hospital for hospitalized children. The goal is to obtain data related to RVGE patients who were recently admitted to a hospital and data related to RVGE patients treated on an outpatient basis. Very few records related to RVGE patients

for whom an ambulatory RV test was requested and treated the same day in an emergency care unit were found (109 members, i.e. 0.3% of all members for whom an ambulatory test was requested), and therefore such patients were not specifically surveyed.

Data related to hospitalizations due to rotavirus infection

In addition to data from the FOD (MKG/MFG), we use data that are available through the Carenet system to estimate the health care costs of RV hospitalizations (described above). Moreover, in order to estimate ambulatory health care costs and non-health care costs (e.g., transportation, absenteeism from work, diapers,…), a survey was conducted (through the postal services combined with a personal telephone interview) using the most recent cases with RVGE as main diagnosis selected in Carenet. A letter was sent to 578 children, and for 90 of them, a complete questionnaire was obtained.

Data related to children with rotavirus infection treated on an outpatient basis

The CM database containing all resource use information is used to identify members who received a test to detect faecal rotavirus since 01/01/2004 in an ambulatory setting (nomenclature: 552311 - only for children younger than 2 years) and who were not admitted to hospital on the same or next day. Next clinical labs were contacted by a medical adviser, and 7 labs (4 dutch/3 walloon, geographically well spread) agreed to indicate which tests were rotavirus positive. A total of 436 children were reported to be tested rotavirus positive in an ambulatory setting. Subsequently, a letter was sent to each of these cases. For 87 of the children a complete questionnaire was obtained (through the postal services combined with a personal telephone interview).

An example of the questionnaires can be found in Appendix D. It gives an overview of all cost items that make up the total health care payer's cost (remgeld+supplements+NHS), as well as co-payment of the patient and his/her private insurance (mainly remgeld+supplements) for a rotavirus episode (ambulatory and hospitalized). Transportation costs were not included in the analysis because it was not possible to estimate these costs reliably.

Most respondents (83.5%) were mothers, 14% were fathers, and the remaining 2.5% had another relationship with the child. Parents of the children in the study were quite well educated (82% of the mothers and 72% of the fathers obtained a degree in higher secondary education; with 66% and 57%, respectively, achieving higher education).

2.2.1.6 KU LEUVEN

Rotavirus samples from gastroenteritis patients admitted to the Gasthuisberg University Hospital (Leuven) are G-typed using molecular methods. Information is provided by Rahman et al.[16], Van Ranst, M. and Matthijnssens, J., personal communication, March 2007).

2.2.1.7 SENTINEL GENERAL PRACTITIONERS

This dataset shows the number of AGE cases per week that visited one of the members of the sentinel general practitioners (GPs) ('peilartsen/médecins vigies') in 2002. For each patient, the year of birth was available, so that age in years could be calculated. Also region (Flanders, Brussels or Wallonia) of the general practitioner was available. For the same year, from 1st January until (included) 30th July, the number of positive RV tests from patients of these sentinel GPs was available.

The sentinel general practitioners are a selection of 150 medical practitioners and reach about 1.5% of the Belgian population (1.6% of the Flemish and Walloon population, and 0.9% of the population in Brussels). The participating sentinel general practitioners are representative of the total group of Belgian GPs in terms of sex and age (with exception of an overrepresentation in the age group 40-49 years)[17]. No age for the patients with a RV positive test is available.

2.2.1.8 INTEGO

In 2004, 55 general practitioners (from 47 clinical offices) were member and their practice population represented 1.3% of the Flemish population. The members sent yearly reports to INTEGO on diagnoses and lab results. However, data is only available per ICPC2 code (D10: vomiting and D11: diarrhoea) and cannot give accurate information about incidences of RVGE. Therefore this database was not further considered (information obtained from http://www.intego.be/, accessed 23/02/2007).

2.2.2 Epidemiology and burden of RVGE in Belgium

Rotavirus is the most common cause of severe diarrhoea in children, and is estimated to lead to about 24 million visits to general practitioners and emergency departments, 2.4 million hospitalizations and 600,000 deaths each year in the world[18]. In this chapter, we attempt to estimate the number of clinical visits, hospitalizations (community-acquired and nosocomial) and deaths due to RVGE in Belgium. Also incidence of infected children who develop symptoms (e.g. vomiting and diarrhoea) but for whom no medical care is sought, is estimated, because it is likely that these children and parents experience RVGE related burden (in terms of extra costs for e.g. diapers, loss of quality of life and for the societal perspective, work loss to take care of their sick child). If we refer in the text to 'health (care outcomes)', we refer to clinical visits and hospitalizations as well as deaths and infected children for whom no medical care is sought.

Moreover, as RV infection in humans can be caused by different strains[18], information on the distribution of these different strains in Belgium is included.

Data are available and used for children under 7 years of age.

Each chapter starts with a box mentioning the parameter estimates that are used in base case analysis to estimate the cost-utility of vaccination. An overview of all these parameters (and their distributions) can be found in Appendix F.

2.2.2.1 Hospitalizations

In base case analysis, the annual number of **hospitalizations** is estimated to be 4648. Age-specific proportions are used. In sensitivity analysis, the annual number of hospitalizations is sampled from truncated normal distributions (lower limit zero, upper limit birth cohort). The age-specific proportions are sampled from beta distributions.

We can distinguish between community-acquired and nosocomial (i.e. hospital-acquired) RV infection (NRV). Rotavirus is believed to cause a large part of nosocomial infections, but estimation is difficult. In Belgium, there is no effective surveillance system for NRV. NRV infection usually becomes apparent between the 2nd and the 6th day of hospitalization [19]. However, in the datasets listed in section 2.2.1., date of RVGE acquisition was only reported in the CM questionnaire. For the MKG and Carenet datasets, we can not directly distinguish community-acquired from nosocomial RV infections, because we only have data about patients with RVGE as main and secondary diagnosis. It is likely that all hospitalized patients with RVGE as main diagnosis acquired RVGE before hospitalization (i.e. community-acquired). The group of patients with RVGE as secondary diagnosis is probably a mixture of community-acquired and nosocomial RVGE cases, because we do not know when patients with RVGE as secondary diagnosis acquired RVGE (i.e. before or during hospitalization). Hence, we cannot assume that patients with RVGE as secondary diagnosis represent only patients who acquired RVGE in the hospital.

Therefore, to estimate the number of hospitalizations due to community-acquired RVGE, we use the number of hospitalizations with RVGE as main diagnosis. To obtain the number of nosocomial RVGE infections, we use the data of the CM questionnaire together with published data for Belgium. Both are explained in detail hereafter.

Community-acquired RVGE hospitalizations

We assume that all patients with RVGE as main diagnosis acquired RVGE before hospitalization (i.e. community-acquired). We also report on patients with RVGE as any

diagnosis (i.e. patients with RVGE as main or secondary diagnosis), because these data are used to estimate the number of nosocomial RVGE hospitalizations (see further).

First monthly incidence of RVGE hospitalizations in Belgium is assessed. These data are used in our cost-utility analysis. Furthermore, the weekly incidence of RVGE hospitalizations is determined, as well as the mean duration of stay in hospital for patients with RVGE diagnosis.

MONTHLY INCIDENCE OF RVGE HOSPITALIZATIONS

Data on hospitalizations with RVGE as main/any diagnosis, for children under 7, are obtained from two different data sources: MKG and Carenet. MKG and Carenet data are compared for the year 2004 and on a monthly basis. 2004 is the only year for which data are available from both the Carenet and MKG dataset, and for MKG only monthly data are available.

The MKG data provide numbers of RVGE hospitalizations for all Belgian people. The Carenet database gives us the number of hospitalizations of only the CM members for a subset of Belgian hospitals (hence only information on a subset of beds is available). Therefore Carenet data are extrapolated to all patients and over all available beds in Belgian hospitals as follows:

Extrapolation to all patients (not only CM members)

The membership population of CM corresponds to 43.7% of the total Belgian population. The number of hospitalizations reported by Carenet is divided by 0.437 to obtain the number of hospitalizations for all people (not only CM members).

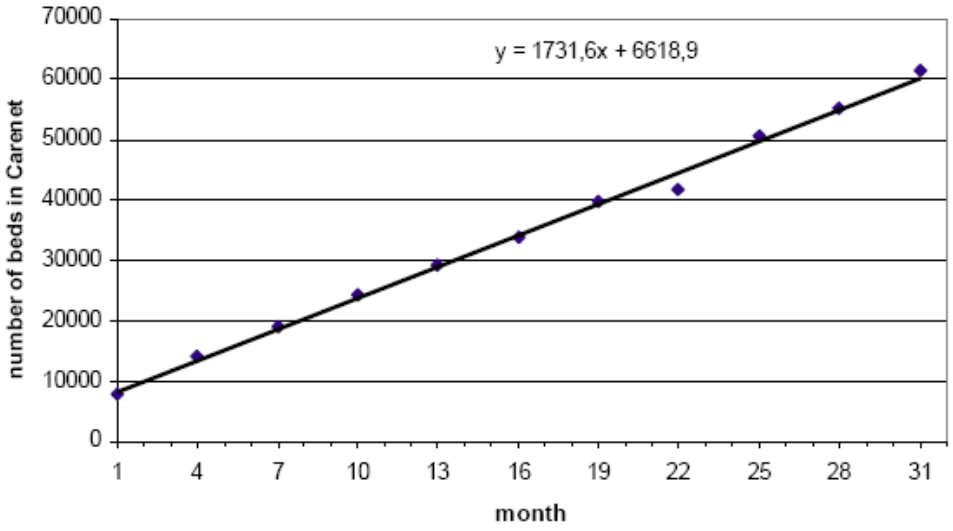
Extrapolation to all available beds in Belgian hospitals

Next, the monthly number of hospitalizations is adjusted according to the number of beds covered in the dataset.

We know the total number of hospitals and beds covered by the Carenet database at discrete time points (i.e. at the first of January, April, July and October, for years 2004 – 2006), and that hospitals can join Carenet at any time (i.e. there are no known discrete jumps in participating numbers of hospitals). The number of hospitals/beds that included in the database increases fast from 1 January 2004 to 1 January 2007 (from 15 to 180 hospitals, and from 7989 to 29239 beds) (see Fig. 2.2 below). We assumed this increase to be linear over time until 1 July 2006. From 1 July 2006 the increase tends to zero, because the proportion of Belgian hospitals/beds included in Carenet tends to 100%. Hospitalizations reported for the period after July 2006 are not considered, because complete data are not available. We estimate the total number of beds for each month based on the regression line through the known points (see Fig. 2.2 below). By dividing the number of hospitalizations for each month by the number of beds covered by Carenet for that month, we obtain the monthly number of hospitalizations per bed. Then this number is multiplied by the total number of beds of all Belgian hospitals to calculate the number of hospitalizations with RVGE as main diagnosis in 2004 for the Belgian population.

The total number of beds of all Belgian hospitals in 2004 (n=69,966) is obtained indirectly: we know that at 1st January 2005, 29,239 beds are included in the Carenet database, and that this represents 41.79% of all beds from both psychiatric and general hospitals. This number seems quite reasonable, because from another source (MKG), a similar value is obtained. From MKG we know that at 12 March 2004, there are 70,970 hospital beds in Belgium (from general, specialised, psychiatric and geriatric hospitals); and 69,743 beds when excluding the geriatric hospital beds.

Figure 2.2: Number of beds included in the Carenet data at different time points (every three months); month 1 represents 1st January 2004).



The resulting monthly number of hospitalizations in Belgium with RVGE as main diagnosis is shown for both MKG and Carenet in Figs. 2.3 and 2.4, by age, for year 2004.

Figure 2.3: MKG data: number of hospitalizations in Belgium in 2004 with RVGE (ICD9 008.61) as main diagnosis, by age (in years).

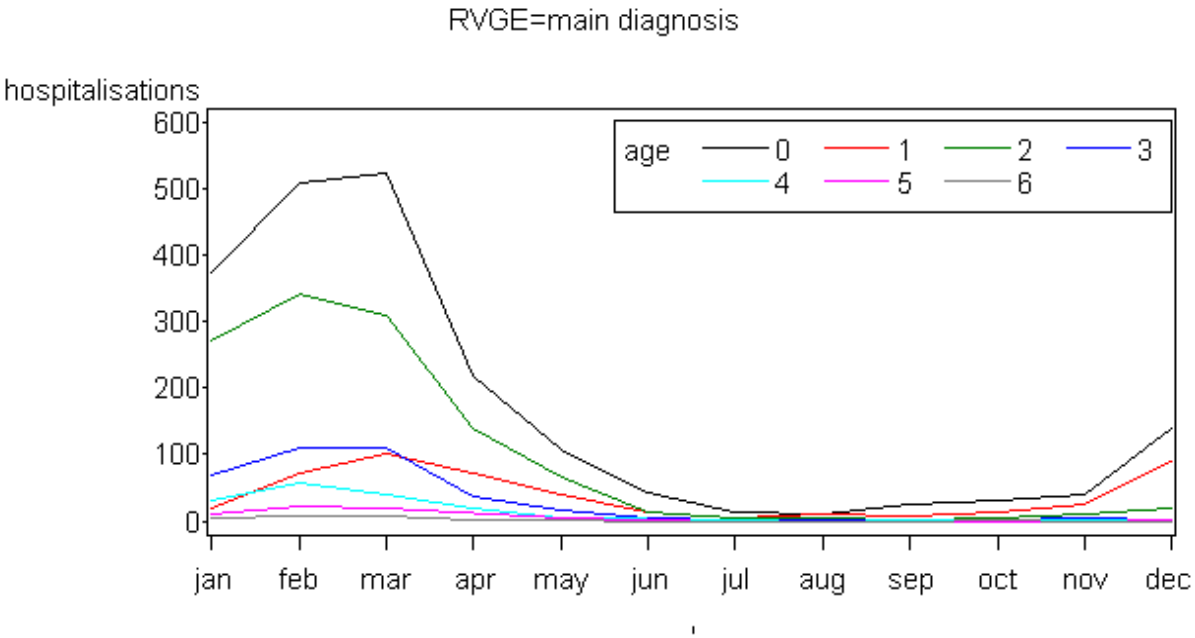
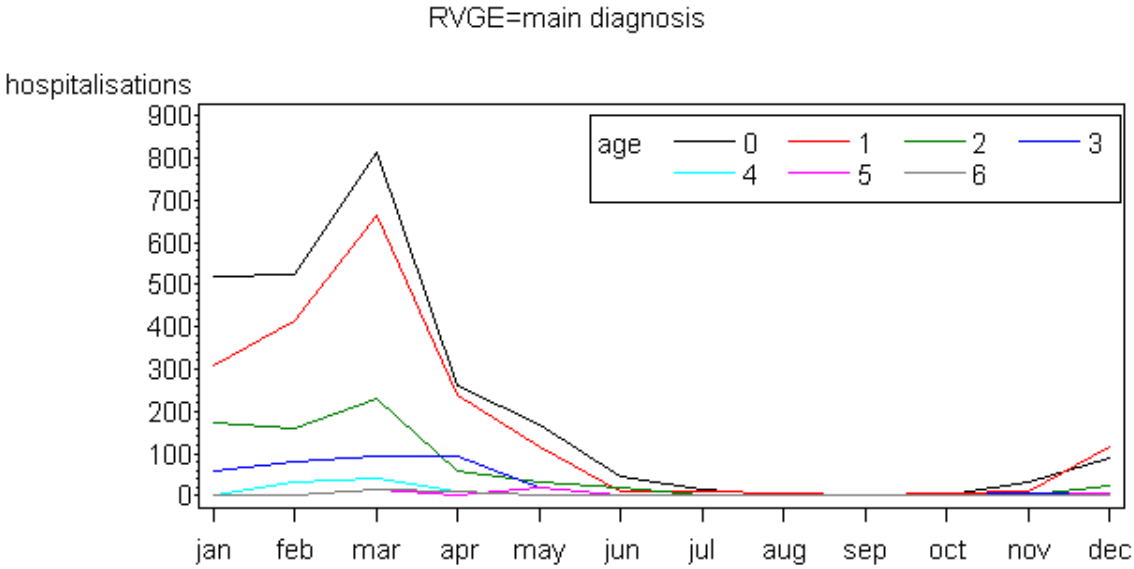


Figure 2.4: Carenet data: number of hospitalizations in Belgium in 2004 with RVGE as main diagnosis, by age (in years). Classification in main and secondary diagnosis is done by a physician, based on the diagnosis description. The original Carenet data (including only CM members) are extrapolated to the total Belgian population, and adjusted for number of beds that are covered by the Carenet database at different time points.



We can see a large discrepancy exists between the two datasets (see also Table 2.1):

- the MKG data show for the **one-year olds 2 peaks** in number of RVGE hospitalizations (December and March), and a **lower number of hospitalizations** for the one-year olds compared to 0 and 2 years olds
- the Carenet data show for all age groups one peak (around March), and the highest number of hospitalizations for the 0 and 1 year olds.
- the **absolute number of hospitalizations** with RVGE as main and any diagnosis reported for 2004 (summed over all months) **is different for the Carenet and the MKG** data (see Table 2.1 and Figs. 2.3 and 2.4)

Table 2.1: Annual number of hospitalizations per age group and age-specific proportion of total number of hospitalizations for children under 7, with RVGE as main and any diagnosis, from the MKG and Carenet datasets.

	ANNUAL NUMBERS				PROPORTION			
	RVGE main diagnosis		RVGE any diagnosis		RVGE main diagnosis		RVGE any diagnosis	
age	Carenet	MKG	Carenet	MKG	Carenet	MKG	Carenet	MKG
0	2466	2037	2772	3560	0.444	0.473	0.466	0.501
1	**1897**	**464**	**1960**	**747**	**0.341**	**0.108**	**0.330**	**0.105**
2	**694**	**1186**	**706**	**1755**	**0.125**	**0.276**	**0.119**	**0.247**
3	354	360	359	619	0.064	0.084	0.060	0.087
4	84	159	84	264	0.015	0.037	0.014	0.037
5	40	70	40	106	0.007	0.016	0.007	0.015
6	25	27	25	53	0.004	0.006	0.004	0.007
ages 0-5	5560	4303	5947	7104				

There seems to be no plausible (clinical) explanation for the 'strange' behaviour of the number of hospitalizations for the 1 year olds in the MKG data. Possibly there is a problem in assigning age to each case in the MKG data (e.g. a problem of the code for calculating age from birth dates and date of admission to the hospital). After consultation with experts in both databases, we assume for the purpose of the current analysis, that the age distribution of the Carenet data is more reliable than the MKG data.

Furthermore, we assume the absolute number of RVGE-related hospitalizations of the MKG data is more reliable than the Carenet data, because they cover all hospitals in Belgium (registration is mandatory for all Belgian hospitals so no extrapolation is needed).

To obtain the most reliable estimate for the monthly number of RVGE related hospitalizations, we use the monthly total number of RVGE cases under age 7 years from the MKG dataset, and use the age-specific proportions of RVGE cases from the Carenet data to calculate the age-specific monthly number of RVGE cases:

MKG data: monthly number of hospitalizations averaged over different seasons

Data for children under 7 years with RVGE as diagnosis are available for seasons 2000-2001, 2001-2002, 2002-2003 and 2003-2004. For each month, the mean number of hospitalizations over the 4 seasons is obtained, both for RVGE as main and any diagnosis (Figs. 2.5 and 2.6).

Figure 2.5: MKG data: Monthly number of hospitalizations in Belgium for children under 7 years with RVGE (ICD9 008.61) as *main* diagnosis.

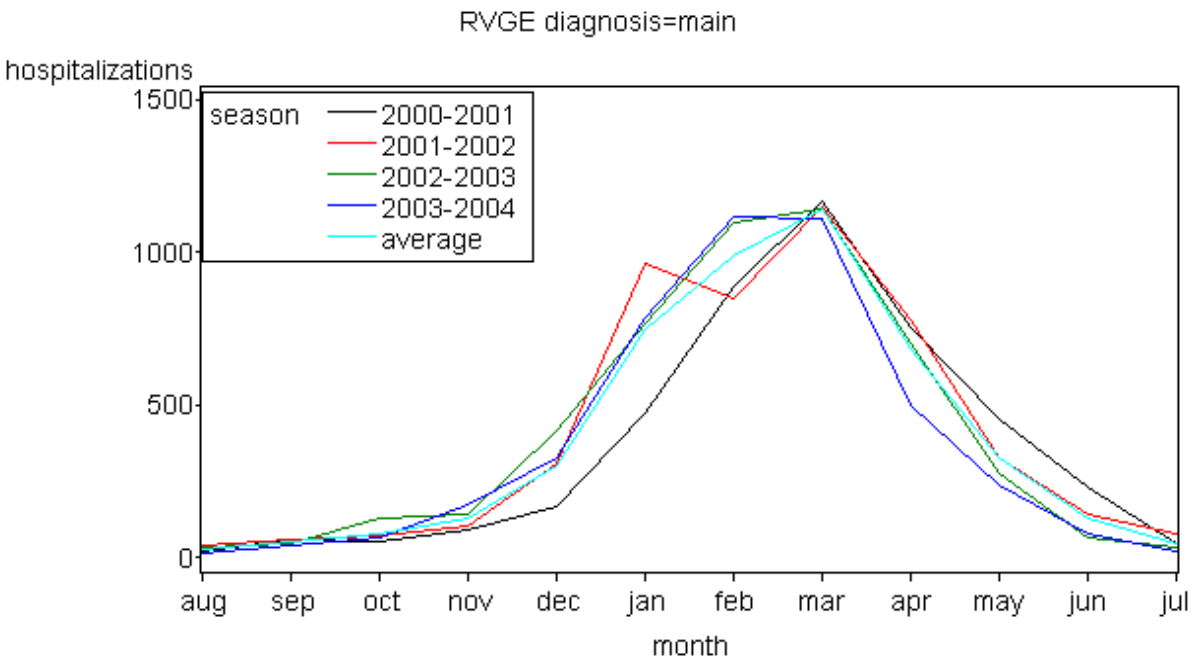
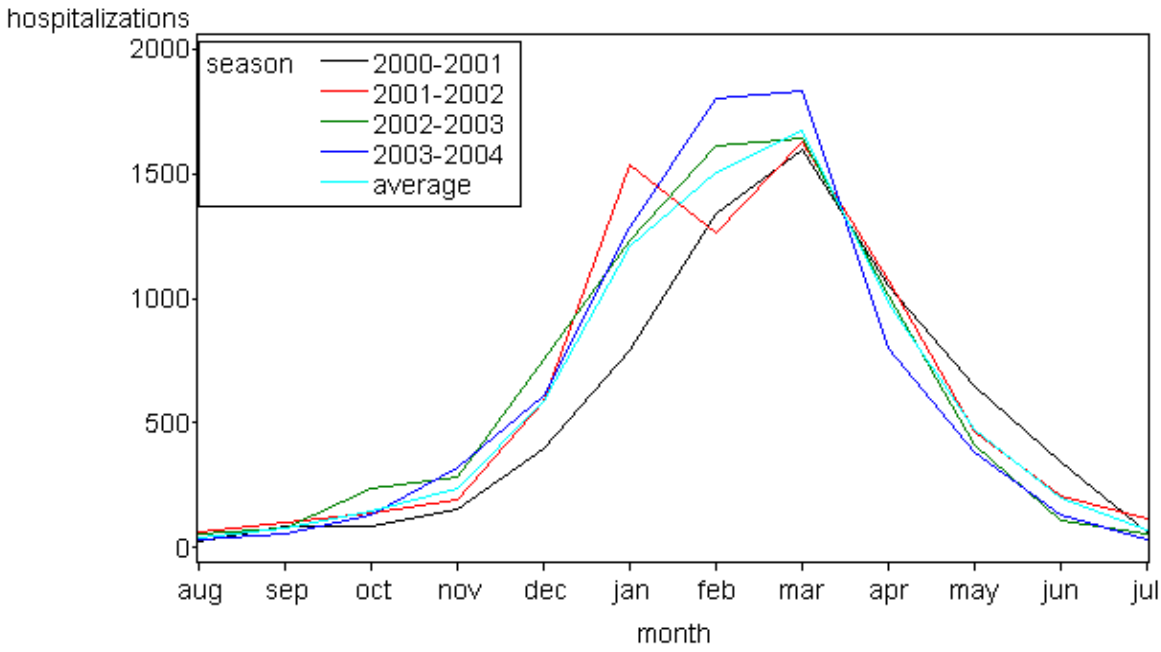


Figure 2.6: MKG data: Monthly number of hospitalizations in Belgium for children under 7 years old with RVGE (ICD9 008.61) as *any* diagnosis.



Carenet data: age-specific proportions of hospitalizations averaged over different months

Data for children under 7 with RVGE as diagnosis are available for years 2004, 2005 and 2006 (without November and December 2006). For each month (from January 2004 until (includes) October 2006), the proportion of RVGE patients with age 0, 1, 2, 3, 4, 5 and 6 was calculated. The monthly proportion of zero and one year old patients with RVGE as main diagnosis is normally distributed with mean + standard error for age zero 0.438 + 0.030, and for age one 0.384 + 0.035. The small standard errors show that the proportion of zero- and one-year old patients with RVGE as main diagnosis stays quite stable over the different months. For the other age groups, the proportion varies much more over the different months and in many months no cases occurred (i.e. proportion zero). However, on average, children contribute less to the monthly total number of hospitalizations with RVGE as diagnosis the older they grow. Similar values are found for proportions of patients with RVGE as any diagnosis (Table 2.2). These mean proportions are used to adjust the MKG prevalence data according to age.

Table 2.2: Mean (and standard deviation) age-specific proportion of patients with hospitalization records showing RVGE as main/any diagnosis. Means are obtained by averaging the monthly proportions reported in Carenet from January 2004 until (includes) October 2006.

	MAIN DIAGNOSIS		ANY DIAGNOSIS	
age	mean	stdev	mean	stdev
0	0,438	0,175	0,468	0,147
1	0,384	0,204	0,356	0,160
2	0,115	0,123	0,103	0,101
3	0,037	0,040	0,048	0,063
4	0,017	0,034	0,015	0,031
5	0,007	0,013	0,009	0,016
6	0,002	0,006	0,002	0,006

Age distribution of the Carenet data applied on the MKG data

The monthly numbers of hospitalizations for each age group are calculated by multiplying the monthly total number of hospitalizations from MKG (average over the different years) by the age-specific mean proportions from Carenet (Figs. 2.7 and 2.8).

Because the number of hospitalizations is much higher in winter (epidemic season), it is likely that more rotavirus episodes will be prevented in children who have completed their vaccination schedule before the epidemic season (e.g. vaccination in the months June till September)) compared to children who are vaccinated after or during the epidemic season. However, because the age bracket for appropriate RV vaccination is very restricted (between 6 weeks and 24/26 weeks of age), the possibilities for catch-up vaccination are very limited for this vaccine (and not recommended). Therefore it is not necessary to use for base case analysis the month-specific incidence estimates, but we can use the average number of hospitalizations per season (mean + standard deviation = 4648 + 246 hospitalizations), divided by twelve. In multivariate sensitivity analysis, the uncertainty related to the mean annual number of hospitalizations (MKG), and the age-specific proportions (Carenet) is incorporated.

Figure 2.7: Monthly number of hospitalizations in Belgium with RVGE (ICD9 008.61) as *main* diagnosis. Monthly numbers are obtained from MKG, age distribution is obtained from Carenet.

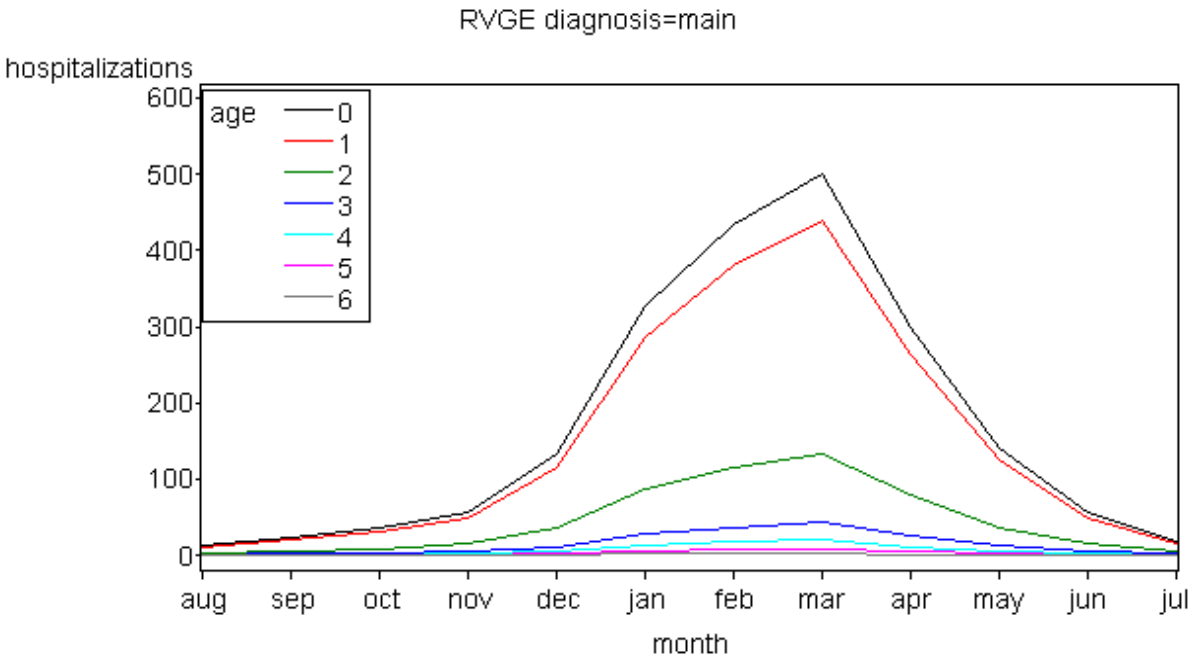
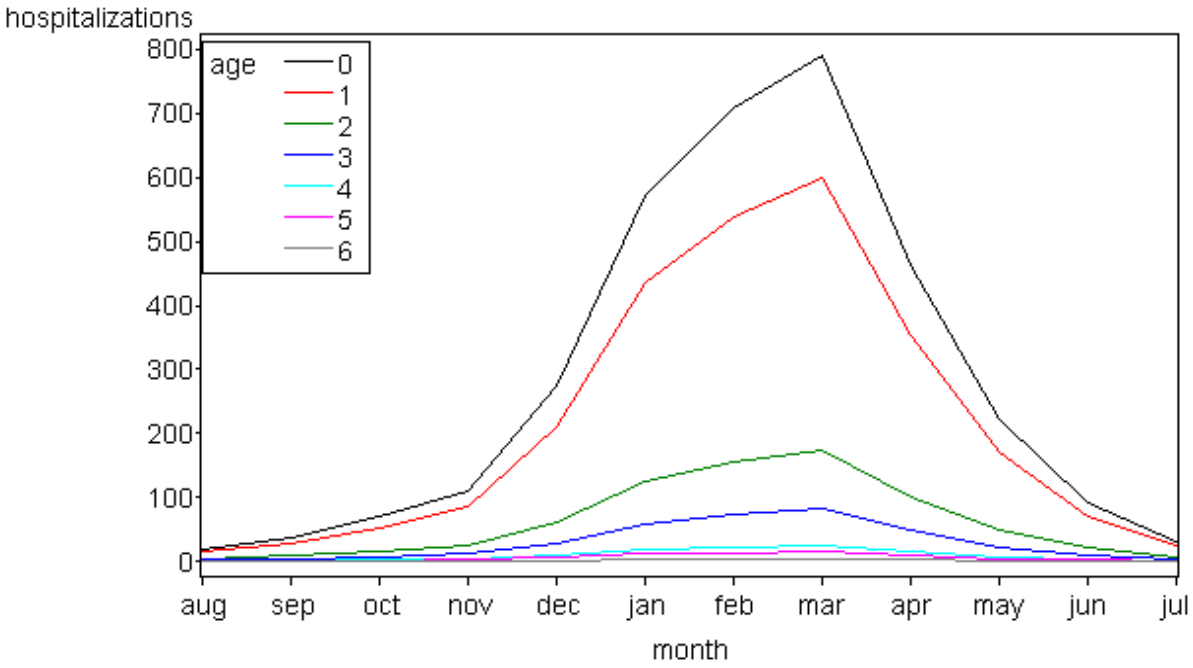


Figure 2.8: Monthly number of hospitalizations in Belgium with RVGE (ICD9 008.61) as *any* diagnosis. Monthly numbers are obtained from MKG, age distribution is obtained from Carenet.

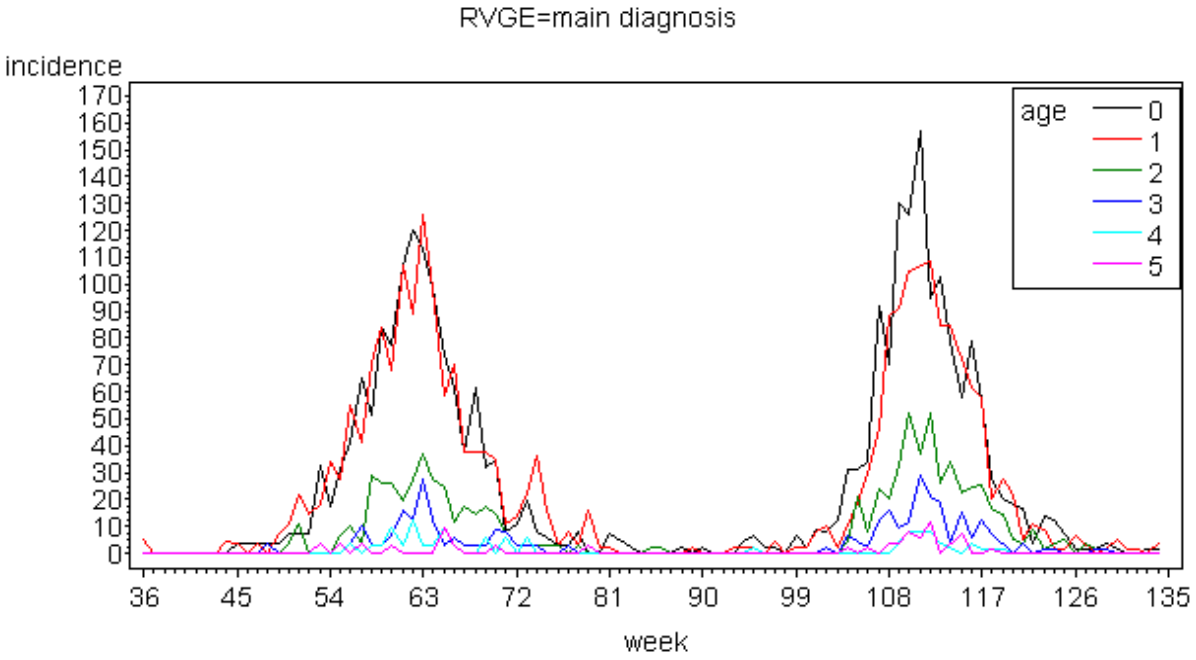


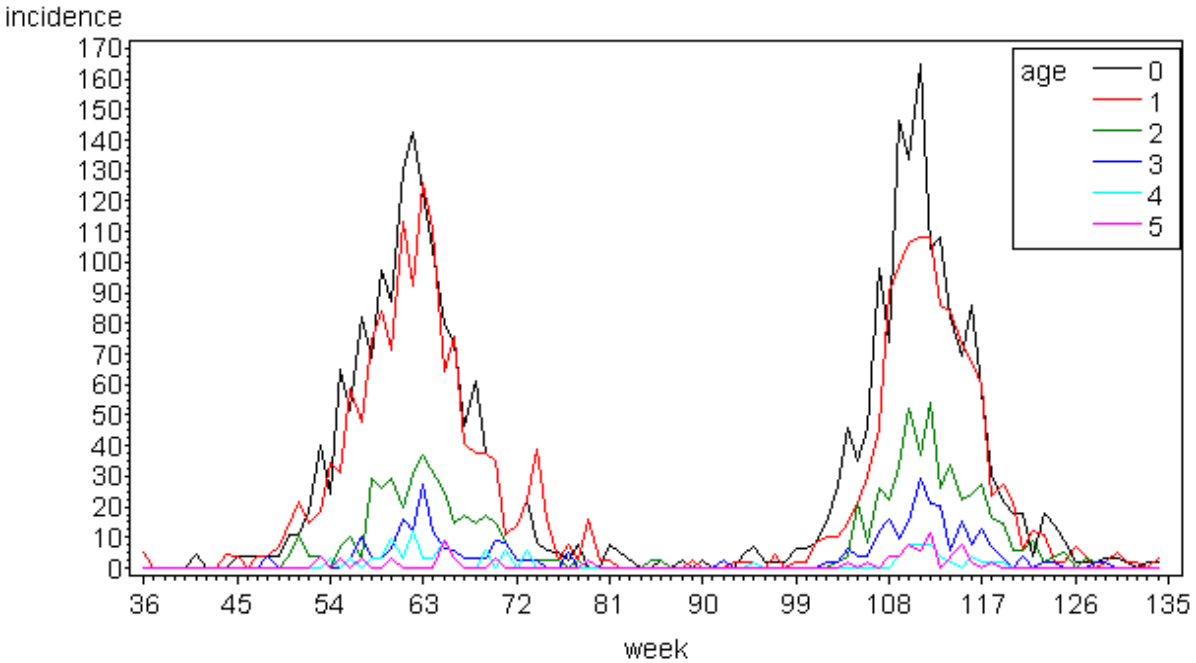
WEEKLY INCIDENCE OF RVGE HOSPITALIZATIONS

The Carenet data allow getting more insight in the weekly (as opposed to monthly) variation in the number of hospitalizations, for more recent epidemic seasons (2004-2005 and 2005-2006). The weekly number of hospitalizations is calculated based on date of hospital admission (weeks start on Sunday). Data are adjusted for the number of beds covered by the Carenet dataset, but data are not extrapolated to all patients (i.e. these data only concern CM members). The latter is not necessary because we are interested in the weekly seasonality, not in estimating nominal incidences (as indicated above, for nominal incidence estimates, we decide to use the MKG data). Figure 2.9 shows the weekly incidence of hospitalizations (for CM members) per 100000 beds for seasons 2004-2005 and 2005-2006, by diagnosis and age.

The weekly data show the same trends as the monthly data. There is almost no difference between the plots for RVGE as main and any diagnosis.

Figure 2.9: Carenet data: weekly incidence of hospitalizations (for CM members) per 100000 beds for seasons 2004-2005 (week 36-83) and 2005-2006 (week 84-134), by RVGE diagnosis (main, any), and per age group (0-5 years old).





RVGE=any diagnosis

LENGTH OF STAY (LOS) IN HOSPITAL WITH RVGE AS DIAGNOSIS

Calculations are based on aggregated MKG data. This data provide mean and median LOS in hospital (minimum, maximum and range) per age, region and year. Means are usually equal or higher than the medians. Table 2.3 gives weighted mean LOS over the different years (of the means given), for different age groups and regions.

Table 2.3: Weighted mean duration of hospitalization with RVGE as main and any diagnosis, by age, by region (1999-2004).

	RVGE main diagnosis			RVGE any diagnosis		
age	Brussels	Flanders	Wallonia	Brussels	Flanders	Wallonia
0-30 days	5.6	7.9	7.2	25.2	17.4	21.8
30 days-1 year	4.5	4.7	4.3	6.5	6.0	6.2
1	3.6	4.1	3.7	4.9	4.7	4.7
2	4.6	3.9	3.7	5.1	4.3	4.2
3	3.6	3.8	3.7	4.7	4.2	4.1
4	3.5	3.7	3.4	4.6	3.9	3.7
5	3.4	3.4	3.3	5.2	3.7	3.6

The number of days in hospital for children with RVGE as main diagnosis is slightly higher for Flanders compared to Brussels and Wallonia (Table 2.3). The youngest infants (under 30 days) remain the longest in the hospital. Children between 30 days and 1 year of age stay on average 4/5 days in the hospital. For Flanders, Brussels and Wallonia, the LOS further decreases with increasing age from 4 days at age 1 until 3 days for children 5 years old (Table 2.3). In Flanders only, the LOS decreases slightly over time from 1999 to 2004 (except for the youngest age group, data not shown).

Compared to children hospitalized with RVGE as main diagnosis only, children with RVGE as any diagnosis stay longer in hospital. The number of extra days in hospital compared to the children with RVGE as main diagnosis is higher for the younger children. In the older age groups, the difference becomes much smaller. The variation in LOS is also larger for children with RVGE as any diagnosis compared to RVGE as main diagnosis Table 2.3).

In contrast with what we find for LOS of children with RVGE as main diagnosis, children with RVGE as any diagnosis (of any age) have the shortest LOS in Flanders and Wallonia. Children stay 1 to 7 days longer in Brussels compared to Flanders (Table 2.3). The largest difference occurs for the infants under 30 weeks old, who remain in hospital on average 25 days in Brussels, compared to 22 and 17 days in Wallonia and Flanders, respectively.

For both main and any diagnosis of RVGE, variation in LOS is largest for infants under 30 days old, and for the region of Brussels.

These data are comparable with data reported by the REVEAL study and Raes et al.[20]. In the REVEAL study, the mean LOS for children under 5 years old was 4.37. Raes et al.[20] assessed LOS for children under 2 years old with laboratory-proven RVGE in one large Belgian hospital. Sample collection was performed in infants who presented with moderate to severe acute gastroenteritis in private practice, emergency department or during hospitalization. The study found for rotavirus seasons 2002-2003, 2003-2004, 2004-2005 and 2005-2006, a mean LOS of respectively, 5.65, 6.05, 5.43 and 5.09 days. According to de Wit et al.[21] the average stay in hospital of community-acquired RV cases was 4 days.

Nosocomial RVGE infections

In base case analysis, we assume 14% of the annual number of hospitalizations with RVGE as any diagnosis are **nosocomial infections**. Age-specific proportions are used. In sensitivity analysis, we vary the proportion of nosocomial infection according to a beta distribution, and the annual number of hospitalizations with RVGE as any diagnosis according to a truncated normal distribution with mean 7243 and standard deviation 218 (lower limit zero).

INCIDENCE OF NOSOCOMIAL RVGE INFECTIONS

The only population-based dataset in which day at which RVGE symptoms started is available, is the CM survey (see above). From this survey, we know that 7.8% (7 out of 90 RVGE patients, virtually all of whom were hospitalized during the rotavirus season 2005-2006) started to vomit/having diarrhoea more than one day after hospital admission. For most of these patients, the reason of hospital admission was not only vomiting and/or diarrhoea, hence suggesting that the RVGE indeed was acquired in the hospital. Hereafter an overview of the reasons for hospital admission for the 7 patients who showed RVGE symptoms more than one day after hospital admission:

"anurie" (vomiting/diarrhoea at day 4 of hospital admission)

"bronchiolite-otit-rota sans diarh au depart" (vomiting/diarrhoea at day 2 of hospital admission)

"reflux gastrique" (vomiting/diarrhoea at day 7 of hospital admission)

"double otite, puis RV" (vomiting/diarrhoea at day 8 of hospital admission)

"huilen" (vomiting/diarrhoea at day 2 of hospital admission)

"vomissement" (vomiting/diarrhoea at day 4 of hospital admission)

"déshydratation - sur 2 jours, avait perdu 2,5kg. " (vomiting/diarrhoea at day 3 of hospital admission)

This proportion (7.8%) corresponds well to what Raes et al.[20] found in their study in a large Belgian hospital for the overlapping rotavirus season (2005-2006). As recounted by clinicians from various hospitals, and reported in Raes et al[20], the proportion of nosocomial RV hospitalizations (i.e. hospitalised patients with a positive RV test result during their stay) varies between seasons. Raes et al[20] estimated nosocomial RV infections (i.e. appearing 48h or more after hospital admission) at 12.8% in 2002-2003, 22.8% in 2003-2004, 15% in 2004-2005 and 7% in 2005-2006 of all hospitalisations with an RV diagnosis. If data from this hospital are summed over all observed seasons, we get that 14% (60 out of 423 RVGE-related hospitalizations) of the total number of hospitalizations with RVGE as *any* diagnosis is nosocomial. This 14% is used in baseline analysis, with data-derived variations on this proportion shown in uni- and multivariate sensitivity analyses (see below). The total number of hospitalizations with RVGE as any diagnosis is obtained from the MKG dataset. Averaged over the four seasons (2000-2004), the yearly number of hospitalizations with RVGE as any diagnosis, for children under 7 years is 7243 $\pm$ 218 (mean $\pm$ standard error). Hence, the yearly number of nosomial infections in base case analysis is 1027. As for RVGE related hospitalizations, age-specific proportions (based on the Carenet data) are used to assign the estimated nosocomial infection to each of the age groups. In probabilistic sensitivity analysis, the proportion of 14% is the average expected value of the beta distribution that was defined according to the observations in Raes et al [20].

EXTRA LENGTH OF STAY (LOS) IN HOSPITAL DUE TO NOSOCOMIAL RVGE INFECTION

A review article[22] of nosocomial infections in European countries reports extra length of stay due to nosocomial RVGE infection between 1.7 days (for a study in Italy) and 5.9 days (for a study in Poland). The study with the largest sample size (N=5470, France[23]) reported an extra length of stay of 4.4 days by comparing the duration of hospital stay for

nosocomial diarrhoea with the duration of hospital stay without nosocomial diarrhoea, for children younger than 5 years. This value is slightly higher than the mean length of stay of hospitalized children with community-acquired RVGE (see above). The value of 4.4 extra days might be slightly overestimated, because it is averaged over all ages below 5 (no age-specific extra length of stay was available from the study of Thuret et al.[23]). We know from our data that very young RVGE infected children stay longer in the hospital, however, we also know that these very young children represent only a small part of all hospitalized children with RVGE.

The extra LOS of 4.4 days due to nosocomial RVGE infection will be used in our analysis as mean value, and will be altered between 1.7 and 5.9 days in sensitivity analysis (triangular distribution).

2.2.2.2 *Outpatient visits ("dag hospitalisaties")*

In base case analysis, the annual number of **outpatient visits** with RVGE as main diagnosis is assumed to be 7. In sensitivity analysis, the annual number of RVGE outpatient visits is altered according to a truncated normal distribution with mean 7 and standard deviation 4 (lower limit zero).

The MKG also records the number of children younger than 7 years with RVGE that went to the hospital but did not stay overnight ('outpatient visits'). Over 5 years (2000-2004) only 37 children with RVGE as main diagnosis and 12 children with RVGE as secondary diagnosis were hospitalized for one day (Table 2.4). The mean annual number of children in outpatient visit with RVGE as main diagnosis is used in base case analysis. In sensitivity analysis, this number is sampled from a truncated normal distribution (lower limit zero).

Table 2.4: Number of children under 7 hospitalized for one day ('outpatient visit') with RVGE as main and secondary diagnosis, per year.

diagnosis	2000	2001	2002	2003	2004	mean	stdev
main	9	3	6	13	6	7	4
secondary	1	1	3	3	4	2	1

2.2.2.3 *Emergency Department Visits (EDV)*

RVGE related **ED visits** cannot be incorporated in our cost-effectiveness model.

From the MKG data, we know that a large part of hospitalized children are admitted via the emergency room (74%). Hence all these children are already included in the incidence value for RVGE related hospitalizations. In the database of patients with an outpatient visit, there are no children with type of stay 'contact with emergency department without hospitalization'. In the CM survey, only for 5 of the 86 ambulatory patients, a visit to ED was reported. However, in the REVEAL study, the largest proportion of children who were screened for AGE and were eligible, was identified via the emergency department (i.e. 446 of the 1008 patients). But due to the very low participation rate of these patients (1.78%), no reliable estimate of the proportion of these children for which the AGE was caused by rotavirus could be obtained. From the five children participating in the study, 2 were tested to be rotavirus positive.

Due to the lack of effective surveillance systems, we are not able to estimate reliably the yearly incidence of RVGE related emergency department visits in Belgium, without ensuing hospitalization. Hence, RVGE related ED visits is not incorporated in our cost-effectiveness model.

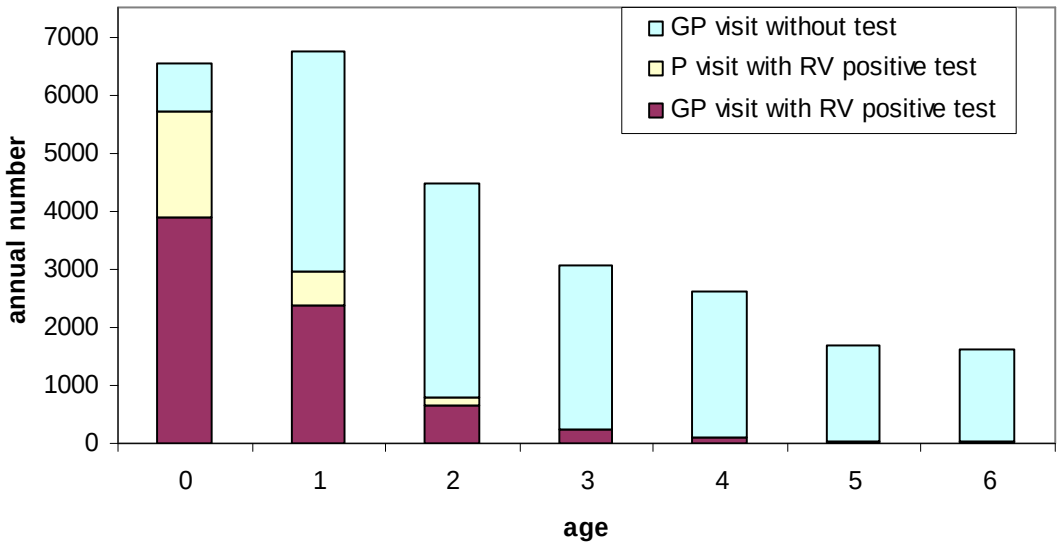
2.2.2.4 *Ambulatory care related to RVGE*

A distinction is made between patients seeking ambulatory care who are tested positive for RVGE and patients who are not tested for RVGE.

First, separate incidences are estimated for RVGE positive tested patients visiting at least once a GP, and for patients visiting only a pediatrician. Because not for all cases of RVGE lab tests are requested, we also estimate incidence for patients who visit a GP because of

RVGE infection, without being tested for it. An overview of the resulting estimates for patients with RVGE younger than 7, seeking ambulatory care is given in the Fig. 2.10 below.

Figure 2.10: Annual estimated number of patients who are tested positive for RVGE and visited at least once a GP ('GP visit with RV positive test'), visited only a pediatrician ('P visit with RV positive test'), and GP consultations for RVGE of patients who are not tested ('GP visit without test').



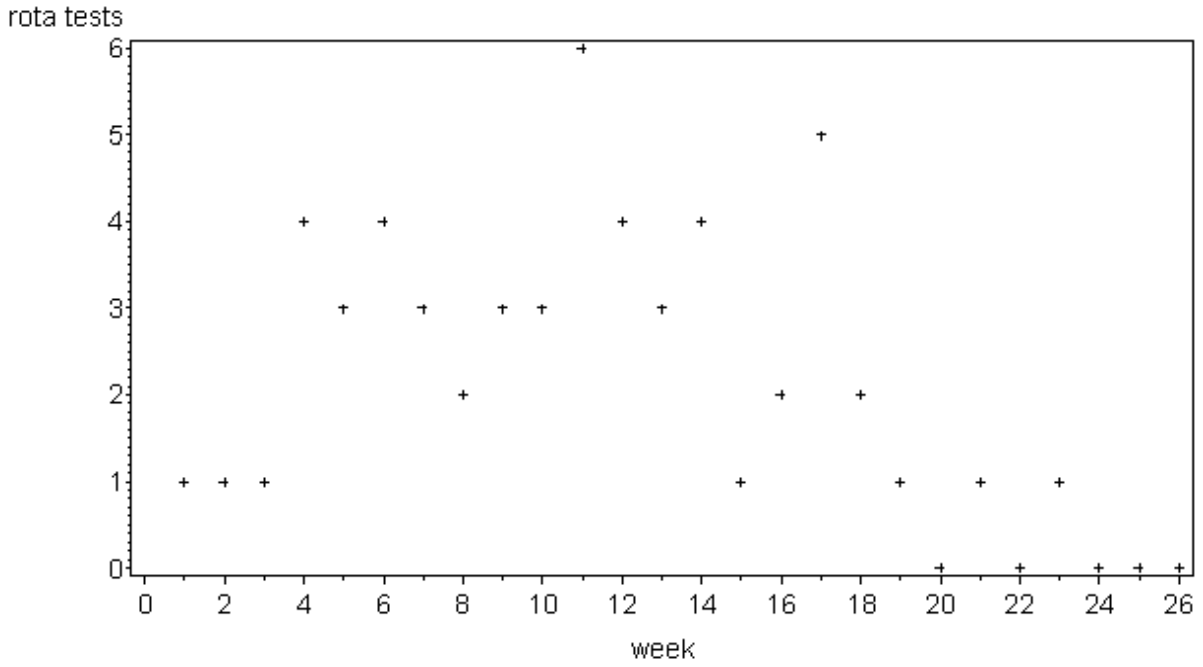
GP visits, RV positive

In base case analysis the annual number of **RVGE positive** patients who visit at least once a **GP**, is assumed to be 7333. Age-specific incidences are used. Uncertainty of the data on which the estimates are based, is incorporated in sensitivity analysis (see below).

Data on RVGE related general practitioners visits are indirectly obtained from the sentinel general practitioners (obtained from WIV). This source gives the weekly number of RV positive tests requested by these sentinel GPs between 1st January and 30 June 2002.

In total there are 55 rotavirus positive lab tests for patients of the sentinel GPs in the period 1st January – 30 June 2002. No age of patients that are tested positively for RV is available, but we assume that no RV tests are performed for patients older than 6 years. The weekly number of positive RV lab tests for patients of the sentinel GPs in the period 1st January – 30 June 2002 is very small (maximum 6 RV positive lab tests a week; Fig. 2.11). Most RV positive lab tests occurred between February and May.

Figure 2.11: Weekly number of RV positive lab tests for sentinel GP patients younger than 7 years with gastroenteritis.



We assume only one test is requested per patient, so that the number of RVGE positive tests reflects the number of RVGE positive tested patients who visit at least once a GP. Because no age-specific data are available for the lab tests requested by the sentinel GP's, age-specific proportions of rotavirus positive lab tests are obtained from the WIV data (sentinel labs). The WIV data contain the number of rotavirus positive test for years 2000, 2001 and 2005 by age, for tests requested ambulatory and for hospitalized patients. Age-specific proportions of RV positive lab tests are assumed to be the same for tests requested ambulatory and for hospitalized patients. The annual age-specific proportions of RV positive lab tests are calculated from the annual mean number of RV positive lab tests as registered by the sentinel labs (e.g. for age 0: mean number of RV positive labs for age 0, divided by number of RV positive labs tests summed over all age groups) (Table 2.5). These proportions are used to assign the 55 RVGE positive lab tests, requested by the sentinel GP's between 1st January and 30 June 2002, to the different age groups. Assuming the same number of lab tests was requested for the period 1 July-31 December 2002, and knowing that the sentinel general practitioners cover 1.5% of the Belgian population, the annual number of patients who visited at least once a GP for RVGE which was confirmed with a lab test, is obtained per age group (Table 2.5). So the final age-specific estimates are based on data from the sentinel GP's and the sentinel labs. In sensitivity analysis, the uncertainty of these data is incorporated. The number of RV positive lab tests requested by the sentinel GP's (i.e. 55 tests) is altered between 40 and 70. The age-specific proportions obtained from the sentinel labs is altered according to a truncated normal distribution (lower limit zero) for the annual mean number of RVGE tests for each age group.

Table 2.5: Column 1, 2 and 3: Annual mean number, standard deviation and proportion of RV positive lab tests as registered by the sentinel labs, by age. Column 4: Assumed annual number of RVGE positive patients who visit at least once a GP, by age group.

age	mean	stdev	proportion	**number**
0	3842	959	0,531	**3896**
1	2343	448	0,324	**2376**
2	660	173	0,091	**669**
3	229	68	0,032	**233**
4	98	19	0,014	**99**
5	38	14	0,005	**39**
6	22	5	0,003	**23**

Pediatrician visits, RV positive

In base case analysis the annual number of RVGE positive tested patients who visit only a pediatrician is assumed to be 2590. Age-specific incidences are used and uncertainty of the data on which the estimates are based, is incorporated in sensitivity analysis (see below).

No direct estimates for the annual number of pediatrician visits due to RVGE are available. However, from the CM survey we know the proportion of children aged zero and one, visiting a pediatrician only, comparatively to visiting at least once a GP. For the children below 1 year of age, 67% visited at least once a GP for their RVGE (some of them visited also a pediatrician), whereas 31% visited only a pediatrician. The remaining 2% are parents who reported no visit to a GP nor a pediatrician related to the RVGE episode of their child. For the children of 1 year of age, 74% visited at least once a GP for their RVGE, whereas 18% visited only a pediatrician. The remaining 8% are parents who reported no visit to a GP nor a pediatrician related to the RVGE episode of their child.

Another source (data from CM members for 2005) provides information about the general frequency with which parents go with their children to a GP as compared to a pediatrician. 53% of CM members below 1 year of age visit at least once a pediatrician (and no GP) in 2005. The remaining 47% are members who visited at least once a GP in 2005. For children 1 year of age, 36% visited only a pediatrician, whereas the other 64% visited at least once a GP in 2005. Hence, the CM survey reveals that specifically for a child with symptoms of RVGE (and positive test result), parents go more frequently to a GP instead of a pediatrician.

Using these percentages (Table 2.6), the annual number of pediatrician visits for RVGE positive tested children is calculated for children under 2 years of age. For instance for children younger than 1 year, the annual number of RVGE positive tested children who visit at least once a GP, is 3896. The CM survey shows that this number is 67% of all children for whom a RVGE positive test is obtained in an ambulatory setting. So dividing 3896 by 67% and multiplying it by 31% (i.e. the percentage of RVGE positive tested children who visit only a pediatrician), gives the annual number of RVGE positive tested children who visit only a pediatrician, i.e. about 1818 children. For patients 1 year of age, the annual number is 594. The CM survey does not include patients older than 1 year of age, so no proportions are available for these age groups. The CM data for 2005 provides information about the general frequency with which parents go with their children to a GP as compared to a pediatrician. This relative importance of pediatrician visits declines with the child's increasing age. Therefore we assume for children aged 2 years, 15% will visit a pediatrician (as compared to 77% visiting at least once a GP). This means that for all children under 7 years, already 64% of Ped visits is attributed to ages 0, 1 and 2. We assume the remaining 36% to be distributed equally over the age groups 3, 4, 5 and 6. For these estimates we allow each time a proportion of 8% not visiting a GP nor a pediatrician, but being tested positively for RVGE.

The resulting annual number of RVGE positive tested patients who visit only a pediatrician are shown in Table 2.7 below, per age group. Uncertainty on these data is incorporated in sensitivity analysis by assigning beta distributions to each of the proportions.

Table 2.6: Proportions of RVGE positive tested children who visit a pediatrician only ('Ped only'), by age.

age	Ped only
0	31%
1	18%
2	15%
3	9%
4	9%
5	9%
6	9%

Table 2.7: Annual number of RVGE positive tested patients who visit only a pediatrician, per age group.

age	number
0	1818
1	594
2	130
3	22
4	10
5	4
6	2

GP visits, not tested

In base case analysis the annual number of RVGE related **GP visits** of patients for whom no test was requested, is assumed to be 17,578. Age-specific incidences are used and uncertainty of the data on which the estimates are based, is incorporated in sensitivity analysis (see below).

Till now, from all ambulatory RVGE episodes, we only have considered information about the patients that were tested positively for RVGE. However, we know that not for all children with RVGE a rotavirus test is requested. A test is less likely to be requested when the symptoms are less severe, and people are more likely to visit a GP instead of a pediatrician. Hence, we assume the annual number of children with RVGE who seek ambulatory medical care but is not tested for RVGE is reflected in the annual number of children who visit a GP without being tested for RVGE.

Regression analysis is used in order to determine indirectly the number of GP visits for gastroenteritis that is attributable to rotavirus.

Weekly RV positive laboratory tests are compared with weekly number of GP visits for gastroenteritis by linear regression to estimate the proportion of GP visits for gastroenteritis attributable to RV. Weekly number of AGE related GP visits are obtained from the sentinel GP's for the year 2002. Data on lab tests for different germs causing childhood gastroenteritis are obtained from the WIV for the year 2001 (which is the year nearest to 2002, and for which data on most germs are available). Data include both ambulatory tests and test requested for hospitalized patients. We assume the seasonality seen in the number of RV positive lab tests to be the same for tests requested for ambulatory and hospitalized patients.

A linear regression model is constructed ($Y_i=a+\sum b_j X_{j,\,i}$) that best estimates the weekly number of visits for gastroenteritis (Y_i) with i being the week (i=1-52) and j being germ for which a test is performed (j=rotavirus, adenovirus, campylobacter, cryptosporidium, giardia, salmonella, shigella, y. enterolitica, listeria, e.coli or e. histolytica). A constant scaling factor (b_j) is assumed for the number of positive lab tests for each germ that can

cause gastroenteritis ($X_{j,i}$) and a constant number of visits attributable to other factors (a). The constant (a) and scaling factors (b_j) are estimated by fitting the model with SAS 9.1.[24, 21, 25] Variables (i.e. germs) are removed if they do not make an important contribution to the model (i.e. $p \geq 0.05$, and their removal did not reduce the adjusted r^2), or if the coefficient is negative as this is not biologically plausible. The number of visits attributable to RV infection is calculated using the final regression model. The number of visits attributable to RV is the scaling factor for rotavirus (b_{rota}) times the number of rotavirus positive lab tests ($\sum X_{rota,i}$) per week. Dividing this by the total number of visits ($\sum Y_i$) gives the percentage attributable to RV infection.

Based on the final model, 18% of the AGE related GP visits are due to rotavirus infection, 28% due to adenovirus infection and 38% due to infection with giardia (Figs. 2.12 and 2.13). These estimates should be handled with care due to the following reasons: (1) the final model has an adjusted r^2 value of 0.30, which means that the proportion of variation accounted for by the germs in our model is rather low. Likely, some important predictor variables are missing in the model. We assumed implicitely that all germs included in the model would be the only ones causing childhood gastroenteritis GP visits that show significant seasonal variation. However, other germs, for which no data were available (Brucella, Vibrio cholerae, Enterovirus, Enterococcus and Norovirus), may also explain some of the seasonal variation for AGE related GP visits. (2)The model assumes the intensity of testing to be the same the whole year round. However, tests for rotavirus are likely to be requested more frequently at the beginning of the epidemic season (autumn) than in summer or at the peak of the epidemic season.

Figure 2.12: Weekly number of observed GP visits, rotavirus, adenovirus and giardia positive lab tests.

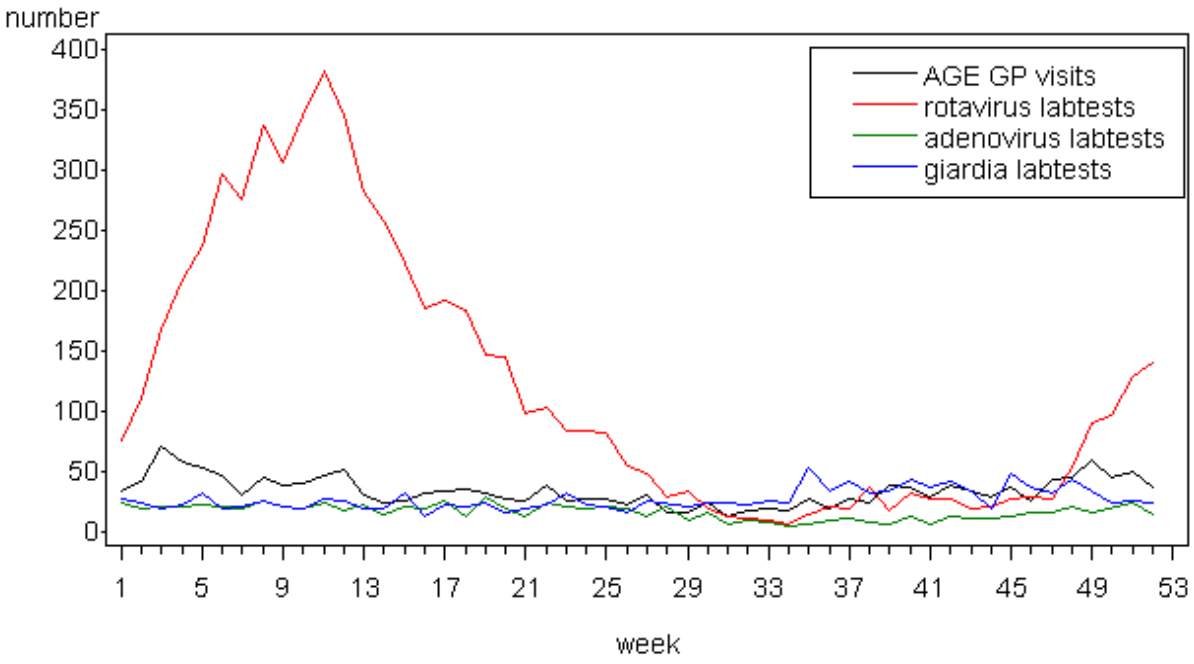
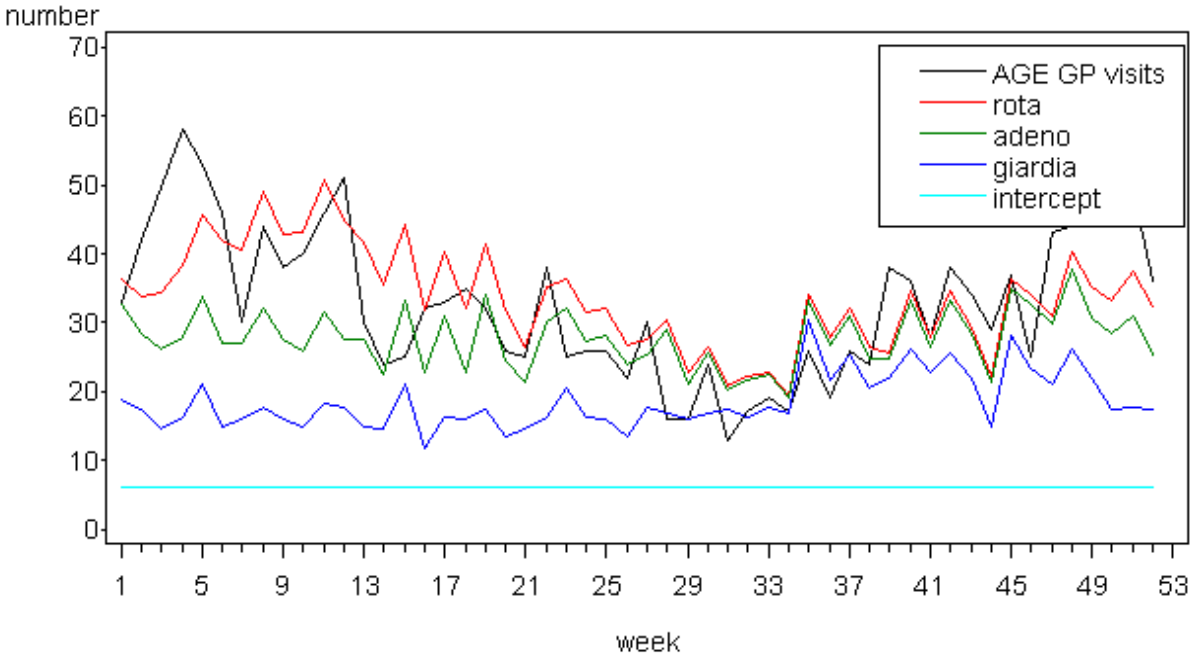


Figure 2.13: Weekly number of observed AGE related GP visits, and predicted proportion attributable to rotavirus, adenovirus and giardia positive lab tests.



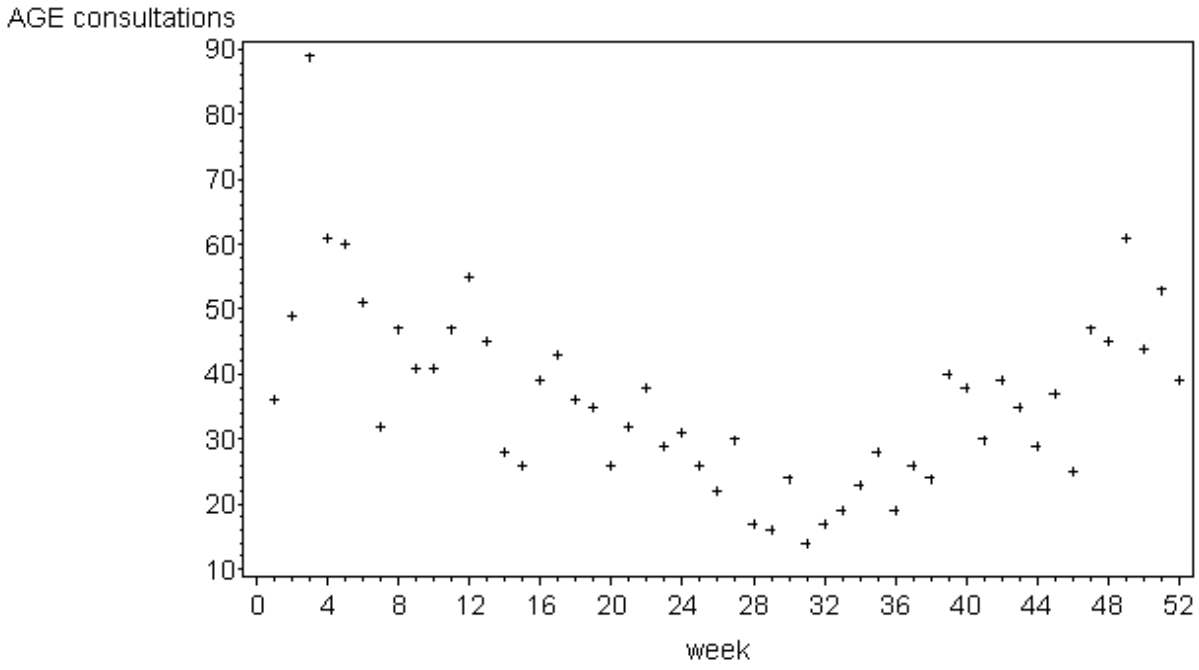
Despite these limitations of the model, the resulting proportion of 18% is consistent with what we find in the literature. Other studies[4, 5] used an estimate of 20% of all GP visits for gastroenteritis that are attributable to RVGE for children under 5. This estimate was for both studies based on published literature. Harris et al.[25] estimated for England and Wales that about 25% of all GP consultations for gastroenteritis were attributable to rotavirus for children under 5 years old. The somewhat lower estimate from our study probably stems from the fact that we included all children under 7, whereas the other studies included all children less than 5 years of age. So we can presume that about 20.75% (the mean of the 4 studies; with range 18%-25%) of GP visits for gastroenteritis are due to rotavirus infection.

The annual mean number of GP consultations for gastroenteritis by age is obtained from the sentinel general practitioners (WIV). This source gives the weekly number of patients who visited one of the sentinel GPs for acute gastroenteritis in 2002. For 146 patients (i.e. 1.3% of all recorded patients) no year of birth is available, and these patients are excluded from analysis. The age distribution of the GP visits for gastroenteritis is given in Table 2.8 below. In the youngest age group (age=0) there are the fewest patients. A possible explanation is that those children, when they show symptoms for AGE, go directly to a pediatrician, ED or hospital. There is an elevated number of sentinel GP visits from December until March (Fig. 2.14). This trend was seen in all age groups and for Flanders (N=831), Wallonia (N=857) and Brussels (N=50) (data not shown).

Table 2.8: Number of sentinel GP visits for gastroenteritis in 2002, by age.

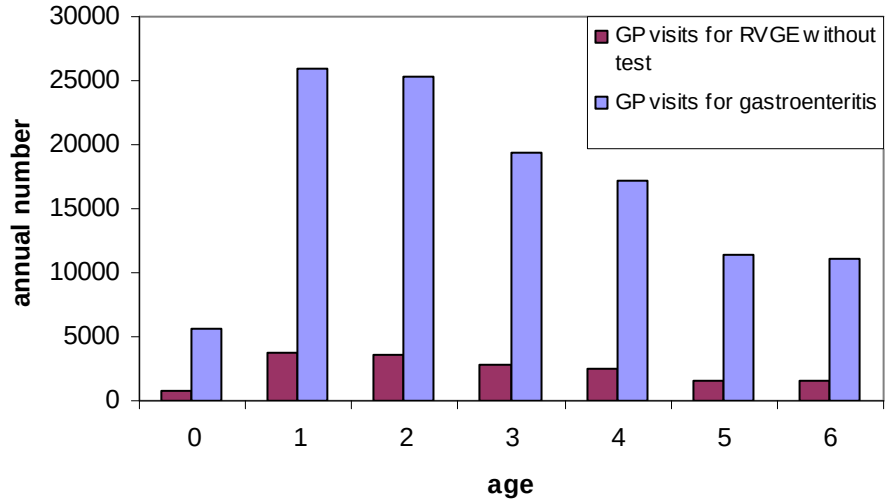
age	number
0	84
1	390
2	380
3	290
4	258
5	170
6	166
all ages	1738

Figure 2.14: Weekly number of sentinel GP visits in 2002 of children younger than 7 years with AGE.



Knowing the sentinel general practitioners cover 1.5% of the Belgian population, the annual number of GP visits for gastroenteritis for the whole of Belgium, per age group is obtained. 20.75% (range 18%-25%) of all GP visits for gastroenteritis is assumed to be attributable to RVGE. Because already 6% (annual number of GP visits for patients who are tested RV positive (7,334) divided by annual number of GP visits for gastroenteritis (115,867)) of these 20.75% is included in the model as GP visits for RV positive tested patients, the remaining 14.75% of all AGE consultations (i.e. about 16,000 consultations) is assumed to be attributable to patients with RVGE who were not tested for RVGE. No age-specific proportions are available for children with RVGE visiting a GP without being tested for RVGE. The resulting age-specific numbers of GP visits for RVGE without a test is shown in Figure 2.15 below. In sensitivity analysis, the proportion of 20.75% is altered between 18 and 25% (lower value based on our regression analysis and upper value on literature estimates).

Figure 2.15: Assumed numbers of GP visits for gastroenteritis and rotavirus gastroenteritis of patients for whom no RVGE test is performed, by age.



2.2.2.5 No medical care

In base case analysis, we include estimates of the age-specific annual numbers of children with symptomatic rotavirus infection for whom no medical care is sought. Both multivariate and univariate sensitivity analysis are done on these parameters.

Every year children are infected by rotavirus, but only a part of them develop symptoms. Only for some of these symptomatic cases medical care is sought. However, children with symptomatic RVGE infection for which no medical care is sought, also experience a burden, i.e. parents may have to buy extra diapers, experience loss of quality of life, and/or have to stay home to take care of their child. Hereafter we estimate the annual incidence of children with RVGE who develop symptoms, but for whom no medical care is sought.

We know of three prospective studies investigating the incidence of rotavirus infection and proportion of symptomatic cases.[26-28] The incidence of infections differs somewhat between the different studies: Gurwith et al.[26] found no symptomatic RV infections in the first 5 months (104 children studied), 25 symptomatic infections in months 6-11 (94 children studied, i.e. 27% infected with symptoms when assuming no child was infected twice), 10 symptomatic infections in months 12-17 (83 children studied, i.e. 12% infected with symptoms) and 5 symptomatic infections in months 18-23 (37 children studied, i.e. 13.5% infected with symptoms). If we sum these percentages, 52.5% of the children are infected with symptoms at the end of two years. Rodriguez et al.[27] finds 4% (5 of the 118 children studied) to be infected with symptoms in the first year of life, and 25% (12 of the 48 children studied) in the second year of life. Velazquez et al.[28] finds 67% of children to be infected at least once after the first year of life, and 96% of the children after the second year of life. Of these infected children, 37% are symptomatic.

A possible explanation for these different results may lie in the methods of detecting rotavirus infections. All three studies gathered stool and blood samples. Regarding the stool sampling, there is probably no difference between the three studies: although Velazquez et al.[28] sampled more frequently than the two other studies, all studies gathered stools when gastroenteritis symptoms were reported. Because rotavirus shed in stool samples is almost only found in symptomatic cases[26], the three studies are likely to be equally successful in the detection of rotavirus infection based on stool samples. Blood samples on the other hand also show asymptomatic rotavirus infections (and mild infections or infections with atypical symptoms). Hence when blood samples are not taken frequently enough, there is a chance to miss these asymptomatic cases. Rodriguez et al.[27] sampled only every 6 months, Velazquez et al.[28] sampled every 4 months and Gurwith et

al.[26] at least once every three months. In the study of Velazquez et al.[28] the presence of both antirotavirus IgA and IgG antibodies was tested. Because IgG antibodies stay relatively long in the blood, the chance of missing rotavirus infections will be quite low. Gurwith et al.[26] and Rodriguez et al.[27] did not specify which antibodies were measured. Also, the studies were conducted in different countries: US[27], Canada[26] and Mexico[28].

From each of the three studies, beta distributions are defined from the available data for the proportion of children of age 0 and 1 that are RV infected with symptoms. As in our opinion, none of the three studies is superior; the estimate for the proportion of children that are RV infected with symptoms is sampled in sensitivity analysis randomly from one of the 3 distributions. For the second year of life (age 2), Rodriguez et al.[27] found 7% (2 out of 30 studied children) of children to be RV infected with symptoms, and for age 3 and 4, 8% (2 out of 26 studied children). We assume the latter symptomatic cases are spread equally over age 3 and 4. For ages 5 and 6 no information is available. We assume the number of infections to decrease further and being half of the proportion used for the previous years (i.e 2%).

With the information described above, the annual number of children with symptomatic RVGE infections per age group can be obtained. We also know the annual number of children seeking medical care for a RVGE infection. Hence, subtracting the latter from the former number, the annual number of children with symptomatic RVGE infection not seeking medical care is obtained. These estimates are incorporated into our model (Appendix F). Note that these estimates are not based on available data for Belgian children, and that uncertainty on these estimates is large. Therefore also univariate sensitivity analysis is performed on these estimates.

2.2.2.6 Deaths

In base case analysis we assume that the annual number of **deaths** due to RVGE is 0.6 (i.e. 3 children died over a period of 5 years (1999-2004)), and is limited to children younger than 3 years of age. In probabilistic sensitivity analysis we vary this number according to a beta distribution.

We were unable to obtain Belgian death certificates for the purpose of our study.

However, MKG reports 3 patients in Belgium who died with RVGE as primary diagnosis for hospitalization, during the period from 1999 until 2004. Two of these patients were 2 years old, and the other one was younger than 28 days at hospital admission.

In the same period, MKG reports 11 patients who died with RVGE as secondary diagnosis, which means an approximate average of 2 patients per year (range 1 (in 2000 and 2004) to 4 (in 2002)). The majority of patients (8) was between 28 days and 1 year of age, one patient was under 28 days old when s/he died, the other patients were 1 and 3 years old.

For each of these patients, complete diagnosis is given in ICD9 codes. We asked 10 Belgian paediatric clinicians to determine for each of these patients if they thought the child would not have deceased if s/he had not been infected by rotavirus (yes/no/I do not know). These clinicians could base their opinion on age, duration of stay in the hospital and the primary and secondary diagnoses of hospitalization (ICD9 codes and definition of these codes) for each patient. This listing presented to the pediatricians can be found in Appendix E. The results based on responses from the 5 clinicians who responded to our request are given in Table 2.9.

Table 2.9: Answers of five clinicians on the question if they think the deceased patients would not have died if they were not infected by rotavirus, based on the primary and secondary diagnoses. 'Yes': without the rotavirus infection, the child would not have died; 'no': even without the rotavirus infection, the child would have died.

3 deceased patients with RVGE as main diagnosis

	clinician 1	clinician 2	clinician 3	clinician 4	clinician 5
patient 1	yes	yes	I don't know	I don't know	yes
patient 2	yes		yes	yes	yes
patient 3	yes	yes	yes	yes	yes

11 deceased patients with RVGE as secondary diagnosis

	clinician 1	clinician 2	clinician 3	clinician 4	clinician 5
patient 4	no	no	no	no	no
patient 5	yes	I don't know	no	no	no
patient 6	yes	no	no	no	no
patient 7	no	no	no	no	no
patient 8	no	no	no	no	no
patient 9	no	no	no	no	no
patient 10	no	no	no	no	no
patient 11	I don't know	I don't know	no	no	no
patient 12	no		no	no	no
patient 13	I don't know	I don't know/no	no	no	no
patient 14	no	no	no	no	no

The clinicians agreed that two of the three patients with RVGE as main diagnosis would not have died if they were not infected by rotavirus; the same conclusion can probably be made for the third patient. Most clinicians agreed that almost all of the patients with RVGE as secondary diagnosis would have died, even without being infected by rotavirus. However, one clinician disagreed on this for 2 of the 14 patients.

Therefore, in base case analysis we assume that 3 children die due to RVGE over a period of 5 years (1999-2004). In probabilistic sensitivity analysis we vary this number according to a beta distribution. Moreover, we assume that only children below 3 years of age die due to RVGE. Jit et al.[29] reported the mean age of children for whom rotavirus was believed to be the aetiological agent responsible for death to be one year of age in England & Wales, with a range of 4 months to 2 years of age.

2.2.2.7 *Genotype-specific distribution of RVGE strains in a Belgian hospital*

The variation in genotype-specific distribution of RVGE strains in Belgium is taken into consideration in sensitivity analysis (see further '2.5.2 Serotype-specific vaccine efficacy').

In literature, different RVGE strains are often referred to as different genotypes or serotypes. The difference between 'genotype' and 'serotype' is explained hereafter.

The genome of rotaviruses consists of 11 segments of double-stranded RNA and is enclosed within three concentric protein layers. VP6 constitutes the middle capsid and determines serogroup antigen specificity (A–G). RVs of Group A are differentiated by

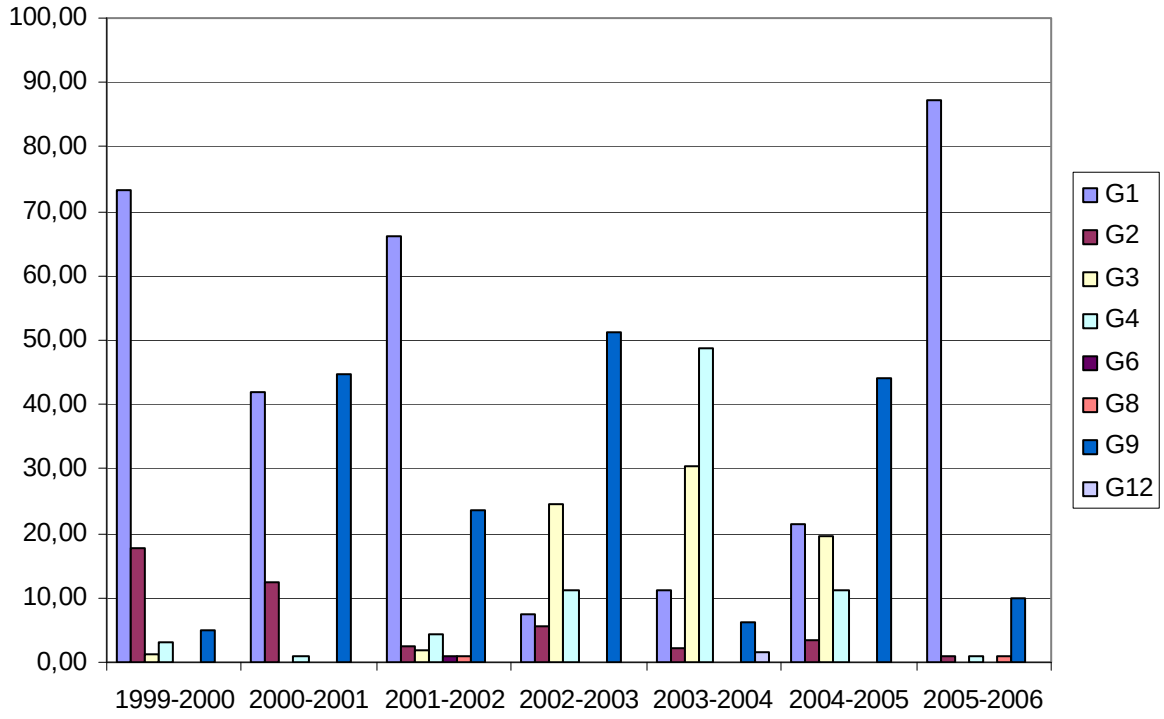
serotype which is determined on the basis of the antigens expressed on the outer viral capsid (viral protein 7 [VP7; glycoprotein defines G-type] or VP4 [protease-cleaved defines P-type]). Similar to the classification of influenza viruses, RV classification is a binary system that includes both the VP4 and VP7 types. The serotype and genotype of a particular G-type antigen usually match, and therefore RVs are generally referred to by their serotype alone (e.g. G1, G2, G3 etc.). Because there are greater numbers of, and variation in, P-type genotypes than serotypes, concordance for P-type antigens is rare. Accordingly, P-type antigens are denoted with their genotype referenced in brackets (e.g. P[4], P[8]). Hence, rotavirus genotypes are different groups of rotaviruses based on their genome (11 double-stranded RNA segments), whereas serotypes are based on their cell surface antigens.

The distribution of rotavirus genotypes can change very abruptly from one season to the next (Fig. 2.16). In the 1999-2000 rotavirus year G1 was the dominant type (72% of all serotyped patients) and G9 was present in 5% of the rotavirus-positive patients. In the 2000-2001, 2002-2003 and 2004-2005 seasonal years, G9 appeared as the dominating strain (45%, 53% and 44%, respectively). In the 2001-2002 seasonal year, (i.e. between two G9 epidemic years), G1 was dominating (66%) but G9 was still present in 24%. In the 2003-2004 seasonal year another genotype, G4, dominated (49%). From 2002 to 2005 also the G3 genotype accounted for 20-30% of the cases. In season 2005-2006 almost all cases were caused by RV genotype G1 (87%) (data 1999-2003: Rahman et al.[16], later data: Van Ranst, M. and Matthijnssens, J., pers. comm. 2007). These data come from a large Belgian hospital in Leuven. For season 2004-2005 also data from the REVEAL study (Antwerp) are available. This study shows a slightly different serotype distribution for season 2004-2005: 28% G1%, 26% G9, 24% G4, 12% G3 and 10% G2, suggesting that serotype distribution is also geographically dependent.

Moreover, a new strain is able to establish itself very quickly as a (temporary) predominant genotype. The first introduction of G9 isolates in the Belgian population was recorded in 1997, and in the 2000-2001 seasonal year, G9 appeared already as the dominating strain [16].

For a small selection of the samples for which the G-genotype was determined, also the P-type was determined. Only one exception on the most common combinations (G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]) was observed: G3P[14].[30, 31] The other G-types were as follows: G12P[8], G8P[4] (for the G8 sample of 2001-2002, no P-type was determined) and G6P[6].[16, 32]

Figure 2.16: Percentage of appearance of different RV genotypes in a large Belgian hospital, for different seasons. Sample sizes for the different seasons are 164 (1999-2000), 112 (2000-2001), 115 (2001-2002), 232 (2002-2003), 181 (2003-2004), 204 (2004-2005) and 111 (2005-2006) (data 1999-2003: Rahman et al.[16], later data: Van Ranst, M. and Matthijnssens, J., personal communication, March 2007)



2.2.3 Costs associated with rotavirus infections

For each of the health outcomes described above, the accompanying costs are determined. Data on costs associated with RVGE were obtained from the coupled MKG-MFG data, Carenet and the CM survey. The MKG-MFG and Carenet datasets contain costs of hospital stays for RVGE diagnosed children, whereas the CM survey provides cost data on children who tested positive for rotavirus in the hospital (costs other than hospital stay, e.g. GP consultation before/after hospital stay) and in an ambulatory setting. The cost due to GP visits without RV test is calculated as the total cost for all GP visits minus 2.7% of the total costs for all RVGE related hospitalizations. This is because 2.7% of all children hospitalized for RVGE are referred to the hospital by a GP (MKG data). This adjustment is made to avoid double counting of costs. The full costs for GP and Ped visits with RV positive tests were taken into account, because these data are based on children for whom a rotavirus test was asked in an ambulatory setting (as compared to the hospital).

Each subheading in this section shows the cost for one health outcome, and starts with a box stating the estimates that will be used in base case and sensitivity analysis in our cost-utility analysis for that health outcome.

2.2.3.1 *Hospitalizations*

The total cost for one rotavirus episode of a child **hospitalized** with RVGE as main diagnosis, is calculated as the sum of the mean total cost for the hospital stay and the mean total cost for health care other than the hospital stay (i.e. €732 + €84 = €816). In sensitivity analysis, both costs are altered according to a gamma distribution (obtained by fitting a distribution through the data).

For each RVGE episode that includes a stay at the hospital, the average costs for that hospitalization is determined. Additionally, the average costs for health care utilisation outside of hospital (eg, GP consultations, medication) are estimated along with personal direct costs (such as extra diapers). We note that the average costs for hospitalizations based on the MKG-MFG include children younger than 7 years whereas the non-hospital costs are obtained from surveying families of children younger than 2 years old (known to have been tested positive for rotavirus).

Costs for hospital stays

Costs for hospitalization due to RVGE as main or secondary diagnosis are obtained from Carenet and MKG-MFG data and are compared hereafter.

CARENET

For each patient included in Carenet, costs paid by the National Health System (i.e. direct health care costs for RIZIV/INAMI) are available together with data on co-payments by the patient and his/her private insurance (mainly "remgeld" and "supplements").

Mean costs of remgeld, remgeld+supplements and total cost (i.e. remgeld+supplements+NHS) are similar for the different age groups (Table 2.11), but slightly different for seasons 2004-2005 and 2005-2006 (Table 2.10). Average total costs and remgeld+supplements for patients with RVGE as main diagnosis are higher in 2004-2005 compared to 2005-2006 (total costs: €855 and €732, remgeld+supplements: €221 and €111). Remgeld is slightly lower in 2004-2005 compared to 2005-2006 (€91 and €100). Patients with RVGE as main diagnosis pay up to €1344 (remgeld+supplements), the maximum total cost for a patient is €4760. The largest costs (maxima) are for children under 2 years old.

Costs for patients with RVGE as any diagnosis are more or less similar as costs for patients with RVGE as main diagnosis.

Table 2.10: Mean and standard error, minimum and maximum cost of hospitalization (euros) for children under 7 years old, hospitalized with RVGE as main and any diagnosis, for epidemic seasons 2004-2005 and 2005-2006.

	RVGE main diagnosis					RVGE any diagnosis				
season	n	mean	ste	max	min	n	mean	ste	max	min
remgeld+supplements+NHS										
2004-2005	1013	855	10	4760	338	1118	895	12	6635	276
2005-2006	1698	732	5	2009	126	1819	762	6	3960	126
remgeld+supplements										
2004-2005	1013	221	5	1344	0	1118	228	5	1344	0
2005-2006	1698	111	1	664	0	1819	116	2	1285	0
remgeld										
2004-2005	1013	91	1	299	0	1118	95	1	1024	0
2005-2006	1698	100	1	263	0	1819	102	1	283	0

Table 2.11: Mean and standard error, minimum and maximum cost of hospitalization (euros) for children hospitalized with RVGE between 2004 and 2006, by age and for RVGE as main and any diagnosis.

	RVGE main diagnosis					RVGE any diagnosis				
age	n	mean	ste	max	min	n	mean	ste	max	min
remgeld+supplements+NHS										
0	1292	781	8	2646	31	1468	840	10	6635	31
1	1147	775	8	4760	332	1198	795	9	4760	332
2	405	764	10	1833	31	418	775	11	1833	31
3	172	752	16	1795	356	183	763	16	1795	356
4	53	773	30	1388	407	54	777	30	1388	407
5	40	774	50	2181	398	42	777	48	2181	398
6	10	737	49	948	500	0				
remgeld+supplements										
0	1292	149	3	1344	0	1468	158	4	1344	0
1	1147	164	4	938	0	1198	170	4	1088	0
2	405	152	5	760	0	418	154	5	760	0
3	172	150	7	684	13	183	156	8	684	13
4	53	165	16	607	23	54	167	16	607	23
5	40	165	18	493	57	42	162	17	493	57
6	10	171	29	369	95	0				
remgeld										
0	1292	95	1	263	0	1468	100	1	1024	0
1	1147	95	1	299	0	1198	96	1	299	0
2	405	97	1	171	0	418	98	1	171	0
3	172	96	2	166	0	183	96	2	166	0
4	53	91	3	136	23	54	92	3	136	23
5	40	98	4	150	12	42	98	4	151	12
6	10	91	9	127	33	0				

MKG-MFG

Costs paid by the National Health System (NHS, i.e. direct health costs for RIZIV/INAMI in Belgium) are also available from the MKG-MFG data, but no data on co-payment of the patient and his/her private insurance are available. We compare the NHS costs of MKG-MFG with the ones obtained from Carenet, and give a short overview of the contribution of different categories of medical care (e.g. nursing days and pharmaceutical products) to the total NHS cost. Data are available for the years 2000 until (includes) 2004, but due to a change in hospital financing in April 2002, we only use cost data of the season 2003-2004. The 'forfaits' for clinical biology (i.e. about 75% of the total cost) are not included in the cost category 'clinical biology and nuclear medicine in vitro', but in the category 'medical deliveries'.

The mean cost paid by NHS for a hospitalization with RVGE as main/any diagnosis is €693 respectively €809 for season 2003-2004 (Table 2.12). The estimate for hospitalization cost

for RVGE as main diagnosis is comparable with the mean NHS cost obtained from Carenet (NHS cost = 'remgeld+supplements+NHS' – 'remgeld+supplements' = €855 – €221 = €634 for season 2004-2005 and €621 for season 2005-2006). For our analysis, we use the data obtained from Carenet from the last season (2005-2006) for the estimate of the total cost of a hospital stay with RVGE as main diagnosis (i.e. NHS+remgeld+supplements).

The largest cost for the NHS related to RVGE hospitalization is due to costs for medical deliveries (62% of all RVGE hospitalization costs for NHS for season 2003-2004), followed by the payment of nursing days (about 30%). The distribution of costs over the different categories is more or less the same for hospitalizations with RVGE as main and any diagnosis (Table 2.12).

Table 2.12: Mean and standard error, minimum and maximum cost of hospitalization for NHS (euros) for children under 7 years old, hospitalized with RVGE as main and any diagnosis, for season 2003-2004. Costs are given for different categories. For each category, also the cost summed over all hospitalizations is given ('sum'), and the percentage of the total costs.

	RVGE main diagnosis (N=4020)					RVGE any diagnosis (N=6708)				
	mean	min	max	sum	%	mean	min	max	sum	%
TOTAL	**693**	8	214			**809**	214	51,598		
nursing days	221	35	2938	889,270	31.90	241	35	4318	1,617,604	29.86
medical deliveries	427	133	14019	1,715,774	61.54	499	133	28049	3,348,033	61.79
clinical biology and nuclear medicine in vitro	25	0	2769	99,784	3.58	30	0	4398	198,188	3.66
pharmaceutical products	20	0	8003	80,712	2.90	34	0	11059	226,463	4.18
blood, blood plasma, mothermilk and radio-isotopes	0.3	0	260	1,234	0.04	3	0	8267	13,610	0.25
implantations	0.3	0	653	1,070	0.04	2	0	2230	14,267	0.26

Non-hospital costs

These data are obtained from the CM survey. Complete questionnaires are obtained for 90 hospitalized (30 Walloon, 60 Flemish) children with RVGE, extracted from the Carenet database. We first investigate influential factors for the costs of RVGE episodes, other than those related to hospital stay. Next, the mean non-hospital cost for rotavirus episodes is discussed.

INFLUENTIAL FACTORS

Some patients are admitted to the hospital for other reasons than vomiting and/or diarrhoea. It is likely that the costs for these patients differ from the costs for patients admitted for vomiting and/or diarrhoea. Therefore we investigate first if the reasons for hospital admission influence the mean cost of hospitalization (other than hospital stay). Moreover we compare the costs of patients who acquired the symptoms of RVGE more than one day after hospital admission with the patients who have symptoms of vomiting and/or diarrhoea at day 0 or 1 of hospital admission. Then we assess whether the costs are less for children who already experienced previous episodes of diarrhoea and/or vomiting with children experiencing for the first time diarrhoea and/or vomiting. We also verify if costs are different for different age groups. Finally, we discuss the factors contributing the most to the total costs.

Effect on the total costs of clinical reason for hospital admission

The clinical reason of hospital admission is for most children vomiting and/or diarrhoea, with the following exceptions:

"varicelle et dehydratatie" (vomiting/diarrhoea at day 1 of hospital admission)

"anurie" (vomiting/diarrhoea at day 4 of hospital admission)

"bronchiolite-otit-rota sans diarh au depart" (vomiting/diarrhoea at day 2 of hospital admission)

"reflux gastrique" (vomiting/diarrhoea at day 7 of hospital admission)

"double otite, puis RV" (vomiting/diarrhoea at day 8 of hospital admission)

"hoge koorts" (vomiting/diarrhoea at day 1 of hospital admission)

"huilen" (vomiting/diarrhoea at day 2 of hospital admission)

Only for the case that is highlighted in italic (a one year old child), the total cost of the rotavirus episode (i.e. €827.51) is far more expensive compared to the total costs for the episodes of the other children (range €0 - €385.51). The large total cost is mainly caused by a large cost for two requested lab tests (€ 594.19). Also, an imaging of € 73.01 was performed. We investigate the impact of this case on the average total cost per rotavirus episode by including and excluding it for calculating average total direct medical costs and copayments ('remgeld+supplements').

Effect on the total costs of day after hospital admission showing vomiting and/or diarrhoea

In the above mentioned cases with diagnoses other than vomiting and/or diarrhoea, there are 5 patients that got diarrhoea or started vomiting more than one day after hospital admission. There are two other cases for which vomiting/having diarrhoea is reported to start more than one day after hospital admission. These cases have the following diagnoses:

"vomissement" (vomiting/diarrhoea at day 4 of hospital admission)

"déshydratation - sur 2 jours, avait perdu 2,5kg. " (vomiting/diarrhoea at day 3 of hospital admission)

Except for the case highlighted above (in italic), the total cost for all these 7 patients (7% of all hospitalized patients) is not substantially different from the average total cost of all hospitalized cases (the total costs vary between €30 and €398.0). Moreover, these patients are not sick for a longer duration than the other patients for which a questionnaire was completed (data not shown). The remaining 57% and 36% of the hospitalized children got diarrhoea/ started vomiting at day 0 of hospital admission, respectively at day 1 of hospital admission. The total cost of a rotavirus episode is not different for patients starting to vomit/have diarrhoea at admission day 0 (mean $\pm$ se= €114 $\pm$ 8) and 1 (mean $\pm$ se= €99 $\pm$ 10). In view of this finding, we choose not to distinguish total costs based on the onset of the symptoms described as vomiting or having diarrhoea.

Effect on the total costs of experiencing previous episodes of diarrhoea/vomiting

For 63% of the children, it was the first time they experienced diarrhoea/vomiting, for 18% it was the second time they had episodes of diarrhoea/vomiting. The total cost is very similar for patients without diarrhoea/vomiting episodes before the rotavirus episode (mean $\pm$ se = €103.66 $\pm$ 6.83, median=104.02) and patients with diarrhoea/vomiting episodes before the rotavirus episode at hand (mean $\pm$ se = €121.80 $\pm$ 14.20, median=107.63).

Effect on the total costs of age

There is no substantial difference in total costs between children of the different age groups (Table 2.13), nor in co-payments ('remgeld+supplements') (data not shown) between children of the different age groups (with the exception for age groups 4 and 5, but only 4 of the 90 children belonged to this age group). Therefore we assume the non-

hospital cost for a child hospitalized for RVGE is the average cost over all age groups (see next subheading).

Table 2.13: Median, quantiles, minimum and maximum of total cost (remgeld+supplements+NHS, in euros) of a rotavirus episode for a hospitalized child, by age (in years).

age	0	1	2	3	4	5	6
Max	260.78	947.51	215.81	398.01	69.92		
90%	184.91	237.11	190.99				
75%	156.04	123.19	157.34	121.36			
Median	**110.56**	**99.49**	**118.54**	**96.22**	**39.45**	**17.75**	**100.09**
25%	75.72	59.19	76.55	82.62			
10%	56.61	32.30	35.03				
Min	24.62	28.50	2.500	75.87	30.80		
N	27	29	20	9	3	1	1

Factors contributing to the total cost

Very few parents/caregivers of patients reported costs for the following categories:

Medical costs:

- EDV (reported for only 5 patients, one of them visited 3 times the emergency department)
- Ambulatory technical investigations: imaging (only 5 patients) and other (0 patients)
- Antibiotics (only 5 patients)
- Ambulatory care products that are reimbursed (only 1 patients)

Non-medical or personal costs:

- Ambulatory special food (only 19 patients): costs between €2.5 and €19.94 (costs are not positively correlated with the number of packages, which ranges from 1 to 4)
- Extra help of remunerated babysitter (only 8 patients): costs between €20 (for one day) and €87.5 (for 5 days); all of the parents of these 8 patients have higher education (except for one mother, she had degree of higher secondary education)

The costs of imaging and lab requests weigh substantially on the total cost of a rotavirus episode. For instance, the total cost of the RV episode for the five patients for whom imaging is requested, is among the 6 highest of all patients in the survey.

COST OF RVGE EPISODE OTHER THAN HOSPITAL STAY

The mean direct costs (other than costs of hospital stay) for a rotavirus episode of a hospitalized child under 7 years old, between 2004 and 2006, is €83.66 (remgeld+supplements+NHS) of which €43.62 are co-payments (remgeld+supplements) (Table 2.14).

Table 2.14: Mean and standard error, minimum and maximum cost (other than costs of hospital stay) of a rotavirus episode of a hospitalized child under 7 years old, between 2004 and 2006, in euros.

	n	mean	ste	max	min
	with extreme observation of €827,51				
remgeld+supplements+NHS	90	**83.66**	10.18	827.51	0
remgeld+supplements	90	**43.62**	3.45	189.65	0
	without extreme observation of €827,51				
remgeld+supplements+NHS	89	75.30	5.87	385.51	0
remgeld+supplements	89	41.98	3.07	184.07	0

2.2.3.2 Nosocomial infections

In base case analysis we assume the cost for a **nosocomial RVGE infection** is the product of the daily cost of a hospital stay for a child with RVGE as main diagnosis and the average additional length of stay due to a nosocomially acquired RVGE, i.e. €209.70 * 4.4 = €922. In sensitivity analysis we alter the daily cost according to a gamma distribution (obtained by fitting a distribution through the data), and the extra length of stay between 1.7 and 5.9 (triangular distribution).

We assume the cost for a nosocomial RVGE case lies in the extension of the duration of hospital stay due to the hospital acquired rotavirus infection. The average extra length of stay due to a hospital acquired RVGE is assumed to be 4.4 days (see above). From the Carenet dataset we calculate the mean daily cost of a hospital stay for children with RVGE as main diagnosis, under 7 years old, averaged over all cases from season 2005-2006. The mean $\pm$ se daily cost (remgeld+supplements+NHS) is € 209.70 $\pm$ 1.64 (range € 12.75 – € 806.21). Hence we assume the cost of an extra day due to RVGE is the same as the mean daily cost when hospitalized for RVGE as main diagnosis. After multiplying this mean daily cost by the average extra length of stay due to a nosocomially acquired RVGE, we get that on average a child that acquired RVGE in the hospital, costs an extra €922.

2.2.3.3 Outpatients ('dag hospitalisaties')

We assume the total cost for a RVGE episode of an outpatient child to be equal to the total cost for an ambulatory RVGE episode (i.e. €129, see below).

2.2.3.4 GP visits, RVGE positive

In base case analysis, we assume the cost of a RVGE episode (positive tested) including at least one **GP visit** is €129. In sensitivity analysis we alter this cost according to a gamma distribution (obtained by fitting a distribution to the data).

These data are obtained from the CM survey. Complete questionnaires are obtained from 86 ambulatory (10 Walloon, 76 Flemish) children that are positively tested for rotavirus. All children are younger than 2 years (with the exception of one child of 2 years old). The lower number of french ambulatory children is due to a smaller number of rotavirus positive tests for Wallonia. We first investigate influential factors on the costs of an ambulatory RVGE episode. Next, the mean cost of an ambulatory RVGE episode is determined.

Influential factors

There is one child (one year old) for which the total cost of the rotavirus episode (i.e. €514.79) is far more expensive compared to the total costs of the other episodes (range €0-€352.06). The large total cost is mainly caused by a large cost for 5 requested lab tests (€ 373.05). We investigate the impact of this case on the average total cost per rotavirus

episode by including and excluding it for calculating average total and 'remgeld+supplements' costs.

Effect on the total costs of experiencing previous episodes of diarrhoea/vomiting

For 64% of the children, it was the first time they had diarrhoea/vomiting, for 18% it was the second time they had episodes of diarrhoea/vomiting. The total cost is very similar between patients with no diarrhoea/vomiting episodes before the rotavirus episode of concern (mean + se = €130 + 10, median=116) and with diarrhoea/vomiting episodes before the rotavirus episode of concern (mean + se = €139 + 14, median=110).

Effect on the total costs of age

The age of ambulatory rotavirus positive children is below or equal to 2. There is no strong difference in total costs between children of the different age groups (Table 2.15), nor in 'remgeld+supplements' costs between children of the different age groups (data not shown). Therefore we can use cost per ambulatory rotavirus episode averaged over all age groups.

Table 2.15: Median, quantiles, minimum and maximum of total cost (remgeld+supplements+NHS, in euros) of a rotavirus episode for a hospitalized child, by age (in years).

age	0	1	2
Max	367.06	565.790	
95%	268.95	222.270	
90%	213.04	191.210	
75% Q3	161.22	155.370	
Median	**127.02**	**105.530**	**91.52**
25% Q1	93.34	97.195	
10%	65.11	80.260	
5%	52.79	53.630	
Min	50.91	7.500	
N	45	40	1

Factors attributing most to the total cost

For the ambulatory cases, the same results are found as for the hospitalized patients: the costs of imaging and lab requests weight substantially on the total cost of a rotavirus episode.

Cost of RVGE episode with at least one GP visit

The mean cost of an ambulatory rotavirus episode of a child under 3 years old, between 2004 and 2006, is €128 (remgeld+supplements+NHS) of which €61 are co-payments (remgeld+supplements) (Table 2.16).

Table 2.16: Mean and standard error, minimum and maximum cost of an ambulatory rotavirus episode of a child under 3 years old, between 2004 and 2006, in euros.

	n	mean	ste	max	min
	with extreme observation of €514.79				
remgeld+supplements+NHS	86	**128**	8	515	0
remgeld+supplements	86	**61**	4	252	0
	without extreme observation of €514.79				
remgeld+supplements+NHS	85	124	6	352	0
remgeld+supplements	85	59	3	171	0

We do not consider the incidence of all ambulatory rotavirus episodes, but only the number of GP visits due to rotavirus gastroenteritis. From the patients for whom the CM questionnaire was completed, 67% visited at least once a general practitioner (the others visited a specialist/pediatrician only, or did not visit a general practitioner/specialist). For these patients, the mean direct medical costs remgeld+supplements+NHS costs (mean $\pm$ se = €129 $\pm$ 7, range €49 – 352) is almost the same as the mean cost for all ambulatory patients.

2.2.3.5 Pediatrician visits, RVGE positive

In base case analysis, we assume the cost of a **RVGE positive** child who visits a **pediatrician,** to be €145. In sensitivity analysis we alter this cost according to a inverse gauss distribution (obtained by fitting a distribution through the data).

These data are obtained from the CM survey. The mean cost of an ambulatory rotavirus episode of a child under 2 years old, between 2004 and 2006, is €145 (remgeld+supplements+NHS) of which €63.79 are co-payments (remgeld+supplements) (N=22).

2.2.3.6 GP visits, not tested

In base case analysis, we assume the cost of a child with RVGE who visits a **GP, but is not tested,** is €54. In sensitivity analysis we alter this cost according to a lognormal distribution (obtained by fitting a distribution through the data).

It is likely that for a child with rotavirus who was not tested, the disease is less severe compared to a child for whom a test was performed. Therefore we do not use the same cost per GP visit with or without the child being tested for RVGE. We assume the cost for a child not tested for RVGE that visits a GP, to be the sum of the cost of one GP visit, plus costs for ambulatory medication, care products, extra diapers and food. To obtain these costs, we use the CM survey. We calculate the average costs for each of the different categories (GP visit, ambulatory medication, care products, etc.) for 58 children from the CM survey who went only once to a GP. The cost of a child with RVGE who visits a GP, but is not tested, is calculated to be €53.95.

2.2.3.7 No medical care

In base case analysis, we assume the cost of a child with RVGE who visits once a **GP** is €17. In sensitivity analysis we alter this cost according to a normal distribution (obtained by fitting a distribution through the data).

The costs for a child for whom no medical care is sought, is assumed to be the sum of the costs for care products, extra diapers and food (not repaid by the NHS). To obtain these costs, we use the CM survey. We calculate the average costs for each of the different categories (ambulatory medication, care products, etc.) for 58 children from the CM

survey who went only once to a GP. The cost of a child with RVGE who visits once a GP is calculated to be €16.9.

2.2.3.8 Deaths

As all patients who **died** are first hospitalized with RVGE as main diagnosis, we assume the cost for these patients is equal to the costs for hospitalized patients (see above).

2.2.3.9 Work loss

In base case analysis, we assume an average **work loss** of €374 for a case of hospitalization, nosocomial infection and death. For a RVGE episode including a GP visit, pediatrician visit or treatment as an outpatient, we assume an average work loss of €218. For parents/caregivers of patients for whom no medical care is sought, we assume an average work loss of €109.

For the societal point of view (as opposed to the health care payer point of view), we add to the aforementioned costs, the work losses caused by an episode of RVGE. These work losses are estimated by the human capital method. Unpaid caregiver/babysitters' time off work (i.e. usually one of the parents) is valued at their average salary, accounting for unemployment. Paid babysitters' time is valued at the remuneration they received for their task. Further information on the theoretical foundations for this approach can be found elsewhere.[33-35]

Data on work loss of caregivers for RVGE infected children is obtained from the CM survey. All parents reported the use of an unpaid babysitter.

Hospitalized RVGE cases: 39% of the unpaid caregivers/babysitters are unemployed, 38% in white collar jobs ('bediende') and 10% in blue collar jobs ('arbeider'). The majority (57%) of the babysitters did not report work loss for caretaking during the rotavirus episode, 33% experienced work loss of 0.5 - 2.5 days. For two babysitters, a work loss of 7 days is reported; however, these 2 are also reported to be unemployed. Eight other people reported work loss of 1 or 2 days of an unemployed, unpaid babysitter.

Ambulatory RVGE cases: 63% of the unpaid babysitters are white collar ('bediende'), 23% unemployed. 55% of the babysitters did not report work loss due to babysitting the rotavirus infected child, the others experienced work loss of 0.5 - 2.5 days, with the exception of one babysitter who experienced 4 days work loss.

To estimate the work loss in costs, we multiply the mean number of days of work loss for ambulatory and hospitalized patients by the average daily costs of labour (data from the RSZ and the National Bank, reported in 'Het absenteïsme in België 2005').

The mean number of half days of work loss for ambulatory and hospitalized patients is sampled from a triangular distribution (obtained by fitting a distribution through the data), with mean 5 for hospitalized cases (minimum zero and maximum 14) and 3 for ambulatory cases (minimum zero and maximum 8). The average daily salary of a blue collar worker ('arbeider') is €112.58, and that of a white collar worker is ('bediende') €164.56 ('Het absenteïsme in België 2005' ZebraZone European Research & Service Center, 2005; costs are inflated to 2006). No salaries are available for self-employed people ('zelfstandigen') (2 of the 86 ambulatory cases and 5 of the 90 hospitalized cases), for which we use a white collar worker's salary. For caretakers reporting to be unemployed, costs due to work losses were set to zero. Taking into account the proportion of caretakers that are white collar and blue collar, the average daily work loss for unpaid babysitters of ambulatory RV positive patients is calculated to be €160.62. This value is taken as an estimate of work loss per RVGE related GP visit, pediatrician visit and outpatient visit. For RVGE hospitalized patients the average work loss is €155.90. This value is taken as an estimate of work loss per RVGE related hospitalization, nosocomial infection and death. The number of extra days in the hospital due to nosocomial RVGE infection is comparable with the number of days in the hospital due to RVGE. Therefore the assumption of equal work loss in both cases seems reasonable. For caregivers who do not seek medical care for their infected child, we assume half of the work loss as for caregivers of ambulatory RV positive patients, i.e. €80.31.

2.3 HEALTH RELATED QUALITY OF LIFE (QOL) IMPACT

In base case analysis we assume for healthcare payer perspective, a **loss** in Quality Adjusted Life Years (**QALY)** for a child with RVGE of 0.0022, and a QALY loss for one caregiver of 0.001839 for all health outcomes except 'no medical care'. For RVGE episodes for which no medical care is sought, QALY loss is assumed half of the QALY loss for the other health outcomes. In univariate sensitivity analysis we investigate the results of the cost-utility analysis with no QALY loss for a caregiver and with QALY loss for two caregivers. Moreover, QALY loss for RVGE infected children not seeking medical care is varied between zero and equal values as for the other health care outcomes. For the societal perspective, no QALY loss for caregiver was assumed (because already incorporated in work loss of the caregiver).

Estimating the Health Related Quality of Life (HRQOL) is complex when it comes to the health of children[36], when the HRQOL impact at the individual level is spread out over a long period of time (e.g., neurological sequelae), or when it relates to mild, generally short-lived disease affecting a large group of people (e.g., chickenpox, influenza).[8] However, in order to create a consistent basis of comparison for health outcomes, a common outcome measure is needed. The most widely accepted measure of health gains (without monetisation) is currently the Quality-Adjusted Life-Year or QALY, in which both aspects of longevity and quality of life are quantified. The theoretical foundation for the methods applied in our analysis, is one of maximisation of aggregate utility (in an extra-welfarist approach approximated by QALYs), given a budget constraint. From the health care payer's perspective this implies that direct costs are accounted for in the numerator of the cost-effectiveness ratio, and that aggregated gains in QALYs are accounted for in the denominator, *no matter who receives them*. Since the expansion of the HRQOL impact from just the patient to the patient's caregivers is a contentious issue. [8, 37] , we are showing the results in sensitivity analysis for various expansion levels in the QALY estimate.

A prospective Canadian study[38] was set up specifically to assess the QOL impact of AGE and RVGE in children and their caretakers. 59 family physician or pediatrician clinics across Canada recruited children less than 3 years of age presenting with gastroenteritis (GE) symptoms, of which 200 were tested to be rotavirus positive. The mean QALY loss for the child with RVGE was found to be 0.0022 (HUI-2 (Health Utilities Index)) and 0.00735 (VAS (Visual Analogue Scale)). For the caregiver the mean QALY loss was calculated to be 0.002 (EQ-5D (EuroQOL)) and 0.003212 (VAS). QALY losses were calculated over a period of several weeks, using point estimates at baseline assessment (when children presented with AGE at primary care practices and hospital clinics and were enrolled in the study), week 1 and week 2 after baseline assessment. QALY loss at onset of symptoms (on average 2.8 days before baseline assessment) was assumed to be equal to QALY loss at baseline assessment. The QALY loss is likely to be slightly overestimated, because the QALY loss is likely lower at onset of symptoms (symptoms are less severe); and, because QALY loss might be lower for infected children of 3 years of age or older. The QALY loss is also dependent on the measurement tool used (the VAS produced larger QALY losses for both children and caretakers). Because the HUI-2 and EQ-5D methods are classification systems based on different valuation methods on a large population, these estimates are used in base case analysis.

Hence, in base case analysis we assume a loss in QALY for a child with RVGE of 0.0022. For the health care payer perspective, we assume also QALY loss for one caregiver of 0.001839 for all health outcomes except 'no medical care'. [38] For RVGE episodes for which no medical care is sought, QALY loss was assumed half of the QALY loss for the other health outcomes. In univariate sensitivity analysis we investigate the results of the cost-utility analysis with no QALY loss for a caregiver and with QALY loss for two caregivers. Moreover, QALY loss for RVGE infected children not seeking medical care is varied from zero up to values for the other health care outcomes.

In line with the costs, also the QALY loss due to GP visits without RV test are calculated as the total QALY loss for all GP visits minus 2.7% of the total QALY loss for all RVGE related hospitalizations. This is because 2.7% of all children hospitalized for RVGE are

referred to the hospital by a GP (MKG data). Thus we avoid double counting of QALY losses.

2.4 INTERVENTION COSTS AND VACCINE UPTAKE

In base case analysis we assume a vaccine cost of €55.62 per dose for RotaRIX, and €37.08 per dose for RotaTEQ. The administration costs per dose are estimated at €5. Vaccination coverage is estimated at 98%, 98% and 97.5% for vaccinations at 2, 3 and 4 months of age.

The marginal intervention costs consist of the purchasing costs as well as the marginal administration costs of the vaccine. The current ex-factory price per dose on the Belgian market (GlaxoSmithKline Biologicals) is €61.8 for RotaRIX, and €41.2 for RotaTEQ (MERCK) ('Aanvraag tot opname aan de Commissie Tegemoetkoming Geneesmiddelen'). For this public program we are assuming bulk purchase, and reduce the ex-factory prices with 10% for the base case analysis. The resulting prices are somewhat higher than the ones used in the cost-effectiveness analyses for England & Wales[3] (RotaRIX €51.21, RotaTEQ €36.58) and Australia (Newall et al., *forthcoming*: RotaRIX €54.63, RotaTEQ €40.97).

Depending on the vaccination schedule and the opportunity of adding a new oral vaccine at an existing visit, marginal administration costs will vary. Since the current infant immunization schedule should easily accommodate the addition of an oral vaccine at months 2, 3 and 4, it can be argued that there is no additional financial payment required to include this new vaccine. However, in order to value, in an opportunity cost approach, the additional time vaccinators will need to take to explain and give the oral vaccine, it is assumed in the baseline that the marginal costs of administration are €5 per dose. In baseline analysis, we assume the administration costs per dose are equal for RotaTEQ and RotaRIX. However, as RotaTEQ is a ready-to-use vaccine whereas RotaRIX needs to be put together before it can be administered, it is likely that administration of RotaRIX is more time-consuming, and hence more costly (personal communication clinicians (under whom Dr. André Vertruyen), winter 2006-2007). Therefore, in univariate sensitivity analysis, total administration cost for two doses of RotaRIX is increased up to being equal to total administration cost for three doses of RotaTEQ (i.e. €15). The model assumes in all the analyses (baseline and sensitivity) that the fixed administration costs (e.g., for training or promotion campaigns) are zero.

As this vaccine was found to be very safe in the review in Appendix A, no costs are assigned to adverse events from vaccination.

Vaccine uptake (or coverage) estimates are based on current uptake figures in Belgium and is estimated at 98%, 98% and 97.5% for vaccinations at 2, 3 and 4 months of age (for children who also received an vaccination at 2 months of age (Theeten et al.[39] and Swennen, Vaxinfo 2005).

Vaccine coverage for option 2 (private vaccination with 2 doses of RotaRIX) is assumed to be 60% at the moment of writing, and is varied between 40% and 80%.

2.5 VACCINE EFFECTIVENESS

In base case analysis overall (i.e. not serotype-specific) **efficacy** estimates are used, in sensitivity analysis we alter the estimates according to lognormal distributions, and explore the impact of serotype-adjusted efficacy estimates.

An extensive overview of the published literature related to the efficacy of RV vaccines is given in Appendix A. Hereafter, we report and argue shortly the choice for each of the vaccine efficacy parameters used in the model.

First we discuss the estimates for overall efficacy, next for serotype-specific efficacy. Then we report about partial protection and waning of vaccine efficacy.

As studies for RotaRIX and RotaTEQ were conducted in different countries and used different endpoints, comparison of efficacy estimates should be handled with great care.

2.5.1 Overall vaccine efficacy

For the vaccine efficacy estimates, we use the estimates based on studies performed in Western countries (RotaRIX: Europe; Vesikari *forthcoming*; RotaTEQ: Finland and USA[40]). Table 2.17 summarizes the assumed vaccine efficacy estimates that are used in the baseline and sensitivity analyses of this report. In sensitivity analysis, efficacy estimates are sampled from normal distributions of the log odds ratio (= log (1-vaccine efficacy), i.e. the odds of having one of the RVGE-health outcomes in the vaccine group compared to the placebo group). Because standard deviations of log odds ratios are not always published, we derive them from the published 95% confidence intervals for the vaccine efficacy estimates using the following formula: $stdev_{logodds}$=(log odds ratio-$LL_{logodds}$)/1.96, with $LL_{logodds}$ = log (1-UL_{ve}), $LL_{logodds}$ is the lower confidence limit for the log odds ratio and UL_{ve} is the upper confidence limit for the vaccine efficacy estimate.

The efficacy estimates are based on According-To-Protocol (ATP) analyses in randomized clinical trials. ATP based estimates are used instead of ITT estimates, because of the following reasons: (1) Intention-To-Treat (ITT) estimates are not available for all of the health outcomes used in our analysis. (2) According-to-protocol estimates include all patients who received all 2 (RotaRIX)/3 (RotaTEQ) doses. If we use the ATP efficacy estimates for the percentage of children projected to receive all 2/3 doses in Belgium (based on the uptake of other vaccines), a reliable efficacy estimate is obtained. (3) Furthermore, the majority of children (for RotaTEQ: 80%) that are included in ITT analysis, but not in ATP analysis, are children who did not receive all 2/3 doses. Only a minority of children was excluded for other reasons, e.g. lost to follow-up.

For RotaTEQ, the only available efficacy estimate against RVGE hospitalizations for developed countries is based on a follow-up period of 2 years (i.e. efficacy after 2nd season, see below). Efficacy is assumed to be the same after the 1st season. This is likely to be a slight underestimation, because efficacy decreases from the 1st to the 2nd season (Appendix A).

For RotaTEQ and RotaRIX, no ATP estimates are available for efficacy against nosocomial infections, outpatient visits, GP and pediatrician consultations and deaths. For nosocomial infections we assume the same efficacy applies as for hospitalizations; for outpatient, GP and pediatrician visits we used efficacy against RVGE of any severity. Note that efficacy against RVGE of any severity includes both hospitalized and non-hospitalized RVGE cases, and hence is likely to overestimate efficacy against outpatient, GP and pediatrician visits. For efficacy against deaths, we use the estimate of efficacy against severe RVGE. We note that the definition for severe RVGE differs between RotaRIX (severe RVGE is defined as a score of 11 or more on the Vesikari scale) and RotaTEQ (severe RVGE is defined as a score of more than 16 on the 24-point severity scale of Clark & Duffy). We currently do not know the inclusion/exclusion criteria for hospitalizations and RVGE of any severity for RotaRIX (Vesikari *forthcoming*).

Table 2.17: Vaccine efficacy (VE) estimates (and lower and upper confidence limits (LCL respectively UCL)) (ATP) used in base case and sensitivity analysis, for the different health outcomes, for RotaRIX and RotaTEQ.

vaccine	health outcomes	VE	LCL	UCL
RotaRIX	Hospitalizations	100	82.3	100
	Nosocomial infections	100	82.3	100
	Outpatient visits	87	80	91.7
	GP visit, RV positive	87	80	91.7
	Ped visit, RV positive	87	80	91.7
	GP visit, no test	87	80	91.7
	Deaths	95.8	90	98.3
RotaTEQ	Hospitalizations	95.8	90.5	98.2
	Nosocomial infections	95.8	90.5	98.2
	Outpatient visits	72.7	65.6	78.4
	GP visit, RV positive	72.7	65.6	78.4
	Ped visit, RV positive	72.7	65.6	78.4
	GP visit, no test	72.7	65.6	78.4
	Deaths	98.0	88.3	100.0

2.5.2 Serotype-specific vaccine efficacy

The distribution of RV serotypes in Belgium differs between different seasons (as described before), and differs from the serotype distribution seen in the clinical trials (Vesikari, *forthcoming*, and Vesikari et al.[40]). In Vesikari *forthcoming*, 86% (31/67) of the serotyped RVGE cases (denominator includes serotypes G1, G3, G4, G9, i.e. the strains for which numbers were available) are of the G1 type. In [40] 89% (358/401) of all serotyped RVGE cases (denominator includes G1, G2, G3, G4 and G9) are of the G1 type. In Belgium, the seasonal proportion of G1 strains in the total number of serotyped strains varies from 7 to 87% for the period of 1999-2006. Therefore, we can adjust the vaccine efficacy according to the serotype distribution in Belgium (cfr. Jit and Edmunds[3]).

For RotaRIX, serotype specific estimates are available for efficacy against severe RVGE (≥ 11 Vesikari score) (ITT, 2 weeks post dose 2 through end of 1st season (mean 6 months)). The estimates for efficacy against G1, G3, G4 and G9-specific severe RVGE are based on Vesikari, *forthcoming*. Efficacy against G2-specific severe RVGE is obtained from a meta-analysis.[41] We note that the different studies included in the meta-analysis used different viral concentrations of the vaccine (i.e. equal to or lower than the final vaccine titre). G1, G3, G4 and G9-specific efficacy estimates are similar, but the G2 efficacy estimate is lower (Appendix A: Table III).

For RotaTEQ, serotype specific estimates of efficacy for the prevention of hospitalizations and emergency department visits (i.e. pooled together) are available (ITT, post 1st dose up to 2 years, MERCK 006 study, unpublished data). Non-serotype specific efficacy for the prevention of hospitalizations is slightly higher than that of non-serotype specific efficacy for the prevention of emergency department visits.[40] G1, G2, G4 and G9 efficacy estimates are similar, but the G3 efficacy estimate is slightly lower. Also serotype specific efficacy estimates against RVGE of any severity are reported, but estimates for serotypes other than G1 were based on very few cases and therefore will not be considered further.[40]

We do not have information about the efficacy against G6, G8 and G12 RVGE: no study yet estimated efficacy against G6 and G8 RVGE, and the reported efficacy estimate against G12 RVGE is uncertain because it is based on very few cases.[40] We adjust our final efficacy by assuming serotype coverage is not equal to 100%. So, we first calculate serotype-adjusted efficacy for the proportion of RV cases caused by the G1 P[8], G2 P[4], G3 P[8], G4 P[8] and G9 P[8] serotypes. Next we lower this efficacy for the proportion of serotypes that are not covered (cfr. Newall et al., *forthcoming*).

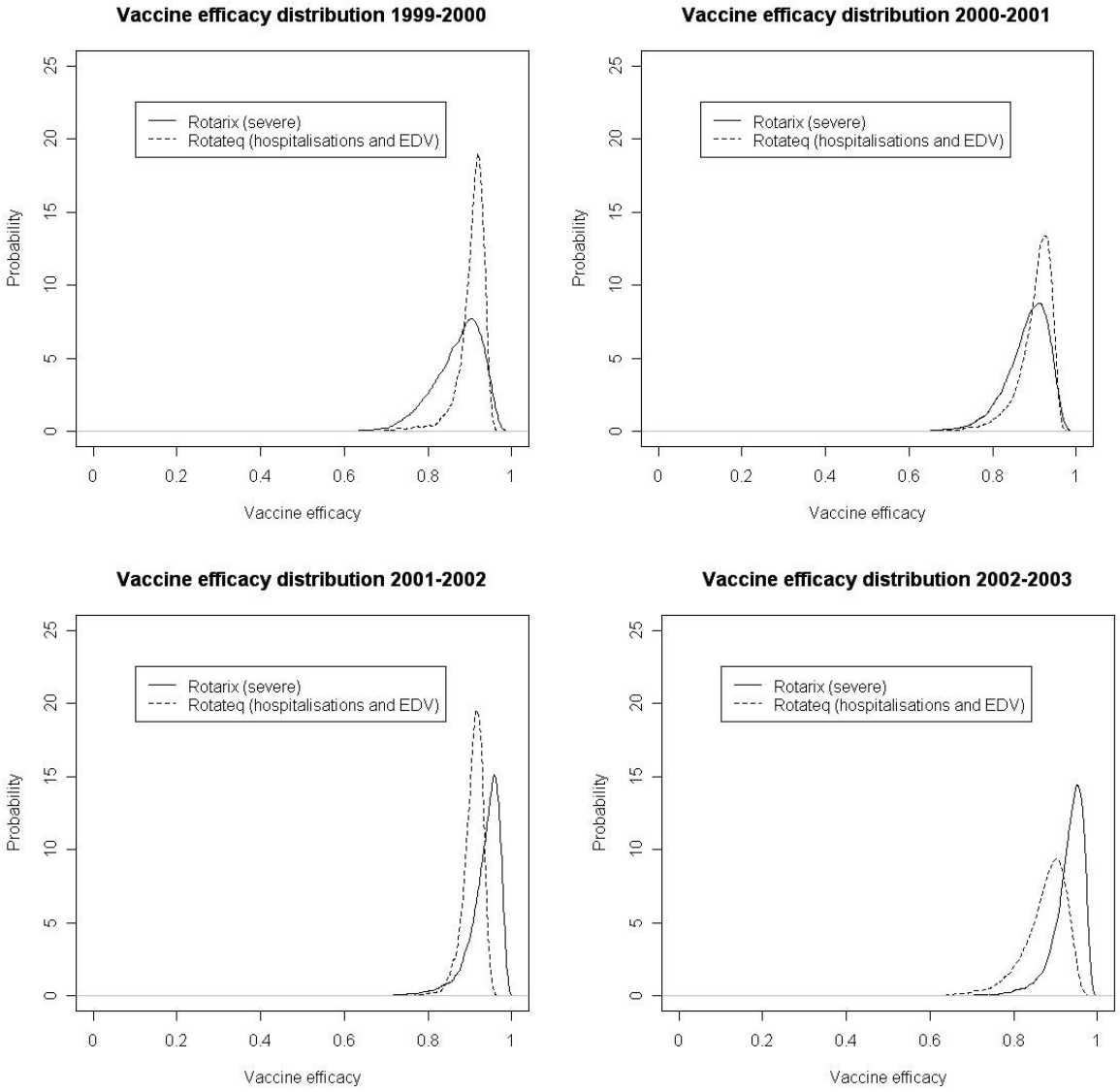
Depending on serotype distribution (i.e. epidemic season), RotaRIX efficacy against severe RVGE varies from 89% (largely caused by substantial proportion of G2P[4] strains) to 97%

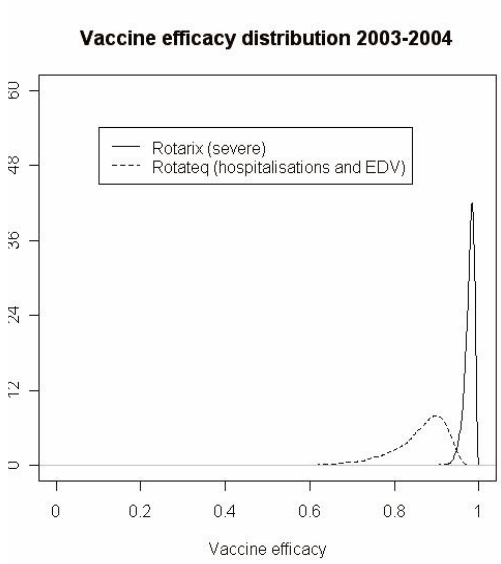
(largely caused by high proportion of G3[8] and G4P[8] strains) (Figure 2.17). RotaTEQ efficacy against hospitalizations and emergency department visits varies from 84% (mainly caused by substantial proportion of G3P[8] strains) to 91% (Figure 2.17). We have to be careful in comparing these serotype-adjusted efficacy estimates with the unadjusted estimates (Vesikari *forthcoming* and Vesikari et al.[40]), because the latter were based on ATP analysis, whereas serotype specific estimates were based on ITT analysis.

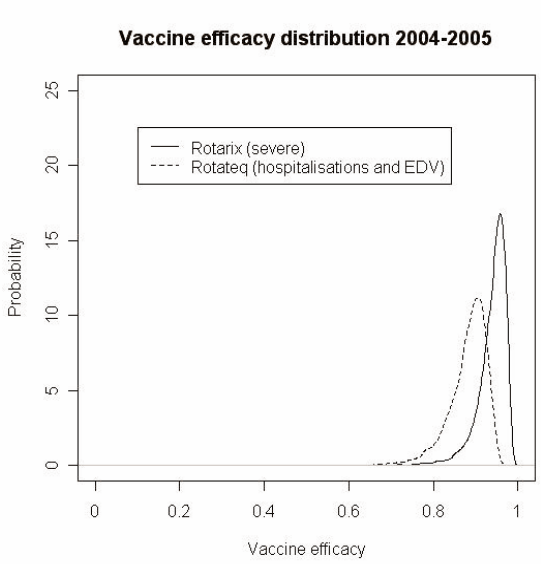
Serotype-adjusted efficacy estimates are not used in base case scenario, because 1) they are not available for all health care outcomes; and 2) the available serotype specific estimates are based on ITT analysis, whereas the overall estimates are based on ATP analysis.

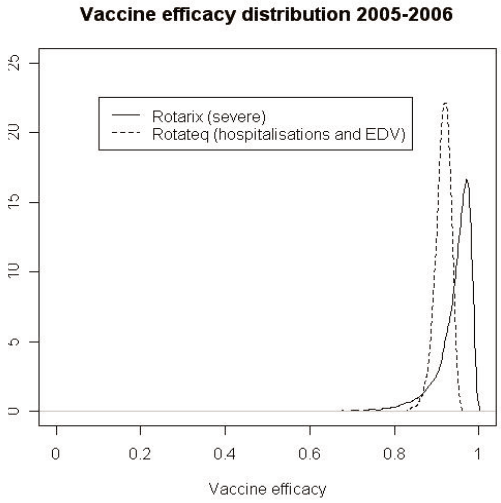
However, in univariate sensitivity analysis, impact of different serotype distributions is investigated by substituting for RotaRIX overall distributions for efficacy values against hospitalizations, nosocomial infections and deaths by serotype-adjusted efficacy against severe RVGE. For RotaTEQ, overall distributions for efficacy values against hospitalizations and nosocomial infections are substituted by serotype-adjusted efficacy against hospitalizations and emergency department visits. This is done by assigning a discrete distribution for efficacy parameter against hospitalizations, nosocomial infections and deaths, with an equal chance for each of the 6 serotype-adjusted efficacy estimates in Fig. 2.17.

Figure 2.17: Serotype-adjusted efficacy against severe rotavirus gastroenteritis (RotaRIX) and RVGE related hospitalizations and emergency department visits (RotaTEQ), for different seasons. Serotype distributions for the different season are obtained from a large Belgian hospital.




Vaccine efficacy distribution 2003-2004
Rotarix (severe)
Rotateq (hospitalisations and EDV)
0
12
24
36
48
60
0
0.2
0.4
0.6
0.8
1
Vaccine efficacy


Vaccine efficacy distribution 2004-2005
Rotarix (severe)
Rotateq (hospitalisations and EDV)
Probability
0
5
10
15
20
25
0
0.2
0.4
0.6
0.8
1
Vaccine efficacy


Vaccine efficacy distribution 2005-2006
Rotarix (severe)
Rotateq (hospitalisations and EDV)
0
5
10
15
20
25
0
0.2
0.4
0.6
0.8
1
Vaccine efficacy

2.5.3 Partial Protection

Efficacy after a single dose is assumed 90% for RotaRIX. Efficacy of RotaTEQ against hospitalizations, nosocomial infections and deaths after one dose is assumed 83%, against the other health outcomes 38%. Efficacy after 2 doses of RotaTEQ against hospitalizations, nosocomial infections and deaths is assumed 81%, against the other health outcomes 39%.

Vaccine efficacy after one dose will not have strong impact on the outcome of our model: 98% of Belgian infants would receive at least 2 doses (vaccine coverage at age 2 and 3 months is 98%), which means efficacy after one dose is only used in the model when our birth cohort is aging from 2 to 3 months. For RotaRIX, vaccine efficacy against hospitalizations after one dose is 90% (95%C.I. 9-100).[42] The same proportion is used for efficacy against the other health outcomes after one dose. For RotaTEQ, vaccine efficacy against hospitalizations and emergency department visits after one dose is reported to be 83% (95%C.I. 38-97), and efficacy against RV of any severity 38% (95%C.I. <0-70).[43] Vaccine efficacy against hospitalizations and emergency department visits after two doses of RotaTEQ is 81% (95%C.I. 50-94), and efficacy against RV of any severity 39% (95%C.I. <0-78).[43]

On the one hand, these partial efficacy values are used for our birth cohort aging from 3 months to 4 months which is vaccinated with RotaTEQ. Moreover, because vaccine coverage at 4 months of age (third dose for RotaTEQ) is 97.5%, compared to 98% at 3 months of age (second dose for RotaTEQ), 0.5% of children will never get a third dose of RotaTEQ. This is taken into account by applying RotaTEQ efficacy estimates after 2 doses for this proportion of our birth cohort.

2.5.4 Waning

In baseline analysis we assume the decrease in efficacy from one year to another (**waning**) lies between 86% and 98% (depending on the health outcome and the vaccine). In sensitivity analysis, waning rates are altered, by assigning lognormal distributions to the efficacy estimates after 1st and 2nd season.

Efficacy is shown for both vaccines to decrease from the first season to the second season (Appendix A). For RotaTEQ, one study (MERCK 005) reported vaccine efficacy after the 3rd season, which was estimated to be lower than after the 2nd season. We determine the proportional efficacy in the 2nd season as compared to the 1st season for each health outcome and vaccine (Table 2.18), and reduced the efficacy of each year/age by multiplying it with this proportion to the power (age). This means that for instance at year 2 efficacy of RotaRIX against hospitalizations is decreased by a rate 0.98^2.

For RotaTEQ estimates for both 1st and 2nd season are available for endpoints severe RVGE and RVGE of any severity. These efficacy estimates are based on a follow-up period through 2nd epidemic season. No efficacy estimates for both 1st and 2nd season against hospitalizations or nosocomial infections is available, hence estimates for decrease in efficacy against severe RVGE from 1st to 2nd season is assumed to represent decrease in efficacy against hospitalizations, nosocomial infections and deaths. Decrease in efficacy against RVGE of any severity from 1st to 2nd season is used as decrease in efficacy against outpatient visits, GP and pediatrician visits (Table 2.18).

For RotaRIX, efficacy estimates after 1st and 2nd season are available for endpoints hospitalizations and severe RVGE from a Latin American study[44]. These efficacy estimates are based on a follow-up period from 2 weeks post dose 2 until 24 months of age. Decrease in efficacy against hospitalizations from 1st to 2nd season is used as decrease in efficacy against hospitalizations and nosocomial infections; decrease in efficacy against severe RVGE as estimate for decrease in efficacy against deaths from one season to the next. No efficacy estimates for both 1st and 2nd season against RVGE of any severity is available, therefore same estimate as for RotaTEQ is used (Table 2.18).

Because for RotaTEQ, the estimate (95.8%) used for efficacy against hospitalizations and nosocomial infections after the 1st epidemic season is based on a follow-up period of 2

years, no waning is assumed for these health care outcomes from the 1st to 2nd epidemic season. For the 2nd to the 3rd season RotaTEQ efficacy against hospitalizations and nosocomial infections is assumed to decrease with a rate of 0.90[l] (Table 2.18).

Table 2.18: Proportional efficacy in the 2nd season as compared to the first season for the different health outcomes used, for RotaRIX and RotaTEQ.

vaccine	our health outcomes	health outcomes for which efficacy after 2nd season was published in studies	rate of decrease in efficacy from one year to another (applied from 1st season)
RotaRIX	Hospitalizations	hospitalizations	0.98
	Nosocomial infections	hospitalizations	0.98
	Outpatient visits	estimate for RotaTEQ	0.86
	GP visit, RV positive	estimate for RotaTEQ	0.86
	P visit, RV positive	estimate for RotaTEQ	0.86
	GP visit, no test	estimate for RotaTEQ	0.86
	Deaths	severe RVGE	0.95
RotaTEQ	Hospitalizations	severe RVGE	0.90 (from the 2nd to the 3rd season)
	Nosocomial infections	severe RVGE	0.90 (from the 2nd to the 3rd season)
	Outpatient visit	RVGE any severity	0.86
	GP visit, RV positive	RVGE any severity	0.86
	P visit, RV positive	RVGE any severity	0.86
	GP visit, no test	RVGE any severity	0.86
	Deaths	severe RVGE	0.90

3 COST-UTILITY ANALYSIS: RESULTS

3.1 DISEASE BURDEN

The disease burden of rotavirus infection in Belgian children is generally described in the chapter on data and methods. Note that the values mentioned in the Methods part are based on point estimates of each parameter (means), whereas the values in Table 3.1 are means of 10,000 simulations (hence taking the distribution of each parameter into account). This explains possible differences between the values reported in the Methods part and hereafter, in Table 3.1.

Table 3.1: Estimated annual disease burden of rotavirus infections in Belgium, for children under 7 years of age, pre-vaccination, discounted with 1.5% (results for a 7 year time span, mean of 10,000 simulations).

BURDEN	
Hospitalizations	4,583
Nosocomial infections	1,013
Outpatient visits	7
GP visits RV+	7,259
P visits RV+	2,659
GP visits not tested	16,082
No medical care	43,738
Deaths	0.6
QALYs LOST	
Assuming loss for one caregiver	243
Assuming no loss for caregiver	144
COSTS	
Health care payer (direct costs)	7,359,898 €
Society (direct costs + work loss)	19,569,102 €

In our opinion, the above estimates (Table 3.1) are the best estimates for Belgium based on the available data. However, some considerations should be made.

Hospitalizatons - The incidence estimate for RVGE related hospitalizations is based on number of hospitalizations for children with RVGE as main diagnosis (ICD9 code). Possibly this is an underestimation, because likely not all causes of a gastroenteritis infection are identified. Moreover, no information is available on the reliability of ICD9 coding.

Nosocomial infections -No direct data are available on the number of RVGE-related nosocomial infections in Belgium. Instead, the incidence estimate is indirectly obtained by using the proportion of children that got rotavirus symptoms 48 hours after hospital admission, from all hospitalized children with RVGE diagnosis. However, this proportion is based on a rather small sample size. Moreover, it is possible that some children show first RVGE symptoms more than 48 hours after infection, and hence are wrongly categorized as being infected in the hospital.

Emergency department visits -No estimates are available for the number of emergency department visits for children with RVGE. However, it is assumed that most children who

go to emergency department, also stay at least one night in the hospital, and hence are included in the incidence estimate for hospitalizations.

Outpatient visits -As expected, the number of RVGE related outpatients visits is very low. Indeed, it is rather unlikely that rotavirus infected children visit a hospital only in the day. The low incidence estimate is not likely to impact significantly on the cost-effectiveness of rotavirus vaccination in Belgium.

GP and pediatrician visits -It is estimated that annually, 26,000 RVGE infected children visit a GP or pediatrician.

No medical care -A large proportion of the children under 7 years old is expected to experience symptomatic RVGE, without medical care being sought for them. In case of symptoms like diarrhoea and vomiting, medical care is not always necessary, but still their caregivers may experience some burden, i.e. extra costs for example for diapers, and time loss. However, no empirical data on this group is available for Belgium. Therefore, when interpreting the results of the cost-effectiveness analysis, it is important to consider the uncertainty of this large estimate.

Deaths -The annual death rate due to RVGE is lower than one, because based on data, 3 children die due to RVGE over a period of 5 years.

3.2 BASELINE INCREMENTAL COST-EFFECTIVENESS ESTIMATES

Fully funded universal rotavirus vaccination would cost €50,024 (95% range: €25,374 - €99,730) per QALY gained with RotaRIX®, and €68,321 (95% range: €35,982 - €132,635) per QALY gained with RotaTEQ™ (health care payer perspective).

Fully funded universal vaccination with RotaRIX is more cost-effective than with RotaTEQ, when assuming the current available estimates for vaccine cost and efficacy.

Private rotavirus vaccination (current situation with partial reimbursement, option 2) is less cost-effective than fully funded universal vaccination, regardless of the choice of the vaccine for universal vaccination.

In baseline analysis, results are given for a 7 year time span, for a birth cohort of 118,366 children. All results are discounted for costs (3%) and effects (1.5%). Assumed parameter estimates and their distributions can be found in the Appendix F. The incremental cost-effectiveness ratios are calculated as the ratio of the mean costs and effects of 10,000 simulations (for each simulation, parameter values are drawn from the given distributions), so that the uncertainty for each parameter is taken into account. First, incremental cost-effectiveness ratios are presented for option 2: private vaccination (current situation with partial reimbursement). Next, results are presented for option 3: fully funded universal vaccination, for RotaRIX vaccination using a 2-dose schedule with vaccine administration at 2 and 3 months of age and RotaTEQ vaccination using a 3-dose schedule with vaccine administration at 2, 3 and 4 months of age. All results are presented for health care payer (QALY loss taken into account for each infected child and one caregiver) and societal perspective (QALY loss taken into account for each infected child, work loss (euros) taken into account for caregiver of each infected child).

3.2.1 Private Vaccination (current situation with partial reimbursement)

Table 3.2: Incremental Cost-effectiveness ratios (ICERs) for private vaccination with RotaRIX (€77.4/dose; current situation with partial reimbursement), from the health care payer and societal perspective (results for a 7 year time span, ratio of the mean (and 95% range) costs and effects of 10,000 simulations (60% coverage), and 1,000 simulations (40 and 80% coverage)).

Outcomes PER COHORT	HEALTH CARE PAYER		SOCIETY	
	mean	95% range	mean	95% range
Private vaccination 60% coverage	80,709 €	45,444 € - 150,478 €	50,533 €	cost-saving – 220,995 €
Private vaccination 80% coverage	80,458 €		49,788 €	
Private vaccination 40% coverage	80,695 €		50,872 €	

Note that the slight differences in estimated cost-effectiveness ratios for different levels of uptake (or coverage) are due to the fact that table 3.2 presents means of different simulation analyses for each level of uptake. Since we assume that vaccination costs and compliance with the schedule is unaffected by different levels of private vaccine uptake, the cost-effectiveness ratio in this static model remains unaffected. For a formal analytical derivation of this phenomenon see Beutels.[45]

The current situation, assuming 60% to 80% coverage (based on personal communications from Kind & Gezin and GSK) and a RotaRIX vaccine price of €77.4/dose (http://www.bcfi.be/ggr/index.cfm?ggrWelk=MAIN, accessed 24/05/2007), is less cost-effective than a fully funded universal vaccination (see below), simply because it costs more and will at best yield the same effects per vaccinated person. Indeed at a coverage of the current program of 60% to 80%, the costs of the program can be estimated at €11,694,633 to €15,592,844. For universal vaccination, the costs of the program (based on the uptake of other vaccines at the same ages and reasonably reduced ex-factory prices), would be €14,052,390 (RotaRIX) to €14,604,690 (RotaTEQ) (see below). Note that with fully funded vaccination the overall uptake and compliance with the schedules are both likely to be greater.

3.2.2 Fully Funded Universal Vaccination

The parameter baseline point estimates with their assumed distribution can be found in Appendix F.

The following Table 3.3 shows the extent to which both options (RotaRIX or RotaTEQ vaccination) impact on the disease burden, distinguishing between prevented effects and extra costs within vaccinated cohorts and non-vaccinated cohorts.

Table 3.3: Estimated baseline costs and effects prevented by vaccination versus no vaccination using RotaRIX or RotaTEQ vaccines, for a 7 year time span (mean (and 95% range) of 10,000 simulations rounded to the nearest unit number, except deaths).

Outcomes PER COHORT	RotaRIX			RotaTEQ		
	mean	lower 95% range	upper 95% range	mean	lower 95% range	upper 95% range
EVENTS AVOIDED						
Hospitalizations	3,974	3,452	4,438	3,746	3,218	4,196
Nosocomial infections	878	679	1,095	828	636	1,033
Outpatient visits	4	1	8	3	1	7
GP visits RV+	5,030	2,710	7,424	3,982	2,147	5,911
P visits RV+	1,868	859	3,172	1,454	666	2,493
GP visits not tested	9,301	4,645	14,744	7,684	3,862	11,936
No medical care	28,977	15,194	47,784	23,239	12,341	37,837
Deaths	0.5	0.0	1.8	0.4	0.0	1.6
QALYs GAINED						
Assuming QALY loss for one caregiver (total)	166	99	252	138	82	215
* Hospital	16	12	20	15	11	19
* Nosocomial	4	2	5	3	2	5
* Outpatient	0	0	0	0	0	0
* GP Rvpositive	20	10	32	16	8	25
* P Rvpositive	8	3	13	6	3	10
* GP not tested	37	17	62	31	14	50
* No medical care	59	22	114	47	17	91
* Deaths	22	0	80	20	0	72
Assuming no QALY loss for caregiver (total)	100	54	170	84	45	146
INCREMENTAL COSTS*						
Vaccine	14,052,388 €	14,052,388 €	14,052,388 €	14,604,692 €	14,604,692 €	14,604,692 €
Health Care Payer (direct costs)	-5,770,854 €	-7,646,309 €	-4,170,779 €	-5,179,825 €	-6,869,300 €	-3,719,447 €
* Hospital	-3,184,464 €	-4,745,222 €	-1,926,811 €	-3,004,584 €	-4,515,882 €	-1,804,117 €
* Nosocomial	-794,195 €	-1,380,816 €	-355,618 €	-750,557 €	-1,300,767 €	-333,042 €
* Outpatient	-492 €	-1,191 €	-77 €	-400 €	-958 €	-62 €
* GP Rvpositive	-639,542 €	-1,229,989 €	-254,376 €	-505,981 €	-964,872 €	-196,930 €
* P Rvpositive	-268,425 €	-663,028 €	-77,243 €	-210,197 €	-526,642 €	-58,457 €
* GP not tested	-398,184 €	-753,734 €	-123,860 €	-318,919 €	-603,909 €	-93,744 €
* No medical care	-485,161 €	-1,003,981 €	-121,046 €	-388,837 €	-818,371 €	-98,372 €
* Deaths	-391 €	-1,449 €	-4 €	-350 €	-1,288 €	-3 €
Society (direct costs + work loss)	-14,091,256 €	-24,356,684 €	-7,063,158 €	-12,110,817 €	-20,236,018 €	-6,278,688 €
Total Health Care	8,281,534 €	6,406,079 €	9,881,609 €	9,424,867 €	7,735,392 €	10,885,245 €
Total Society	-38,868 €	-10,304,296 €	6,989,230 €	2,493,875 €	-5,631,326 €	8,326,004 €

* Negative costs indicate savings for universal vaccination versus doing nothing.

The Table 3.4 below shows that, under our assumptions for vaccine efficacies and costs, fully funded universal vaccination with RotaRIX is more cost-effective than with RotaTEQ. Fully funded universal vaccination with RotaRIX would cost €50,024 per QALY gained, with RotaTEQ €68,321 per QALY gained. Regardless of the vaccine used, private vaccination (Table 3.2) is more expensive, less effective (as uptake is lower) and less equitable (as still a substantial amount is copaid) than fully funded universal vaccination.

Table 3.4: Incremental Cost-effectiveness ratios (ICERs) for RotaRIX and RotaTEQ (results for a 7 year time span), health care payer and societal perspective (ratios of mean and 95% range of costs and effects from 10,000 simulations).

Outcomes PER COHORT	RotaRIX			RotaTEQ		
	mean	lower 95% range*	upper 95% range	mean	lower 95% range*	upper 95% range
HEALTH CARE PAYER						
Cost/QALY gained	**50,024 €**	25,374 €	99,730 €	**68,321 €**	35,982 €	132,635 €
Cost/prevented case	**166 €**	90 €	299 €	**231 €**	134 €	399 €
Cost/hospitalization saved	**2,084 €**	1,443 €	2,863 €	**2,516 €**	1,843 €	3,383 €
Cost/averted death	**16,980,510 €**	3,642,620 €	2,149,603,954 €	**21,576,809 €**	4,896,823 €	2,681,988,008 €
Cost/life year saved	**371,298 €**	79,667 €	47,010,039 €	**471,673 €**	107,105 €	58,653,730 €
SOCIETY						
Cost/QALY gained	**cost-saving**	cost-saving	128,662 €	**29,618 €**	cost-saving	183,164 €
Cost/prevented case	**cost-saving**	cost-saving	212 €	**61 €**	cost-saving	305 €
Cost/hospitalization saved	**cost-saving**	cost-saving	2,025 €	**666 €**	cost-saving	2,587 €
Cost/averted death	**cost-saving**	cost-saving	1,520,407,906 €	**5,709,349 €**	cost-saving	2,051,423,086 €
Cost/life year saved	**cost-saving**	cost-saving	33,250,048 €	**124,808 €**	cost-saving	44,863,592 €

* Negative costs indicate savings for universal vaccination versus doing nothing.

The differences between RotaRIX and RotaTEQ vaccinations are the result of the different assumptions for vaccine-related parameters (Table 3.5), and their respective distributions.

Table 3.5: Baseline parameter for efficacy and vaccine cost of RotaTEQ and RotaRIX.

	RotaTEQ	RotaRIX
VACCINE EFFICACY		
Hospitalizations	96%	100%
Nosocomial infections	96%	100%
Day hospitalizations	73%	87%
GP consultations RVGE positive	73%	87%
P consultations RVGE positive	73%	87%
GP consultations not tested	73%	87%
No medical care	73%	87%
Deaths	98%	96%
Partial protection after 1st dose:		
Efficacy against hospitalizations	90%	83%
Efficacy against RVGE of any severity		38%
Partial protection after 2nd dose:		
Efficacy against hospitalizations		81%
Efficacy against RVGE of any severity		39%
Waning from one year to another for:		
Hospitalizations &nosocomial infections	91%*	98%
Outpatient, GP and P visits	86%	86%
Deaths	91%	95%
VACCINE COST		
Vaccine cost (per dose)	37,08 €	55,62 €
Administration cost (per dose)	5 €	5 €

*starts from 2nd to 3rd season

Almost all efficacy estimates for RotaTEQ are lower than for RotaRIX. Therefore fewer outcomes and related costs are prevented. Moreover, the total cost of vaccination is higher for RotaTEQ than RotaRIX, because RotaTEQ requires 3 doses (i.e. 3 times administration costs per fully vaccinated child), whereas RotaRIX only requires 2 doses (i.e. 2 times administration costs per fully vaccinated child). Hence the difference between the two vaccines could possibly be compensated by additional efficacy data for both vaccines, or by an appropriate price revision for RotaTeq™, relative to Rotarix® 's price. Hereafter, the estimates of both vaccines (and their uncertainties) are explored in more detail.

Efficacy estimates against hospitalizations and nosocomial infections for RotaTEQ for the first year after complete vaccination can be underestimated, because estimates are based on a follow-up period up to two years after administration of the 3rd dose. For RotaRIX, efficacy estimates for the first year after complete vaccination are based on a follow-up period up to the end of the 1st epidemic season.

Efficacy estimates against outpatient, GP and P visits and no medical care are much lower for RotaTEQ than RotaRIX. In Vesikari et al[40] an efficacy estimate of 74% is published for RotaTEQ, however, substituting the baseline estimate with this value does not influence the results much. Efficacy estimates for both vaccines are based on efficacy estimates against RVGE of any severity, with follow-up period up to the end of the 1st epidemic season. However, it is possible that case definitions of RVGE of any severity are different between the studies performed for RotaRIX and RotaTEQ. For the RotaRIX study, no exact

case definition is available at this moment, because the results are not yet published in detail.

Although the estimates for **partial protection** are higher for RotaRIX than RotaTEQ, this difference will not have a large influence, because only a very small proportion of children in Belgium does not get complete vaccination (all children who received one dose are assumed to get also the second dose, only 0.5% of the children who got 2 doses, do not get the third dose).

The estimates for **waning** for health care outcomes hospitalizations, nosocomial infections and deaths are higher for RotaTEQ than RotaRIX. However, this difference is not the main reason for the large difference between the two vaccines (when assuming equal waning for vaccines, the large difference remains, results not shown).

Vaccine purchasing cost (without administration cost) is slightly higher for RotaRIX (€12.893.333) compared to RotaTEQ (€12.869.344). However, if administration cost per dose is taken into account, the total vaccine cost becomes higher for RotaTEQ (€14.604.690) than for RotaRIX (€14.052.390), because RotaTEQ is given in 3 doses, and RotaRIX only in 2 doses.

Note also that the efficacy estimates for both RotaRIX and RotaTEQ against outpatient, GP and pediatrician visits, and no medical care are likely overestimated. For efficacy against these health care outcomes, efficacy estimates against RVGE of any severity is used, which was based on both hospitalized and non-hospitalized RVGE cases (and not non-hospitalized RVGE cases only, as this is not available for either vaccine).

3.3 SENSITIVITY ANALYSIS

Sensitivity analysis focuses on parameter uncertainty. First multivariate uncertainty in the cost-effectiveness plane is shown, as well as cost-effectiveness acceptability curves, and cost-effectiveness at different years after vaccination. Next, we show simple univariate sensitivities to parameter changes.

3.3.1 Multivariate Sensitivity Analysis

For the **health care payer perspective**, the cost/QALY gained for vaccination versus no vaccination is most influenced by the uncertainty regarding waning of efficacy against outpatient, GP and pediatrician visits, and RV episodes left without medical care and regarding the number of RV related deaths. Also the uncertainty of the cost of staying at the hospital, the QALY loss for children and their caregivers and the proportion of children who get symptomatic RV infections influence the cost/QALY gained substantially.

For the **societal perspective**, the cost/QALY gained for vaccination versus no vaccination is very highly influenced by the uncertainty of the number of days caregivers have to stay home from work because of an infected child (ambulatory case).

From the societal perspective, 44% of the 10,000 simulations are cost-saving for RotaRIX vaccination, versus 26% for RotaTEQ vaccination.

In multivariate probabilistic sensitivity analysis, all parameters in the model are varied according to a specified distribution. In this analysis, the distributions (Appendix F) are almost always specified by data (usually normal distribution for incidence rates (truncated between zero (minimum value) and birth cohort (maximum value)) and beta distributions for proportions, gamma distributions for costs (truncated up to 99% of the data (i.e. extreme high costs with probability lower than 1% are not taken into account), and normal distributions for the logarithm of the estimated odds ratios of efficacy (truncated to zero (maximum value)). For those few parameters for which no data driven distribution can be specified, a triangular distribution is defined, based on a plausible range (and plausibility based on the literature where possible).

The only parameters that are not varied in this multivariate sensitivity analysis are number of caregivers for whom QALY loss was taken into account, vaccination costs per dose and discount rates. The latter two are known to be highly influential (see below), but not a source of the type of uncertainty we wish to explore here. The former parameter (number of caregivers, and related estimates) is varied in univariate sensitivity and scenario analysis (see below).

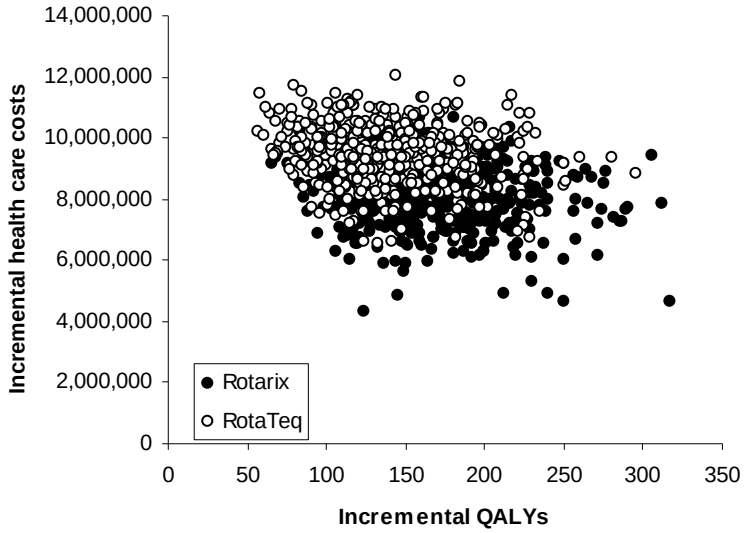
The multivariate sensitivity analysis is based on 10,000 simulations, using Latin Hypercube sampling. For clarity, the cost-effectiveness planes depicted below, and the other plots show results for a random sample of only 500 of these 10,000 point estimates. To determine influential factors and to depict CE acceptability curves, the complete set (i.e. 10,000) of costs, effects and cost-effective ratios (cost/QALY) were used.

First, results are presented for the health care payer perspective (the focus of Belgian health policy in practice) , next, for the societal perspective.

3.3.1.1 Health care payer perspective

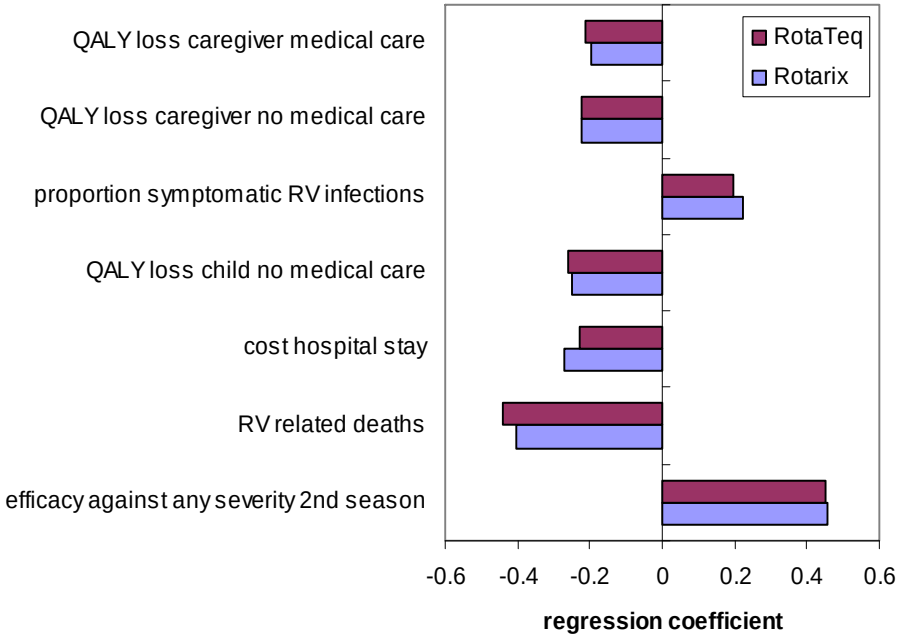
The cost-effectiveness plane (Fig. 3.1) shows the dispersion of the estimates in multivariate sensitivity analysis.

Figure 3.1: Cost-effectiveness plane for incremental costs and effects of RotaRIX and RotaTEQ vaccination versus doing nothing (health care payer perspective).



Parameters that have the strongest linear relationship with the cost/QALY gained in case of vaccination versus no vaccination are shown in the Tornado graph (Fig. 3.2).

Figure 3.2: Tornado graph showing the parameters having the largest effect (regression coefficients > 0.2) on cost/QALY gained of vaccination with RotaRIX and RotaTEQ versus doing nothing (health care payer perspective).



The most influential parameters are the same for RotaRIX and RotaTEQ.

The most influential parameter is efficacy against any severity after the 2nd season (which is assumed the same for RotaRIX and RotaTEQ, i.e. 63% (44-75%)). Although the regression coefficient is positive, efficacy is negatively correlated with cost/QALY gained. This is because the parameter used in the model is the log of the odds ratio of RVGE related health care outcomes in the vaccine group compared to the placebo group (e.g. the

number of hospitalizations that occur, not the number that is prevented). The parameter for efficacy against severity after the 2nd season is used for the estimated waning rate from one year to the next (for efficacy estimates against all outcomes, i.e. outpatient, GP and pediatrician visits, and children with RV disease for whom no medical care is sought). The larger waning assumed (i.e. the smaller the efficacy against any severity after the 2nd season), the less cost-effective vaccination is versus no vaccination (Fig. 3.3 (RotaRIX) and 3.4 (RotaTEQ)).

Figure 3.3: RotaRIX vaccination versus no vaccination: direct cost per QALY gained (HCP) relative to efficacy against RVGE of any severity after the second season. A random selection of 500 simulations is shown.

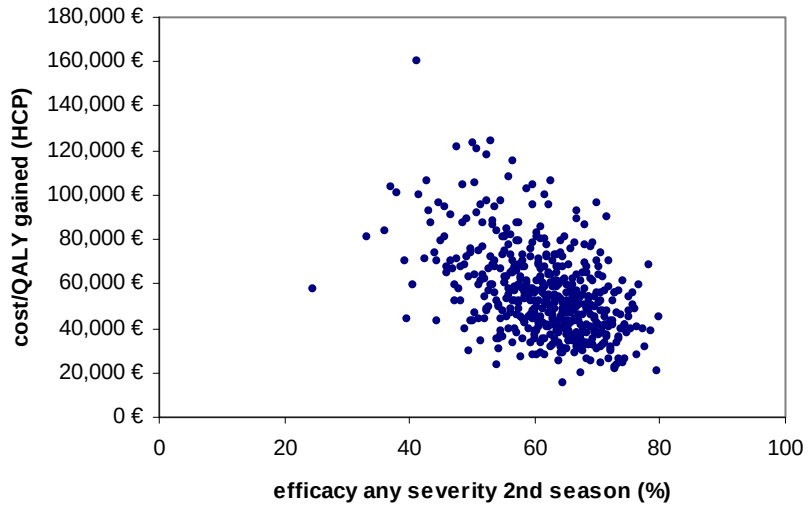
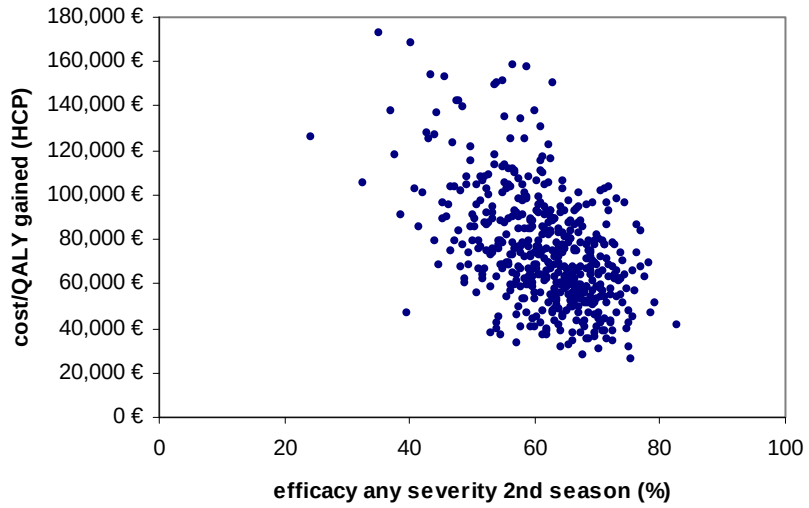


Figure 3.4: RotatTEQ vaccination versus no vaccination: direct cost per QALY gained (HCP) relative to efficacy against RVGE of any severity after the second season. A random selection of 500 simulations is shown.



The second most influential parameter is number of RV related deaths. The uncertainty around the number of RV related deaths is large, because we were unable to obtain Belgian death certificates for the purpose of our study. The number of deaths has a large impact on the QALY loss due to RVGE (one RV related death increases the QALY loss due to RVGE substantially, Figs. 3.5 (RotaRIX) and 3.6 (RotaTEQ)). Hence, the more RV

related deaths, the more deaths will be prevented by vaccination, hence the lower cost-effectiveness of vaccination.

Figure 3.5: RotaRIX vaccination versus no vaccination: QALY loss (HCP) relative to number of RV related deaths. A random selection of 500 simulations is shown.

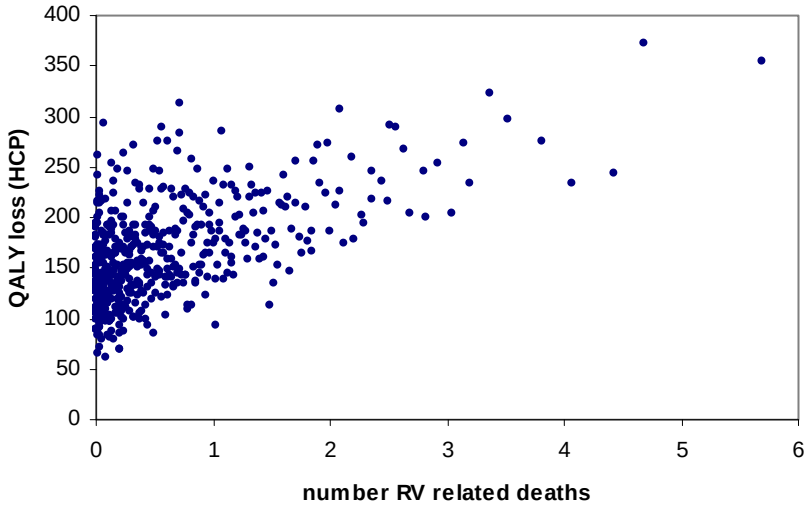
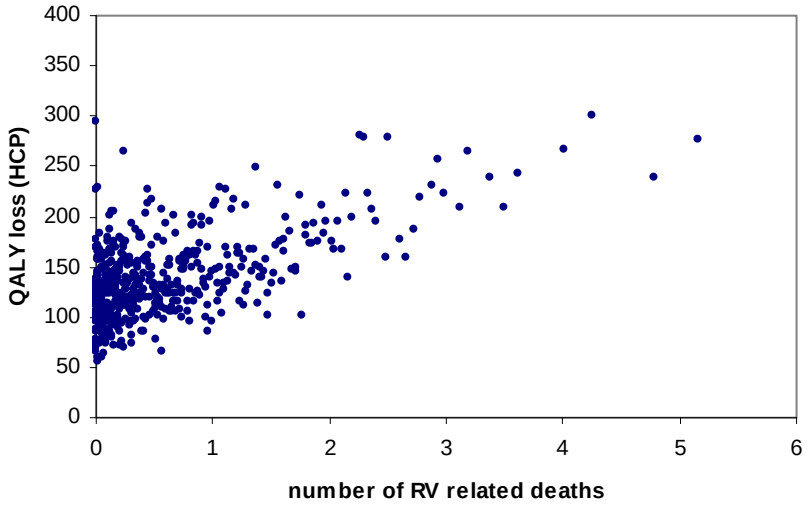


Figure 3.6: RotaTEQvaccination versus no vaccination: QALY loss (HCP) relative to number of RV related deaths. A random selection of 500 simulations is shown.



Other influential parameters are the cost for staying in the hospital due to RVGE, the proportion of symptomatic RV infections and QALY loss for children and their caregivers. The proportion of children who acquire a symptomatic RV infection was obtained from three studies and differed substantially (i.e. for age 0: 4%, 25% and 27%; for age 1: 11%, 25% and 25%, see data and methods section). That is why the random choice of one of the three parameters affects substantially the cost-effectiveness of vaccination.

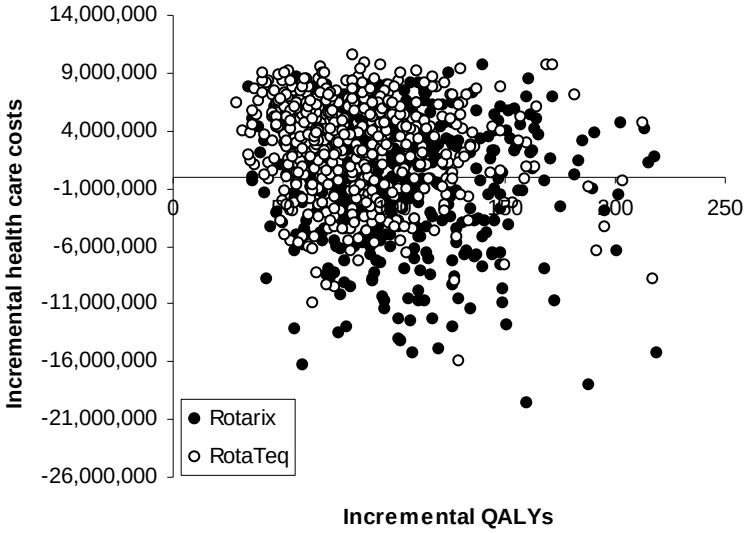
The parameter of QALY loss for children and their caregivers when no medical care is sought has a very large uncertainty. Because no data are available, we assumed it to vary between 0 and the QALY loss of children and caregivers when medical care is sought (using as a mean half of the QALY loss of children and caregivers when medical care is

sought). That is why the uncertainty on this parameter influences the cost/QALY gained for vaccination compared to no vaccination substantially. Also the QALY loss of the caregiver of a child for whom medical care is sought is influential. Note the estimate for this parameter is an EQ-5D score and based on a study in 200 rotavirus positive children. The same study also presented QALY loss for caregivers of rotavirus positive children based on another method, i.e. VAS. The impact of using this measurement instead of the EQ-5D estimate is investigated in univariate sensitivity analysis (see below).

3.3.1.2 Societal perspective

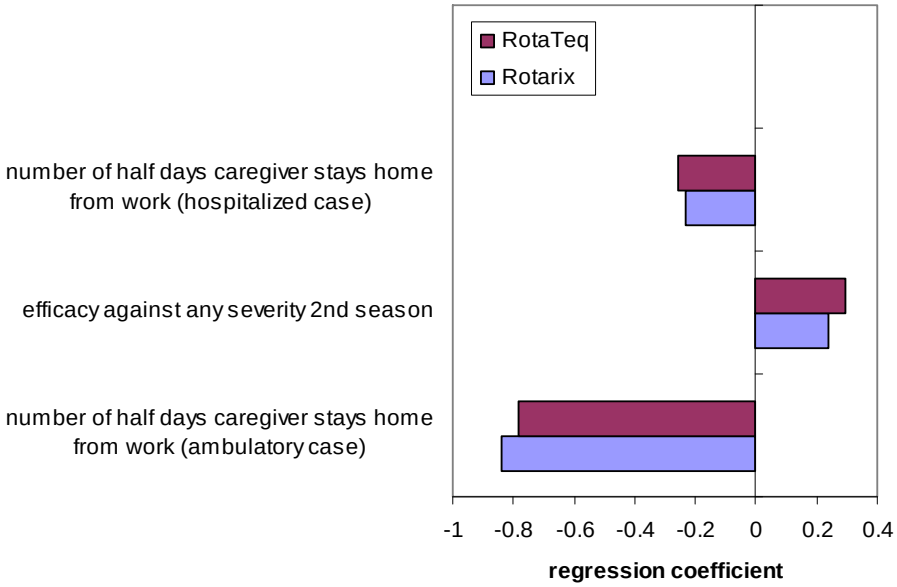
The cost-effectiveness plane (Fig. 3.7) shows the dispersion of the estimates by the multivariate sensitivity analysis. Under the societal perspective, 42% of the 10,000 simulations are cost-saving for RotaRIX vaccination, versus 25% for RotaTEQ vaccination.

Figure 3.7: Cost-effectiveness plane for incremental costs and effects of RotaRIX and RotaTEQ vaccination versus doing nothing (societal perspective).



Parameters that have the strongest linear relationship with the cost/QALY gained in case of vaccination versus no vaccination are shown in the Tornado graph below (Fig. 3.8).

Figure 3.8: Tornado graph showing the parameters having the largest effect (regression coefficients ≥ 0.2) on cost/QALY gained by vaccination with RotaRIX and RotaTEQ (societal perspective).



Influential parameters are the same for RotaRIX and RotaTEQ.

There is one parameter very highly correlated with the cost/QALY gained of vaccination versus no vaccination, i.e. the number of days a caregiver stays home from work for an infected child (ambulatory case). This parameter has an influence on the estimated work loss due to an ambulatory rotavirus case. Vaccination becomes cost-saving when the assumed number of days the caregiver stays home from work increases (Figs. 3.9 (RotaRIX) and 3.10 (RotaTEQ)). Also the number of days a caregiver stays home from work for a child who is hospitalized for RVGE is quite influential. The third most influential parameter is similar to the one from the health care perspective (i.e. efficacy against any severity after the 2nd season).

Figure 3.9: Cost/QALY gained for vaccination with RotaRIX versus no vaccination, against number of half days caregiver stays home from work for an infected child (ambulatory case) (societal perspective). A random selection of 500 simulations is shown.

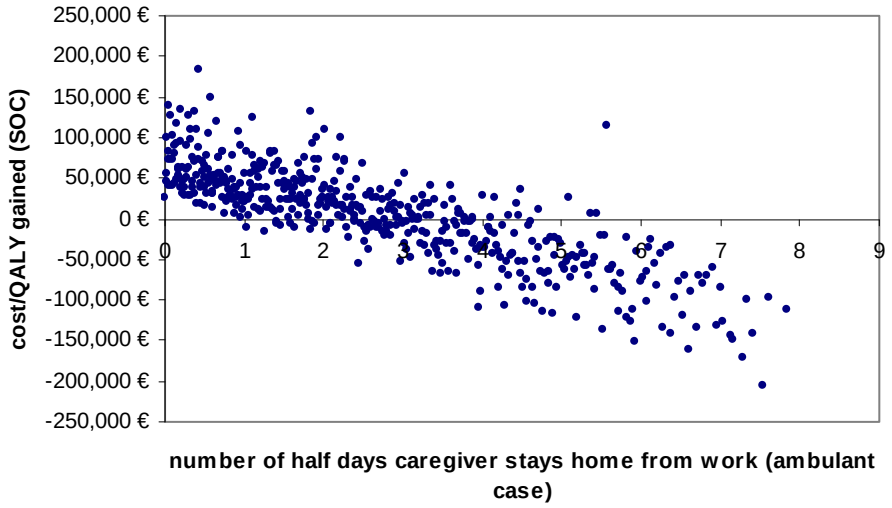
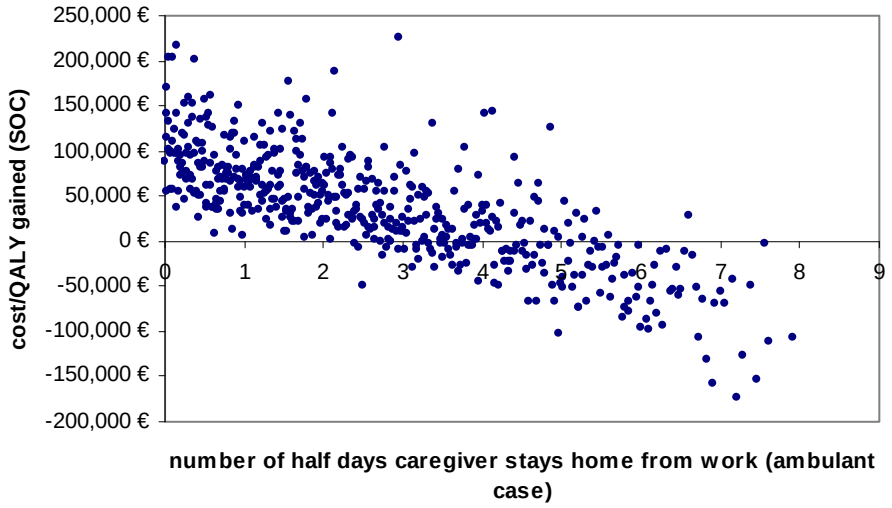
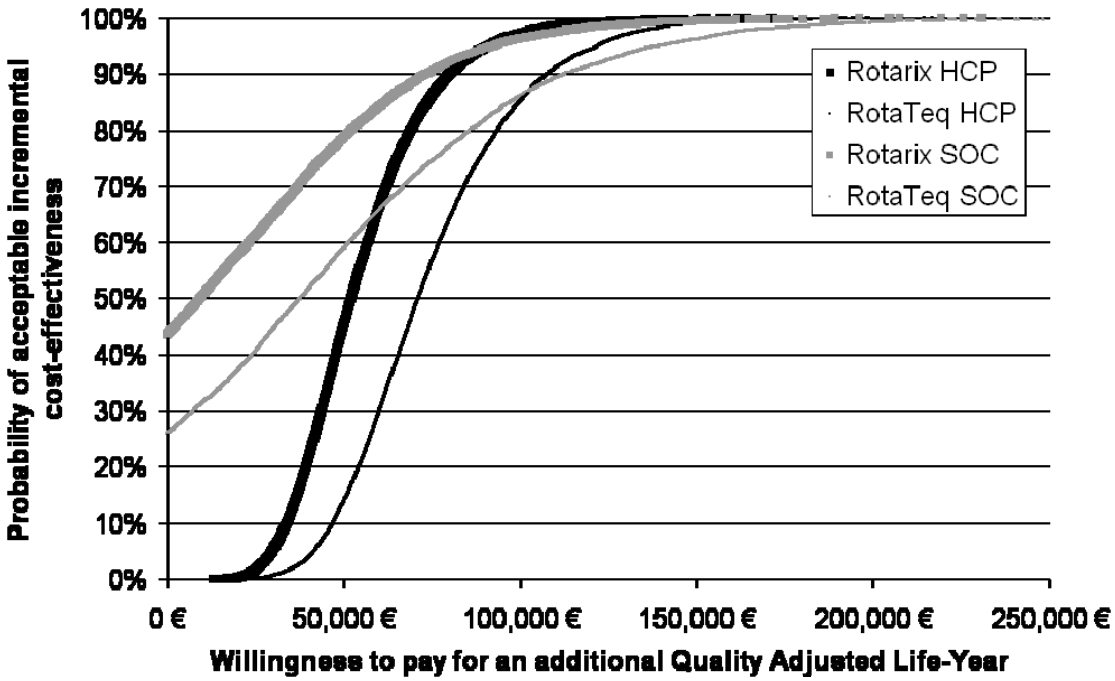


Figure 3.10: Cost/QALY gained for vaccination with RotaTEQ versus not vaccination, against number of half days caregiver stays home from work for an infected child (ambulatory case) (societal perspective). A random selection of 500 simulations is shown.



3.3.1.3 Cost-effectiveness acceptability curves

Figure 3.11: Cost-effectiveness (cost/QALY gained) acceptability curves for RotaRIX and RotaTEQ vaccination versus doing nothing, for health care payer and societal perspective.



The information from the cost-effectiveness planes is 'translated' into cost-effectiveness acceptability curves, by relating the probability of ending up in one of the quadrants of the cost-effectiveness plane to willingness to pay for an increase in health. A point in the south-east quadrant (less costly, more effective) shows dominance to be accepted (i.e. cost-saving at any level of willingness to pay) over the comparator (plotted in the origin of the cost-effectiveness plane). A point in the north-west quadrant shows dominance to be rejected by the comparator, whereas the acceptability of points in the north-east and south-west quadrants depends on the willingness to pay of the decision maker.

Figure 3.11 shows, for instance, that from the health care payer perspective, the probability of RotaRIX to be cost-effective versus doing nothing is 46% at a willingness to pay of €50,000 per QALY gained. For RotaTEQ this is only 14% at a willingness to pay of €50,000 per QALY gained. For the probability of vaccination to be cost-effective versus nothing to be 90%, the willingness to pay for RotaRIX is €79,528/ QALY gained, for RotaTEQ €107,526/QALY gained. Figure 3.11 also illustrates that the uncertainty is greater for the societal perspective.

3.3.1.4 *Cost-effectiveness over time since vaccination*

Figure 3.12: Incremental Cost-effectiveness ratios (ICERs) for RotaRIX and RotaTEQ, results for an increasing time span, health care payer perspective (ratios of mean costs and effects from 10,000 simulations).

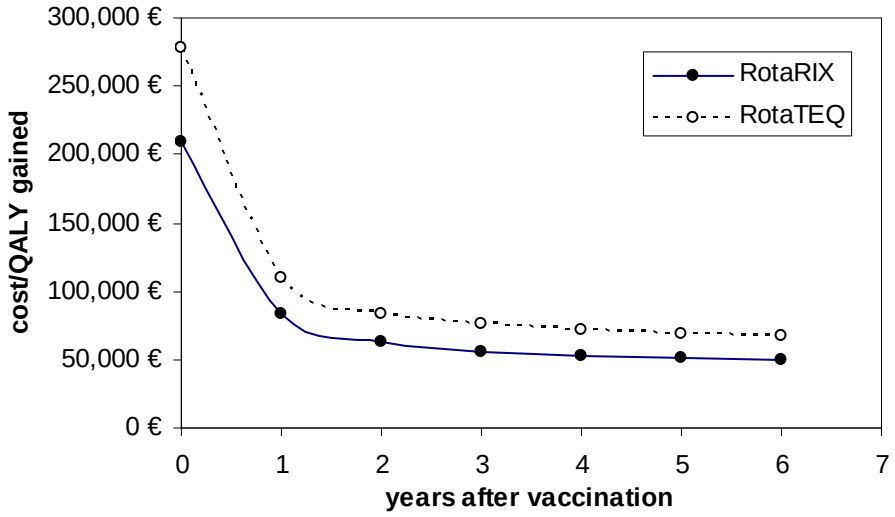


Figure 3.12 shows that that the ICERs stabilise very rapidly at 2-3 years after vaccination. This is what we expect, given the epidemiology and disease burden of rotavirus. That is, the burden of rotavirus infection is largest in the first years of life, i.e. almost all gains from vaccination are obtained in the first years after vaccination. Additionally, discounting reduces the benefits of vaccination more, the further in the future these occur.

Figure 3.12 also indicates what the cost-effectiveness ratio would be if vaccine protection were shorter than the full 7 year horizon. It shows, for instance, that if RotaRIX protects for 2 years, and RotaTEQ for 7 years, the former would still be preferable to the latter, ceteris paribus.

3.3.2 Univariate Sensitivity Analysis

For the health care payer perspective fully funded universal vaccination with RotaRIX respectively RotaTEQ is cost-saving under our assumptions when **vaccine cost/dose** is about 68% respectively 66% lower than the baseline price.

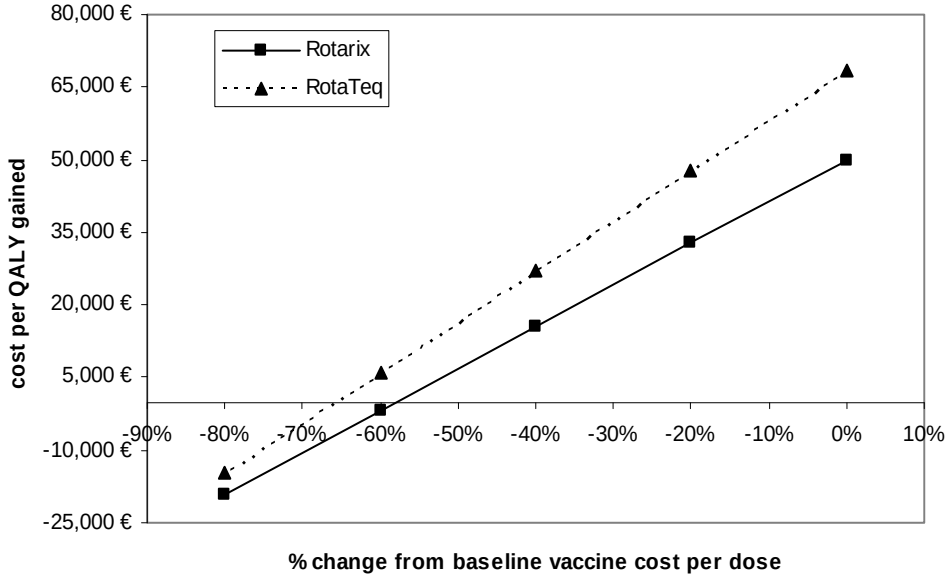
The choice of the score used to estimate **QALY loss** for children and their caregivers (i.e. HUI-2 and EQ-5D scores, or VAS scores), and the **number of caregivers** for which QALY loss is taken into account (zero, one or two) influences largely the incremental cost-effectiveness ratios for RotaRIX and RotaTEQ. Moreover, the inclusion/exclusion and the estimation of costs and QALY losses for children (and their caregivers) for whom **no medical care** is sought, impacts highly on the incremental cost-effectiveness ratio.

Univariate sensitivity analyses are based on 1,000 simulations each.

3.3.2.1 *Cost per dose of vaccine*

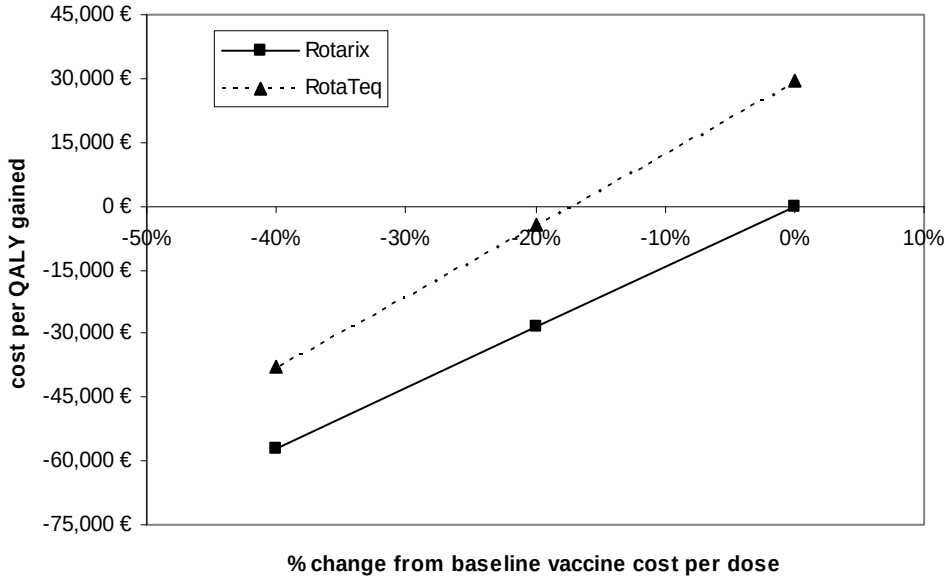
Baseline vaccine cost is €37.08/dose RotaTEQ and €55.62/dose RotaRIX. For the health care payer's perspective fully funded universal vaccination is cost-saving under our assumptions when vaccine cost/dose is 58% respectively 66% lower than baseline price with RotaRIX and RotaTEQ, respectively. (Fig. 3.12). For the societal perspective fully funded universal vaccination with RotaTEQ is cost-saving under our assumptions when the vaccination costs per dose are 18% lower than estimated in our baseline scenario (Fig. 3.13), whereas it is already slightly cost-saving with RotaRIX in the baseline.

Figure 3.12: Sensitivity for options for vaccination (RotaRIX or RotaTEQ) to changes in vaccination costs per dose in the baseline (health care payer perspective).



Note that one can easily derive from figure 3.12 that RotaTEQ could be considered more attractive than RotaRIX given an disproportionate price drop for RotaTEQ versus RotaRIX (eg, RotaRix at baseline price and RotaTEQ minus 20% yields similar costs per QALY gained for both), all else remaining equal.

Figure 3.13: Sensitivity for options for vaccination (RotaRIX or RotaTEQ) to changes in vaccination costs per dose in the baseline (societal perspective).



For the above analysis, administration cost per dose is assumed to be equal for RotaRIX and RotaTEQ, i.e. €5 per dose. If on the other hand, assuming for two doses of RotaRIX the same total administration cost as for three doses of RotaTEQ, the results do not change substantially. The total vaccination cost for a universal vaccination program with

RotaRIX then increases from €14,052,390 to €14,631,920, which results in an increase in the cost-effectiveness ratio for universal RotaRIX vaccination from €50,024 to €53,381 (health care payer perspective) and from cost-saving to €5,358 (societal perspective). Hence the difference between both vaccines is not substantially affected.

3.3.2.2 Other parameters

Table 3.6 shows that the discount rate for costs and effects, the proportion of nosocomial hospital infections, the costs for children with RVGE for whom no medical care is sought and the use of serotype-adjusted efficacy estimates do not have a major impact on the results. However, the choice of the score used to estimate QALY loss for children and their caregivers (i.e. HUI-2 and EQ-5D scores, or VAS scores), and the number of caregivers for which QALY loss is taken into account (zero, one or two) have a more substantial impact on the costs per QALY gained of RotaRIX and RotaTEQ vaccination versus no vaccination.

The choice of the scores for QALY losses has a large impact on the incremental cost-effectiveness ratios. However, the HUI-2 and EQ-5D methods used in baseline analysis are more reliable, because these classification systems are based on the evaluation of different methods in a large population. Still, the estimation of QALYs remains difficult for small children[36], and when disease is mild and/or of short duration.

Table 3.6: Univariate sensitivity analysis of costs per QALY gained of RotaRIX and RotaTEQ vaccination versus no vaccination, for a range of potentially influential parameters, for the health care payer and societal perspective.

Outcomes PER COHORT	HEALTH CARE PAYER		SOCIETY	
	RotaRIX	RotaTEQ	RotaRIX	RotaTEQ
base	50,024 €	68,321 €	cost-saving	29,618 €
Discount rates				
5% costs, 5% effects	57,338 €	78,780 €	2,941 €	40,769 €
3.5% costs, 3.5% effects	54,655 €	74,852 €	1,287 €	34,922 €
3% costs, 3% effects	53,473 €	73,358 €	cost-saving	32,930 €
5% costs, 0% effects	45,333 €	61,778 €	2,473 €	27,993 €
3% costs, 0% effects	45,096 €	60,841 €	651 €	25,043 €
0% costs, 0% effects	43,771 €	59,668 €	cost-saving	20,872 €
Proportion nosocomial infections				
7% nosocomial	53,107 €	71,752 €	5,552 €	35,765 €
22.8% nosocomial	46,610 €	63,859 €	cost-saving	22,079 €
no cost for children for whom no medical care is sought	53,023 €	70,711 €	5,029 €	33,673 €
serotype-adjusted efficacy	52,257 €	69,988 €	3,448 €	33,284 €
VAS score for QALY loss	20,795 €	28,585 €	103 €	10,726 €
no caregiver	82,589 €	111,993 €	NA	NA
2 caregivers	35,926 €	49,164 €	NA	NA

3.3.2.3 *RVGE infected children not seeking medical care*

In base case analysis, the annual incidence of children experiencing rotavirus disease but not seeking medical care was taken into account, as these children and their caregivers also experience burden (e.g. stress), costs (e.g. extra diapers) and work loss (to take care of their sick child) due to rotavirus infection. However, data on the incidence of such cases is not available for Belgium and had to be derived from studies performed in other countries (US, Canada and Mexico). Because of the relatively large uncertainty of the assumed incidences for infected children not seeking medical care, univariate analysis is performed, looking at (1) basecase scenario (100% of the burden and costs of children not seeking medical care included), (2) scenario excluding the burden and costs of children not seeking medical care, and (3) "medium" scenario (half of the burden and costs of children not seeking medical care included).

Moreover, in base case scenario the QALY loss for an infected child for whom no medical care is sought and one of his/her caregiver is assumed to be half of the QALY loss of an infected child and his/her caregiver for whom medical care is sought. This assumption is not based on available data, and therefore the QALY loss for an infected child not getting medical care and his/her caregiver is varied between zero (similar as scenario (2) described above, because acknowledging the costs for children for whom no medical care is sought, has very little impact on the cost-effectiveness (Table 3.6)), half of the QALY loss for an infected child getting medical care and his/her caregiver and equal to the QALY loss for an infected child getting medical care and his/her caregiver (health care payer perspective: Figs. 3.14 (RotaRIX) and 3.15 (RotaTEQ); societal perspective: Figs. 3.16 (RotaRIX) and 3.17 (RotaTEQ)).

Note that under the most favourable scenario for vaccination (RotaRIX, assuming 100% of the burden and costs of children not seeking medical care included, and that these RV episodes cause the same quality of life impact as RV episodes for which medical care is sought), the willingness to pay for a QALY must be EUR 50,000 in order to have made the right decision in at least 90% of the simulations, irrespective of the decision maker's perspective. This illustrates that the uncertainty of a decision on the introduction of RV vaccine is great, even when this influential pro-vaccine analytical choice is made.

Figure 3.14: Cost-effectiveness acceptability curves for RotaRIX vaccination versus doing nothing, for different assumptions of incidence of rotavirus infected children for whom no medical care is sought, and QALY loss for those children and their caregivers (health care payer perspective).

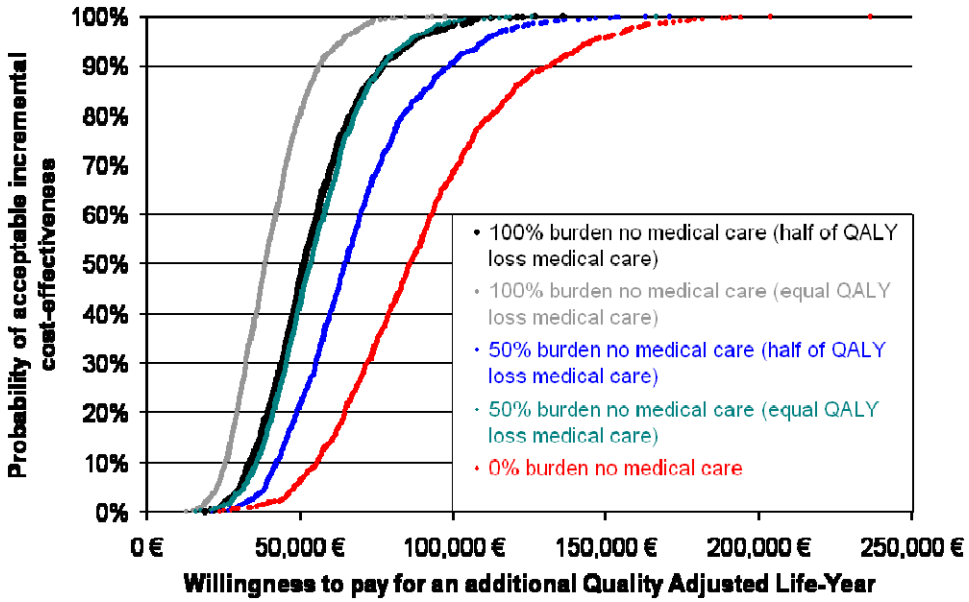


Figure 3.15: Cost-effectiveness acceptability curves for RotaTEQ vaccination versus doing nothing, for different assumptions of incidence of rotavirus infected children for whom no medical care is sought, and QALY loss for those children and their caregivers (health care payer perspective).

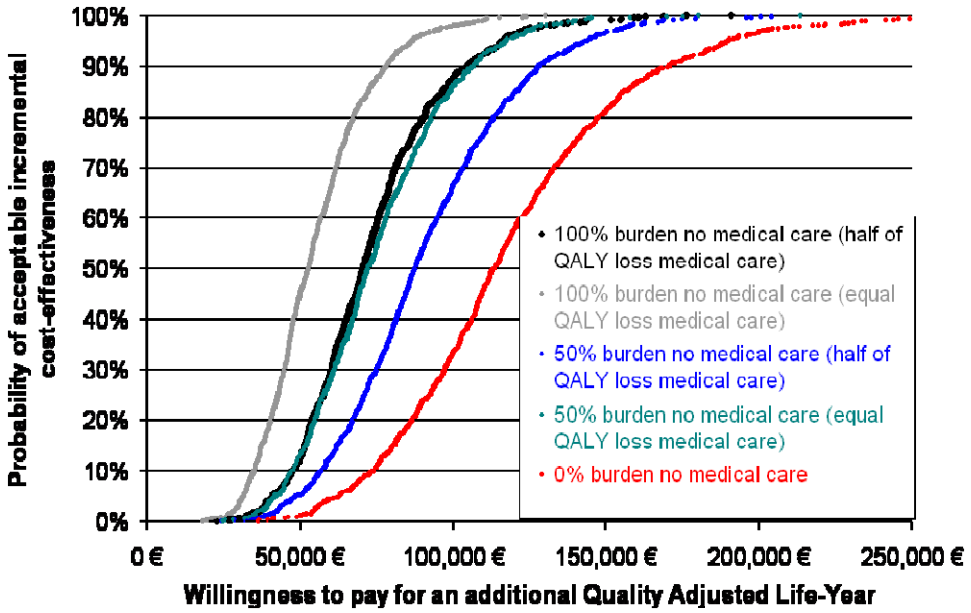


Figure 3.16: Cost-effectiveness acceptability curves for RotaRIX vaccination versus doing nothing, for different assumptions of incidence of rotavirus infected children for whom no medical care is sought, and QALY loss for those children and their caregivers (societal perspective).

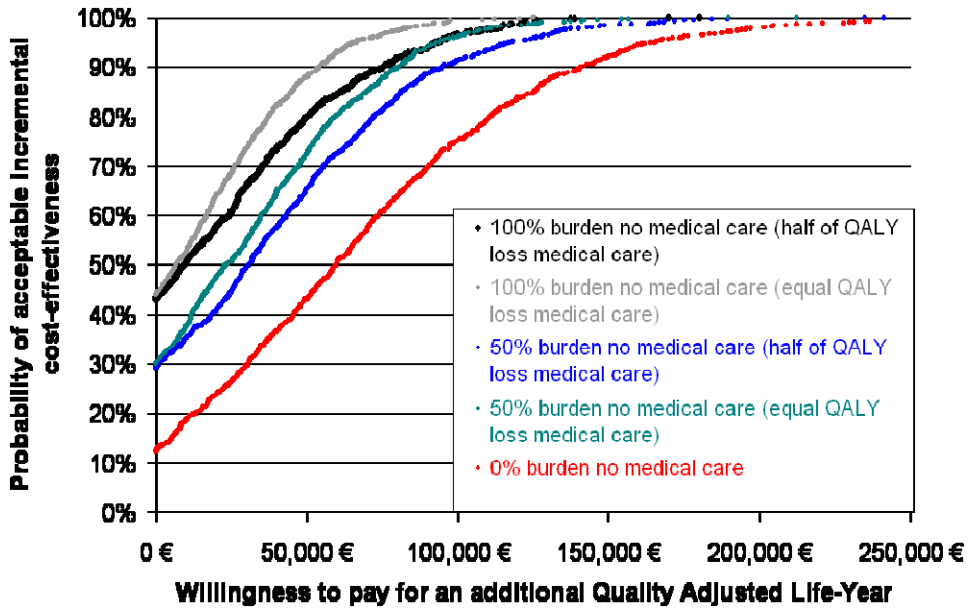
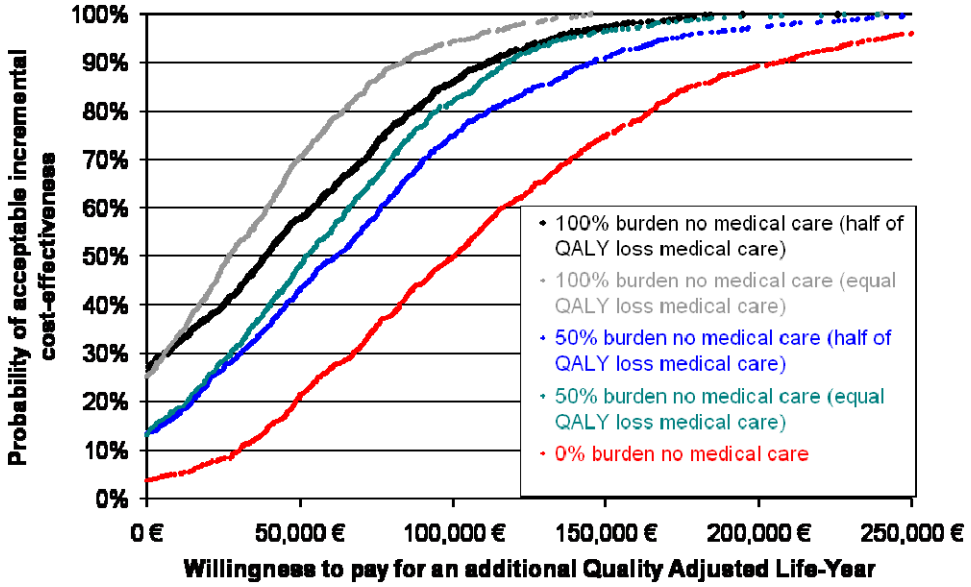


Figure 3.17: Cost-effectiveness acceptability curves for RotaTEQ vaccination versus doing nothing, for different assumptions of incidence of rotavirus infected children for whom no medical care is sought, and QALY loss for those children and their caregivers (societal perspective).



All graphs (Figs. 3.14-3.17) show that the choice of estimates for QALY losses and incidence rate of rotavirus infected children for whom no medical care is sought, are highly influential for the cost-effectiveness of rotavirus vaccination in Belgium. Note that all previous economic evaluations on this subject have excluded this group of infected children.

4 CONCLUSIONS

A mathematical simulation model, by definition, is not reality. It is a tool, which helps to understand complex issues, and project a range of scenarios that cannot be tested in the real world, because of time, ethical and practical constraints. In this case, it may help understand the implications of deciding on the use of the currently available oral rotavirus vaccines (Rotarix® and RotaTeq®) to our greatest advantage. In health economic evaluation, as applied in this report, what is to our society's greatest advantage is defined as the combination of interventions leading to the greatest possible health gains, for as many people as possible (i.e. maximization of health gains (expressed here mainly as life-years and Quality-Adjusted Life-Years (QALYs gained)), under a given budget constraint.

We have reviewed the international published and unpublished literature, and collected and analyzed a wide range of Belgian epidemiological and cost data. A simulation model was developed, parameterized and fitted by using scientifically validated data, as much as possible from Belgian sources. Simulations were performed to estimate how effective and cost-effective universal rotavirus vaccination of Belgian children would be.

The results of these simulations were highly dependent on the decision maker's perspective (that of the health care payer or society), and can be summarised as follows.

Health care payer perspective:

The results are influenced considerably by the number of caregivers assumed to experience an impact on their health related quality of life (HRQOL), and the valuation of care for which no health care resources are used (non-medical costs and HRQOL impact for the child and caregiver(s)).

According to the most plausible and in our opinion most relevant scenario, fully funded universal rotavirus vaccination would cost €50,024 (95% range: €25,374 - €99,730) per QALY gained with Rotarix®, and €68,321 (95% range: €35,982 - €132,635) per QALY gained with RotaTeq® (health care payer perspective).

Multivariate sensitivity analysis showed the cost-effectiveness of a universal vaccination program versus no vaccination to depend mainly on the uncertainty of the estimates for waning of efficacy and number of RV related deaths.

At an average of €80,709 per QALY gained, the current situation (private rotavirus vaccination with Rotarix® or Rotateq™ at intermediate levels of uptake, partially reimbursed by the National Health Insurance (RIZIV/INAMI)) is less cost-effective than fully funded universal vaccination. This is a very robust result given that per vaccinated child, the effects are equal (at best) and vaccination costs are higher for private versus universal vaccination (with universal vaccination a reduction can be obtained on the purchase price).

Considering all the currently available information for both vaccines, fully funded universal vaccination is more cost-effective with Rotarix® than with RotaTeq®. The same probably applies for private vaccination.

Societal perspective:

On average, fully funded universal rotavirus vaccination is more cost-effective for society than for the health care payer, but the impact of parameter uncertainty on the results is also greater for society than for the health care payer. Fully funded universal rotavirus vaccination would be slightly cost-saving with Rotarix® (95% range: cost-saving to €128,662), and would cost €29,618 (95% range: cost-saving to €183,164) per QALY gained with RotaTeq®.

Multivariate sensitivity analysis showed the cost-effectiveness of a universal vaccination program versus no vaccination to depend mainly on the

uncertainty around the number of days away from work in order to care for a child with clinical symptoms of rotavirus infection.

In line with the health care payer perspective, fully funded universal vaccination is more cost-effective with Rotarix® than with RotaTeq®, and universal vaccination is more cost-effective than private vaccination.

We discuss these results for both perspectives in more detail below.

Health care payer perspective

Within the health care payer perspective, the results are substantially influenced by the analytical choice of whether or not to consider the HRQOL impact of rotavirus illness on one or more caregivers in addition to the child's HRQOL itself (Table 4.1). Currently there exists no consensus on how this choice should be made. The cost-effectiveness analysis for Australia included loss in quality of life for one caregiver (baseline), whereas the England&Wales study included QALY losses for two caregivers. As rotavirus disease in a child is likely to impact on the parents, but is not likely to impact to the same extent on both parents (and as not all families are two-parent families), we chose to consider only one affected caregiver per child in our model. Note that in health economic evaluation in general, the HRQOL impact on other people than the patient is usually ignored.

Not so much an analytical choice, but a problem of missing information, the cost and QALY burden for rotavirus infected children, experiencing clinical disease, but for whom no medical care is sought, has often been ignored in cost-effectiveness analyses. Indeed, the Australian and England&Wales cost-utility studies do not include this group of children in their model, whereas the US and UK cost-effectiveness analyses do. Although estimation of this burden requires some assumptions to be made, it seems realistic to assume this burden to be non-negligible. Therefore we chose to consider in our model to some extent the burden (consisting of a small impact on HRQOL and a small personal direct cost per episode for many children) associated with children experiencing rotavirus clinical disease but for whom no medical care is sought. Moreover, the estimation of the loss in quality-of-life in children and their caregivers when children are sick, but no medical care is sought, is difficult. In our analysis, we varied the latter QALY loss between zero (no QALY loss) and the 'full' QALY loss for cases for whom medical care is sought (based on a study that was set up especially for this purpose), hence taking into account the uncertainty of this estimate.

Note that even in an optimistic scenario (i.e. including burden for sick children for whom no medical care is sought, and the QALY loss for two caregivers of the child), the willingness to pay for a QALY gained needs to be €55,700 and €75,800 for Rotarix® and RotaTeq®, respectively in order to take the right decision with at least 90% certainty by fully funding these vaccination programs.

Table 4.1: Proportion of acceptable incremental cost-effectiveness simulations, at a willingness to pay of €50,000 for an additional Quality Adjusted Life-Year gained (based on 1,000 simulations), for Rotarix® and RotaTeq® vaccination (health care payer's perspective). Scenarios considering no, one or two caregivers per child, with and without including plausible estimates of the burden of children (and their caregivers) for whom no medical care is sought.

	ROTARIX®		ROTATEQ®	
	'no medical care' not considered	'no medical care' considered	'no medical care' not considered	'no medical care' considered
no caregiver	2%	8%	1%	2%
1 caregiver	6%	46%	1%	13%
2 caregivers	26%	81%	6%	46%

On average, based on the most plausible input parameter distributions, fully funded universal rotavirus vaccination with Rotarix® would cost €50,024 per QALY gained, and with RotaTeq®, €68,321 per QALY gained (health care payer perspective). For Rotarix®, it would cost €166 to prevent a case, €2084 to prevent a hospitalization, €371,298 to gain

a life-year and €16,980,510 to avert a death. For RotaTeq® these costs are €231, €2516, €471,673 and €21,576,809, respectively.

These results lie in between the results obtained for universal rotavirus vaccination in other countries (Table 4.2). For Australia, Newall et al. (*forthcoming*) considered both vaccines to be possibly cost-effective, depending largely on the application of QOL utilities and the perspective used (health care provider or society). Although this study did not consider burden for children for whom no medical care is sought, costs for RVGE-related hospitalizations are higher than in Belgium, and a substantial part of the children went to an emergency department for their rotavirus infection. Moreover, no waning was assumed in their analysis. In France and England&Wales universal rotavirus vaccination was considered to be cost-**in**effective. Details on the French study are not yet available, but in England&Wales universal vaccination is less cost-effective than in Belgium and Australia, mainly because (1) the incidence rate of RVGE-related hospitalizations is estimated much lower; (2) only illness in children for whom medical care was sought, was considered preventable; (3) Rotarix® efficacy estimates were based on the Latin American, and not the European study (which showed higher efficacy estimates).

Table 4.2: Cost per QALY gained for universal vaccination with Rotarix® or RotaTeq™ versus no vaccination in different Western countries.

		HEALTH CARE PAYER	SOCIETY
Belgium	Rotarix®	€ 50,024	cost-saving
(current study)	RotaTeq®	€ 68,321	€ 29,618
Australia	Rotarix®	€ 30,051	cost-saving
(Newall et al, *forthcoming*)	RotaTeq®	€ 46,699	cost-saving
France		€ 138,000	
(Institut de Veille Sanitaire, 2006)			
England&Wales*	Rotarix®	€ 89,251	€ 79,741
(Jit & Edmunds, 2007)	RotaTeq®	€ 116,904	€ 108,272

*An additional study set in the UK (Lorgelly et al, 2007), did not use QALYs as an outcome measure and hence cannot be compared here.

In the current analysis for Belgium, depending on the analytical choices made, cost-effectiveness ratios (cost/QALY) vary between €4979 and €201,945 (minimum and maximum Rotarix®) and between €13,508 and €250,823 (minimum and maximum RotaTeq®). Multivariate sensitivity analysis showed that the higher cost/QALY estimates are mainly due to high values for waning (of efficacy against outpatient, GP and pediatrician visits, and RV episodes left without medical care) and low values for number of RV related deaths. As for many vaccines at the time of introduction, there are no data on the long-term effects of these new rotavirus vaccines. In the analyses for Australia and England&Wales, no waning of efficacy was assumed. However, for both vaccines estimates are available on efficacy for the first and the 2nd season for some endpoints, and this information is used to estimate waning from one season to the next in our model. In the England&Wales study, cost-effectiveness was particularly sensitive to the number of deaths attributable to rotavirus. In our analysis too, the number of deaths has a large impact on the QALY loss, and the uncertainty around this parameter is large, because we were unable to obtain Belgian death certificates for the purpose of our study.

The current situation in Belgium whereby parents and their insurers pay private market prices for the 2-dose Rotarix® vaccine is less cost-effective than fully funded universal vaccination (with Rotarix® as well as RotaTeq®). Private vaccination is more expensive (as the cost per dose is higher), less effective (as uptake is lower) and less equitable (as still a substantial amount is copaid) than fully funded universal vaccination. Indeed at a coverage of the current program of 60% to 80% (based on personal communications from Kind & Gezin and GSK) the costs of the program can be estimated at €11,694,633 to €15,592,844 per vaccinated cohort (implying these are annual costs). For universal vaccination, the costs of the program (based on the uptake of other vaccines at the same ages and ex-factory prices reduced by 10%), would be €14,052,390 (Rotarix®) to

€14,604,690 (RotaTeq®) per year. As shown in the analyses the negociated price of the vaccine impacts the cost-effectiveness ratio to a large extent.

Fully funded universal vaccination is more cost-effective with Rotarix® than with RotaTeq® mainly due to the higher efficacy against rotavirus of any severity of Rotarix® compared to RotaTeq®. Similar results were found in other countries (Table 4.2).

Although higher efficacy against rotavirus of any severity is the main reason why vaccination with Rotarix® is more attractive, the following considerations can be made regarding the advantages and disadvantages of the two vaccines. One could think optimistically that RotaTeq® is effective against a broader range of rotavirus serotypes than Rotarix®, because it contains 5 different reassortant rotavirus strains (whereas Rotarix® contains only one). However, at present there is no empirical evidence to support this. Another consideration can be made in relation to vaccine shedding: after Rotarix® vaccination, a substantial shedding of the vaccine is observed whereas almost no vaccine shedding is observed after RotaTeq® vaccination. Vaccine shedding could give rise to herd immunity, which for this vaccine would be a positive effect. However, vaccine shedding can also lead to gene reassortments of vaccine strain with wild strains, and hence to changes in rotavirus genotypic distribution. Therefore the genotypic distribution should be followed up after widespread use of rotavirus vaccines. Additional elements that may plead for the use of the 2-dose schedule of Rotarix® (compared to the 3-dose schedule of RotaTeq®) are related to overcrowding of the schedule, and the knowledge that more new vaccines are expected to become available for introduction soon.

Societal perspective

For the societal perspective, fully funded universal rotavirus vaccination would be cost-saving with Rotarix® (95% range: cost-saving to €128,662), and €29,618 (95% range: cost-saving to €183,164) per QALY gained with RotaTeq®. Hence, on average fully funded universal rotavirus vaccination is more cost-effective for society, than for the health care payer, but uncertainty is larger than for the health care payer perspective. This uncertainty is mainly due to the wide range for the number of days parents are away from work to care for their sick child. Some parents will not miss work, whereas other parents stay home from work for up to 7 days to care for their child. This heavy impact of work loss on the cost-effectiveness of vaccination also explains the large difference in cost-effectiveness between Rotarix® and RotaTeq® vaccination. Because it offers greater efficacy against rotavirus of any severity, Rotarix® vaccination would prevent more mild RVGE episodes than RotaTeq®, and consequently would reduce the work loss due to RVGE infections more. This results in substantially lower (i.e. better) cost-effectiveness ratios of Rotarix® versus RotaTeq®, making the difference between the two vaccines more pronounced under a societal perspective.

Key Points

In Belgium rotavirus vaccination would reap by far most of its benefits from preventing short lived mild disease in virtually all young children (expressed mainly through QALY losses and indirect costs). The effectiveness and cost-effectiveness of rotavirus vaccination is considerably determined by the value a policy maker wishes to give to the prevention of mild disease, and his/her willingness to pay for a QALY.

When the burden of illness is taken into account for all children (including those not seeking health care) and two of their caregivers in a best case scenario, the willingness to pay for a QALY gained needs to be €55,700 and €75,800 for Rotarix® and RotaTeq®, respectively, in order to take the right decision with at least 90% certainty by fully funding a universal rotavirus vaccination program instead of having no rotavirus vaccination at all.

The current situation in Belgium whereby parents and their insurers pay private market prices for the 2-dose Rotarix® vaccine (and recently also the 3-dose Rotateq vaccine) is clearly less preferable than fully funded universal vaccination, because it is more expensive and –at best- equally efficacious per vaccinated person, less effective (as uptake is lower) and less equitable (as still a substantial amount is copaid by the parents). The program of universal vaccination (at >97% uptake) is estimated to cost €14.0 million (Rotarix®) to €14.6 million (RotaTeq®) per vaccinated cohort, whereas private vaccination at 60% to 80% uptake is currently estimated to cost €11.7 to €15.6 million (Rotarix®).

On average, based on the most justified analytical choices and the most plausible input parameter distributions, fully funded universal rotavirus vaccination would cost €50,024 (95% range: €25,374 - €99,730) per QALY gained with RotaRIX®, and €68,321 (95% range: €35,982 - €132,635) per QALY gained with RotaTeq® (health care payer perspective). In Belgium there is currently no publicly available value for the societal willingness to pay for a gain of one QALY.

Research Agenda

Sub-analyses of data from recent clinical trials indicated that the instantaneous efficacy of a reduced schedule (i.e. one dose of Rotarix® or two doses of RotaTeq®) would be very high. Unfortunately none of these trials were designed to study the longer term efficacy of using fewer doses than currently recommended for either vaccine nor the immediate comparison with the currently recommended schedules, and therefore do not offer a sufficient basis to make a model-based analysis of reduced schedule options. It is in the best interest of developed and developing countries around the world that clinical efficacy trials be set up urgently to specifically compare the current schedules of rotavirus vaccines with reduced ones.

5 REFERENCES

1. CDC. Postmarketing monitoring of intussusception after RotaTeq™ vaccination - United States. MMWR. 2007;56(10):218-22.
2. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis. 2003;9(5):565-72.
3. Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales Part II. The potential cost-effectiveness of vaccination. Vaccine. 2007;25(20):3971-9.
4. Lorgelly PK, Joshi D, Iturriza Gómara M, Gray J, Mugford M. Exploring the cost-effectiveness of an immunisation programme for rotavirus gastroenteritis in the United Kingdom. Epidemiol Infect. 2007:1-12.
5. Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Cost-effectiveness and potential impact of rotavirus vaccination in the United States. Pediatrics. 2007;119(4):684-97.
6. Beutels P. Economic evaluation of vaccination programmes in humans: a methodological exploration with applications to hepatities B, varicella-zoster, measles, pertussis, hepatitis A and pneumococcal vaccination. Antwerp: University of Antwerp. 2002.
7. Beutels P, Edmunds WJ, Antonanzas F, De Wit GA, Evans D, Feilden R, et al. Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics. 2002;20(1):1-7.
8. Beutels P, Van Doorslaer EK, Van Damme P, Hall J. Methodological issues and new developments in the economic evaluation of vaccines. Expert Rev Vaccines. 2003;2(5):649-60.
9. Brisson M, Edmunds WJ. Economic evaluation of vaccination programs: the impact of herd-immunity. Med Decis Making. 2003;23(1):76-82.
10. Vandenberghe H, Ducoffre G, Hanquet G. Oefening in de bestudering van de representativiteit van het peillaboratorianetwerk.
11. 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:S26-35.
12. Giaquinto C, Van Damme P, Huet F, Gothefors L, Van der Wielen M. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: The REVEAL Study. J Infect Dis. 2007;195 Suppl 1:S36-44.
13. Van Damme P, Giaquinto C, Huet F, Gothefors L, Maxwell M, Van der Wielen M. Multicenter Prospective Study of the Burden of Rotavirus Acute Gastroenteritis in Europe, 2004-2005: The REVEAL Study. J Infect Dis. 2007;195 Suppl 1:S4-S16.
14. Van Damme P, Giaquinto C, Maxwell M, Todd P, Van der Wielen M. Distribution of Rotavirus Genotypes in Europe, 2004-2005: The REVEAL Study. J Infect Dis. 2007;195 Suppl 1:S17-25.
15. Beutels P, Van Damme P, Oosterhuis-Kafeja F. Effects and costs of universal infant pneumococcal conjugate vaccination in Belgium. KCE reports vol.33A. 2006:132 pp, available from http://kce.fgov.be/index_nl.aspx?ID=0&SGREF=5301&CREF=7195
16. Rahman M, Matthijnssens J, Goegebuer T, De Leener K, Vanderwegen L, van der Donck I, et al. Predominance of rotavirus G9 genotype in children hospitalized for rotavirus gastroenteritis in Belgium during 1999-2003. J Clin Virol. 2005;33(1):1-6.
17. Van Casteren V, Bossuyt N. Survey site visit Belgium July 15th 2002. Belgian Sentinel Network of General Practitioners. 2002.
18. Glass RI, Parashar UD, Bresee JS, Turcios R, Fischer TK, Widdowson MA, et al. Rotavirus vaccines: current prospects and future challenges. Lancet. 2006;368(9532):323-32.

19. Languepin J, Doit C, Cezard JP, Bingen E, Navarro J. [Pediatric nosocomial diarrhea]. Pathol Biol (Paris). 2000;48(8):764-9.

20. Raes M, Aerssens P, Alliet P, Gillis P, Verjans M, Mewis A. Rotavirus gastroenteritis: epidemiological data from a regional hospital in Belgium. Eur J Pediatr. 2007.

21. de Wit MA, Koopmans MP, van der Blij JF, van Duynhoven YT. Hospital admissions for rotavirus infection in the Netherlands. Clin Infect Dis. 2000;31(3):698-704.

22. Gleizes O, Desselberger U, Tatochenko V, Rodrigo C, Salman N, Mezner Z, et al. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. Pediatr Infect Dis J. 2006;25(1 Suppl):S12-21.

23. Thuret A, Patural H, Berthelot P, Benzait F, Martin I, Jusot JF, et al. [Prospective follow-up of hospital-acquired diarrhoea in 28 paediatric wards of the south-east part of France during a winter season]. Pathol Biol (Paris). 2004;52(3):131-7.

24. Carlin JB, Chondros P, Masendycz P, Bugg H, Bishop RF, Barnes GL. Rotavirus infection and rates of hospitalisation for acute gastroenteritis in young children in Australia, 1993-1996. Med J Aust. 1998;169(5):252-6.

25. Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales Part I. Estimating the burden of disease. Vaccine. 2007;25(20):3962-70.

26. Gurwith M, Wenman W, Hinde D, Feltham S, Greenberg H. A prospective study of rotavirus infection in infants and young children. J Infect Dis. 1981;144(3):218-24.

27. Rodriguez WJ, Kim HW, Brandt CD, Schwartz RH, Gardner MK, Jeffries B, et al. Longitudinal study of rotavirus infection and gastroenteritis in families served by a pediatric medical practice: clinical and epidemiologic observations. Pediatr Infect Dis J. 1987;6(2):170-6.

28. Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022-8.

29. Jit M, Pebody R, Chen M, Andrews N, Edmunds WJ. Estimating the number of deaths with rotavirus as a cause in England and wales. Hum Vaccin. 2007;3(1):23-6.

30. De Leener K, Rahman M, Matthijnssens J, Van Hoovels L, Goegebuer T, van der Donck I, et al. Human infection with a P[14], G3 lapine rotavirus. Virology. 2004;325(1):11-7.

31. Matthijnssens J, Rahman M, Martella V, Xuelei Y, De Vos S, De Leener K, et al. Full genomic analysis of human rotavirus strain B4106 and lapine rotavirus strain 30/96 provides evidence for interspecies transmission. J Virol. 2006;80(8):3801-10.

32. Rahman M, Matthijnssens J, Yang X, Delbeke T, Arijs I, Taniguchi K, et al. Evolutionary history and global spread of the emerging g12 human rotaviruses. J Virol. 2007;81(5):2382-90.

33. Brouwer WB, Koopmanschap MA, Rutten FF. Productivity costs measurement through quality of life? A response to the recommendation of the Washington Panel. Health Econ. 1997;6(3):253-9.

34. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed ed. New York: Oxford University Press; 1997.

35. Tranmer JE, Guerriere DN, Ungar WJ, Coyte PC. Valuing patient and caregiver time: a review of the literature. Pharmacoeconomics. 2005;23(5):449-59.

36. Griebsch I, Coast J, Brown J. Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. Pediatrics. 2005;115(5):e600-14.

37. Beutels P, Viney RC. Comments on the Prosser et Al approach to value disease reduction in children. Pediatrics. 2004;114(5):1375; author reply -6.

38. Sénécal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, et al. Quality of life lost associated with rotavirus gastroenteritis in Canadian families: a prospective community based study [poster]. 7th Canadian Immunization conference, Winnipeg, Canada. 2006;December 3-6.

39. Theeten H, Hoppenbrouwers K, Vandermeulen C, Rolants M, Depoorter A, Van Damme P. Studie van de vaccinatiegraad bij jonge kinderen en adolescenten in Vlaanderen in 2005. Universiteit Antwerpen, in opdracht van Ministerie van de Vlaamse Gemeenschap. 2006.

40. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23-33.

41. De Vos B, Gillard P, Cheuvart B, Debrus S, Han HH, Bouckenooghe A. RIX4414 Vaccine efficacy against Rotavirus gastroenteritis due to G2P[4] strain. In. ICAAC, San Francisco; September 2006.

42. De Vos B. Rotarix-state of the art. 25th Annual meeting of ESPID, Porto, Portugal. 2007;May 2-4.

43. Vesikari T, Matson D, Dennehy P, Dallas M, Itzler R, DiNubile M, et al. Efficacy of the Pentavalent Rotavirus Vaccine (PRV) in subjects after 1 or 2 doses in the Rotavirus Efficacy & Safety Trial (REST). 44th Annual meeting of IDSA, Toronto, Ontario, Canada. 2006;October 12-15.

44. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11-22.

45. Beutels P. Economic evaluations of hepatitis B immunization: a global review of recent studies (1994-2000). Health Econ. 2001;10(8):751-74.

46. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med. 2001;344(8):564-72.

47. Vesikari T, Karvonen A, Puustinen L, Zeng SQ, Szakal ED, Delem A, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. Pediatr Infect Dis J. 2004;23(10):937-43.

48. Salinas B, Perez Schael I, Linhares AC, Ruiz Palacios GM, Guerrero ML, Yarzabal JP, et al. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: A randomized, placebo-controlled trial in Latin American infants. Pediatr Infect Dis J. 2005;24(9):807-16.

49. Araujo EC, Clemens SA, Oliveira CS, Justino MC, Rubio P, Gabbay YB, et al. Safety, immunogenicity, and protective efficacy of two doses of RIX4414 live attenuated human rotavirus vaccine in healthy infants. J Pediatr (Rio J). 2007;83(3).

50. Phua KB, Quak SH, Lee BW, Emmanuel SC, Goh P, Han HH, et al. Evaluation of RIX4414, a live, attenuated rotavirus vaccine, in a randomized, double-blind, placebo-controlled phase 2 trial involving 2464 Singaporean infants. J Infect Dis. 2005;192 Suppl 1:S6-S16.

51. Vesikari T, Clark HF, Offit PA, Dallas MJ, DiStefano DJ, Goveia MG, et al. Effects of the potency and composition of the multivalent human-bovine (WC3) reassortant rotavirus vaccine on efficacy, safety and immunogenicity in healthy infants. Vaccine. 2006;24(22):4821-9.

52. Block SL, Vesikari T, Goveia MG, Rivers SB, Adeyi BA, Dallas MJ, et al. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatrics. 2007;119(1):11-8.

53. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis. 1990;22(3):259-67.

54. Duffy LC, Byers TE, Riepenhoff-Talty M, La Scolea LJ, Zielezny M, Ogra PL. The effects of infant feeding on rotavirus-induced gastroenteritis: a prospective study. Am J Public Health. 1986;76(3):259-63.

55. Clark HF, Bernstein DI, Dennehy PH, Offit P, Pichichero M, Treanor J, et al. Safety, efficacy, and immunogenicity of a live, quadrivalent human-bovine reassortant rotavirus vaccine in healthy infants. J Pediatr. 2004;144(2):184-90.

56. Dennehy PH, Brady RC, Halperin SA, Ward RL, Alvey JC, Fischer FH, Jr., et al. Comparative evaluation of safety and immunogenicity of two dosages of an oral live attenuated human rotavirus vaccine. Pediatr Infect Dis J. 2005;24(6):481-8.

57. Macias M, López P, Velázquez FR, Vergara RF, Salmerón J, Tavares JL, et al. The Rotavirus vaccine RIX 4414 (Rotarix) is not associated with intussusception in one year old infants. In: Proceedings of the; October 2005; IDSA, San Francisco October 2005.

58. Vesikari T, Karvonen A, Korhonen T, Espo M, Lebacq E, Forster J, et al. Safety and immunogenicity of RIX4414 live attenuated human rotavirus vaccine in adults, toddlers and previously uninfected infants. Vaccine. 2004;22(21-22):2836-42.

59. Dennehy P. An Update on the Safety Profile of Pentavalent Rotavirus Vaccine from the REST Study. In: Proceedings of the; June 2006; ICID, Lisbon; June 2006.

60. Heaton PM, Goveia MG, Miller JM, Offit P, Clark HF. Development of a pentavalent rotavirus vaccine against prevalent serotypes of rotavirus gastroenteritis. J Infect Dis. 2005;192 Suppl 1:S17-21.

61. Vesikari T, Clark, HF, Offit PA et al. The effect of dose and composition of a pentavalent rotavirus rea&ssortant vaccine (RotaTeq) upon efficacy and immunogenicity in healthy infants [abstract 35]. In: Proceedings of the Infectious Diseases Society of America.; 2002; Infectious Diseases Society of America, Alexandria, Virginia; 2002.

62. Ward RL. Mechanisms of protection against rotavirus in humans and mice. J Infect Dis. 1996;174 Suppl 1:S51-8.

63. Velazquez FR, Matson DO, Guerrero ML, Shults J, Calva JJ, Morrow AL, et al. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis. 2000;182(6):1602-9.

64. Newall AT, MacIntyre R, Wang H, Hull B, Macartney K. Burden of severe rotavirus disease in Australia. J Paediatr Child Health. 2006;42(9):521-7.

65. Velazquez FR. 46th Annual meeting of ICAAC, San Francisco, California, US. 2006;September 27-30.

6 APPENDICES

APPENDIX A: EFFICACY, SAFETY AND IMMUNOGENICITY OF ROTAVIRUS VACCINES

Two rotavirus vaccines from GlaxoSmithKline Biologicals (RotaRIX) and Merck (RotaTEQ) have been licensed in Europe and the USA respectively and in several other countries.[18] Efficacy, safety and immunogenicity of these two vaccines are discussed in detail hereafter. At the end of each chapter (efficacy, safety and immunogenicity), the main results are summarized in a box.

The first rotavirus vaccine, Rotashield, was included in the US program in 1998, with an efficacy against RVGE and AGE largely comparable to that of RotaTEQ and RotaRIX. However, the vaccine was taken off the market in 1999 because of its strong relationship with intussusception.[46] For this reason, clinical trials on new rotavirus vaccines test specifically for safety with respect to intussusception (see below). Another vaccine, "Lanzhou lamb rotavirus vaccine" was licensed in 2001 in China. However, only little data is available about the safety, immunogenicity and efficacy of this vaccine. There is scant information that other vaccines against rotavirus are currently in development, most of them in pre- or early clinical trial phase.[18]

EFFICACY

Overview randomized clinical trials for assessing efficacy of RIX4414 (RotaRIX) and pentavalent bovine-human reassortant vaccine (RotaTEQ)

RotaRIX: Five randomized, double-blinded, placebo-controlled trials have been conducted in different countries and in different conditions (Tables I (i), at the end of this Appendix A).

Study GSK 004[47] was done in Finland in order to evaluate the efficacy of 2 doses of the vaccine given at 2 and 4 months of age, without concomitant administration of the usual pediatric vaccines. 368 patients were followed through the first and second season of rotavirus in 2001 and 2002.

In study GSK 006[48, 49], 2155 children from Mexico, Venezuela and Brazil were randomized to receive the vaccine or placebo at 2 and 4 months of age. Widely used pediatric vaccines (DTPw-HBV/Hib) were administered concomitantly. The oral polio vaccine was administrated 2 weeks apart from the RIX4414 vaccine. 1846 subjects were followed for the efficacy from dose 1 (day 0) through to 12 months of age.

In study GSK 007[50] in Singapore, 2464 children were randomized to get the RIX4414 vaccine or placebo at 3 and 4 months. Widely used pediatric vaccines (DTPa-IPV/Hib and HBV) were administered concomitantly. Patients were followed from 2 weeks post dose 2 through to 18 months of age.

Study GSK 023[44] is the most extensive study, in which the efficacy of the vaccine is evaluated in a subgroup of 17867 out of a total of 63225 randomized patients from 11 Latin American countries and Finland. Vaccine or placebo was given at 2 and 3 to 4 months of age, together with common pediatric vaccines. Patients were followed from 2 weeks post dose 2 through to 12 months of age.

Another study (study GSK 036; Vesikari et al, *forthcoming*) was performed in 6 European countries (France, Germany, Spain, Czech Republic, Italy and Finland), including 3874 patients. Usual pediatric vaccines (DTPa-IPV/Hib, HBV; 8.6% also MCV; 10.9% also PCV) were administered concomitantly according to local immunisation schedules and patients were followed from 2 weeks post dose 2 through to the end of the 1st season (with a mean of 6 months follow up).

RotaTEQ: Three randomized, double-blinded, placebo-controlled trials have been conducted in Finland and the US in order to assess the efficacy of the pentavalent human-bovine reassortant rotavirus vaccine (Tables I (ii)).

Study MERCK 006[40] was made in Finland and the US for evaluating the efficacy against (severe) RVGE of 3 doses of the vaccine given 4 tot 10 weeks apart, with concomitant routine immunisations (excluding oral polio vaccine (OPV)) in healthy children between 6 and 12 weeks of age. 5673 children have been followed from 2 weeks post dose 3 through to the end of the first full epidemic season and a subgroup through the second epidemic season. Efficacy for the prevention of hospitalizations and/or emergency department visit for RVGE has been conducted in 12 countries (European and Latin American countries, US and Taiwan), where 70301 children have been followed up.

Another study in Finland (MERCK 005[51]) followed 1349 children 2 to 8 months of age from 2 weeks post dose 3 through the end of the first, second and third full epidemic season.

Study MERCK 007[52] followed 1310 children (6-13 weeks of age) for one full epidemic season in Finland and US for evaluating efficacy, immunogenicity and safety at the end of the vaccine's shelf life in healthy infants.

All efficacy estimates reported hereafter are based on a period of follow up of 12 months or one full epidemic season, and are calculated based on according-to-protocol (ATP) analysis, unless stated otherwise. The estimates and confidence intervals reported hereafter, are based on tables obtained confidentially from the ESPID/ESPGHAN expert group (European Society of Pediatric Infectious Diseases/European Society of Pediatric Gastroenterology, Hepatology and Nutrition). These tables will be published in the Journal of Pediatric Gastroenterology and Nutrition (they are currently under revision and conditionally accepted). The yet published estimates and confidence intervals are presented in Table I at the end of this Appendix. As studies for RotaRIX and RotaTEQ were conducted in different countries and used different endpoints (see below), comparison of efficacy estimates should be handled with great care. Moreover, none of the studies adjusted their efficacy estimates for multiple endpoints; hence confidence intervals should be interpreted with care, especially for the marginal significant values. The RV vaccines currently marketed in Europe are formulated with aggregate viral titer of approximately $6.7x10^7$ to $12.4x10^7$ infectious units per dose (RotaTEQ) and $10^{6.5}$ median cell-culture infective doses (RotaRIX).

1. Efficacy of RotaRIX and RotaTEQ for the prevention of rotavirus gastroenteritis (RVGE) of *any severity* (Tables I A)

RotaRIX:

In studies GSK 004, 006 and 007 the primary endpoint of efficacy of RIX4414 was taken to be RVGE of any severity. Study GSK 004 showed a reduction of risk ratio (RRR) of 73% (35.7-88.6) through the first epidemic season for a vaccine titre of $10^{4.7}$ (i.e. lower than the finally chosen titre of $10^{6.5}$). A lower reduction was found in study 006 for vaccine titres of $10^{4.7}$ (58% (29-76)), $10^{5.2}$ (56% (25-75)) and $10^{5.8}$ (70% (46-84)) (RRR for different titres grouped together is 61.4% (44.4-73.1). During study GSK 007, only 6 cases of gastroenteritis occurred in children followed up to 18 months of age (2 in the vaccine group with titre $10^{4.7}$ and 4 in the placebo group). RRR for different titres grouped together in this study is 81.9% (15.9-96.1).

Preliminary data for the study in Europe (study GSK 036) shows slightly higher efficacy rates. The study found an 87% (80-91.7) reduction against RVGE of any severity (similar results for ITT analysis).

RotaTEQ:

In study MERCK 005 and 006 primary endpoint was efficacy of the pentavalent human-bovine reassortant vaccine against RVGE of any severity. MERCK 005 (Finland) showed highest efficacy for an intermediate dose of $7.9*10^6$ pfu (74.3% (37.9-91.0)), compared to 57.6% (11.8-80.9) for the lower, $2.4*10^6$ pfu dose, and 68.0% (31.1-86.4) for the higher,

$2.7*10^7$ pfu dose. Efficacy for three vaccine titres together was calculated at 59% (40-72). For modified ITT analysis, a slightly higher efficacy was found: 62.8% (41.8-76.1). MERCK 006 tested the final titre of the vaccine ($6.7*10^7$ to $12.4*10^7$ infectious units per dose) on a large sample size, and found efficacy against RVGE of 72.7% (65.6–78.4) for the ATP analysis and 60% (51.5–67.1) for the ITT analysis. MERCK 007 (efficacy at end of shelf life) showed similar efficacy rates: 72.6% (50.6-85.6) for ATP analysis, 57.2% (34-72.3) for ITT analysis.

2. Efficacy of RotaRIX and RotaTEQ for the prevention of *severe* RVGE (Tables I B)

For both vaccines, efficacy against severe RVGE was found to be higher than efficacy against RVGE of any severity.

RotaRIX:

In studies GSK 004, 006 and 007 efficacy against severe RVGE was defined as RVGE with a severity score ≥11 on the 20-point scoring system described by Ruuska and Vesikari[53]. Efficacy against severe RVGE was estimated for study GSK 004 90% (36-98.4), and for study GSK 006 respectively 66%, 71% and 86% for increasing titres of the vaccine (RRR for different titres grouped together is 74% (56-85)).

The extensive study GSK 023, which used the final vaccine titre of $10^{6.5}$, had as primary endpoint efficacy against severe RVGE, i.e. severe GE with RV positive ELISA test. Severe gastroenteritis was defined as an episode of diarrhoea (the passage of three or more loose or watery stools within a 24-hour period), with or without vomiting, that required overnight hospitalization or rehydration therapy equivalent to World Health Organization plan B (oral rehydration therapy) or plan C (intravenous rehydration therapy) in a medical facility such as a hospital, clinic, or supervised rural health care centre. Efficacy against severe RVGE and severe RVGE (≥11 on Vesikari scale) was 84.7% (71.1-92.4) for according-to-treatment (ATP) analysis, and slightly lower, i.e. 81.3% (69-88.7) for intention-to-treat (ITT) analysis, for children followed up to 12 months of age. Most of these results are based on trials conducted in developing countries.

Preliminary data for a separate study in Europe (study GSK 036) shows slightly higher efficacy rates. The study found a 95.8% (90-98.3) relative risk reduction against severe RVGE (≥11 on Vesikari scale) (similar results for ITT analysis).

RotaTEQ:

The MERCK 006 study (Finland, USA) estimated efficacy against severe RVGE (defined as score >16 according to the 24-point severity scale[54, 55] to be 98.0% (88.3–100.0). MERCK 005 and MERCK 007 showed similar efficacy of 100% (83.5-100), respectively 100% (13-100).

3. Efficacy of RotaRIX and RotaTEQ for the prevention of RVGE *hospitalizations and emergency visits* (Tables I C)

RotaRIX:

Study GSK 006 found an efficacy against any hospitalization due to RVGE of 79% (53-91) for all doses and vaccine titres combined.

Study GSK 023 found higher efficacy against hospitalization (85% (70-93.5)), but this was for hospitalizations due to severe RVGE only (definition see above).

Preliminary data for the study in Europe (study GSK 036) showed the highest efficacy rate (100% (82.3-100)).

RotaTEQ:

The MERCK 006 showed similar efficacy for the prevention of hospitalizations and emergency department visits for RVGE: 95.8% (90.5-98.2) and 93.7% (88.8–96.5) (mostly in USA and Europe). ITT analysis estimated lower efficacy of 88.9% (84.9-91.9), whereas subgroup ITT analysis (only Europe) estimated efficacy of 92% (88-95). Patients were followed up for 2 years.

4. Efficacy of RotaRIX and RotaTEQ against different *serotypes*

RotaRIX:

During study GSK 023, serotype G1 was identified in the stool of 39 of the 90 identified severe RVGE cases, serotype G9 in 23 cases (in 2 cases this was found together with G1 serotype, and in one case with G1 and G2 serotype), serotype G2 in 16 cases, and serotype G3 and G4 in respectively 9 and 3 cases (Table A.1). Efficacy against severe RVGE (with a score ≥11 on the 20-point Vesikari scale) serotype G1 was determined to be 90.8% (70.5-98.2) and against severe RVGE serotype G3, G4 and G9 together 86.9% (62.8-96.6). Sample size for serotype G2 cases is too low to reliably interpret the efficacy estimate. Efficacy against severe RVGE gives similar efficacy estimates for the different serotypes. These data were not reported in Table III.

Again, the Europe study GSK 036 showed higher efficacy estimates against severe RVGE (-≥11 Vesikari score): G1: 96.5% (86-99.6), G3: 100% (56.7-100), G4: 100% (64.7-100) and G9: 95% (80.2-99.4).

Meta-analysis of 5 studies (GSK 004, 006, 007, 023 and 036) indicated a vaccine efficacy after the first dose against G2P[4] RVGE of 81.0% (31.6;95.8) (4 cases in vaccine, 9 cases in placebo group) and against severe RVGE due to G2P[4] of 71.4% (20;91) (9 cases in vaccine, 15 cases in placebo group) [41]. Studies used different viral concentrations of the vaccine (ranging from $10^{4.7}$ ffu to $10^{6.5}$ $CCID_{50}$).

Table A.1: Number of infants with ≥1 episode of serotype-specific (severe) RVGE during the period from two weeks after dose 2 (RotaRIX) until one year of age in the GSK 023 study (table adapted from Ruiz-Palacios et al.[44]). HRV denotes human rotavirus, CI confidence interval.

	No. Of infants with ≥ 1 episode	
	HRV vaccine (n=9009)	**Placebo (n=8858)**
Serotype-specific RVGE		
G1P[8]*	3|	36**
G3P[8], G4P[8], G9P[8]	4°	31°°
G2P[4]	6	10§
Serotype-specific severe RVGE (score of >11 on the Vesikari scale)#		
G1P[8]*	3	32
G3P[8], G4P[8], G9P[8]	4	30
G2P[4]	5	9

* All G1 types isolated were wild-type rotavirus.

| G1P[8] type alone was isolated from two infants; G1P[8] and G9P[8] types were isolated from one infant.

** G1P[8] type alone was isolated from 34 infants; G1P[8] and G9P[8] types were isolated from one infant; and G1, G2, and G9 types were isolated from one infant.

° G3P[8] type alone was isolated from one infant; G4P[8] alone from one infant, and G9P[8] alone from one infant; both G1P[8] and G9P[8] types were isolated from one infant.

°° G3P[8] type alone was isolated from 8 infants; G4P[8] alone from 2 infants, and G9P[8] alone from 19 infants; both G1P[8] and G9P[8] types were isolated from one infant and G1P[8], G2P[4] and G9P[8] from one infant.

§ G2P[4] alone was isolated from nine infants, and G1P[8], G2P[4] and G9P[8] were isolated from one infant.

Scores on the Vesikari scale range from 0 to 20, with higher scores indicating more severe cases. An episode with a score of 11 or greater was considered severe.

RotaTEQ:

During study MERCK 06, serotype G1 was identified in the stool of the majority of RVGE cases (358 from the 401 serotypes stools). Efficacy against RVGE serotype G1 is 74.9%

(67.3-80.9), but there is a stronger reduction in the number of hospitalizations and emergency department visits for serotype G1, i.e. 95.1% (91.6-97.1). Also a substantial reduction in the number of hospitalizations and emergency department visits for serotypes G3, G4 and G9 was shown. Data for G2 and G12 are also given, but based on a very small sample size. Reduction in number of RVGE cases serotypes G2, G3, G4 and G9 was also indicated, but again based on very small sample sizes and not significant for G3, G4 and G9 (Tables A.2 and A.3). These data are not reported in Table III.

Unpublished data from MERCK 006 estimated efficacy for the different serotypes against hospitalizations and emergency department visits post 1st dose up to 2 years (ITT analysis): G1: 92% (88-95), G2: 92% (35-99), G3: 85% (50-96), G4: 90% (57-98) and G9: 92% (66-98). These values differ from the published values and were based on higher number of cases in both vaccine and placebo group.

Table A.2: Clinical efficacy against RVGE of any severity, and against hospitalizations and emergency department visits in the per-protocol population of the clinical-efficacy substudy (MERCK 006), according to G serotype identified in the subject's stool (table adapted from Vesikari et al.[40]). The number of subjects in each group is the number who received at least one dose of RotaTEQ. Some subjects had more than one event. CI denotes confidence interval.

	No. Of cases of RVGE		**Percent efficacy [95% CI]**
	vaccine group (n=2834)	**placebo group (n=2839)**	
Serotype-specific RVGE of any severity			
G1	72	286	74.9% [67.3;80.9]
G2	6	17	63.4% [2.6;88.2]
G3	1	6	82.7% [<0;99.6]
G4	3	6	48.1% [<0;91.6]
G9	1	3	65.4% [<0;99.3]
Serotype-specific RVGE-related hospitalizations and emergency department visits			
G1	16	328	95.1 [91.6;97.1]
G2	1	8	87.6 [<0;98.5]
G3	1	15	93.4 [49.4;99.1]
G4	2	18	89.1 [52.0;97.5]
G9	0	13	100.0 [67.4;100.0]
G12	0	1	100.0 [<0;100.0]

Efficacy of RotaRIX and RotaTEQ during the *second epidemic season* after vaccination

RotaRIX:

Study GSK 004 showed almost equal efficacy against RVGE of any severity through the first (RRR=73% (35.7-88.6)) and second (RRR=73% (30.7-89.3)) epidemic season for a vaccine titre of $10^{4.7}$ (which is lower than the final used titre of $10^{6.5}$). Efficacy against severe RVGE however, showed a decrease from 90% (36-98.4) through the first epidemic season to 84.4% (29-96) through the second epidemic season.

The study performed in Latin America (GSK 023), showed a decrease in efficacy against severe RVGE and severe RVGE (≥11 on Vesikari scale) from 84.7% (71.1-92.4) for children followed up to 12 months of age to 80.5% (71.3-87.1) when children were followed up to 24 months of age. For efficacy against hospitalizations, also a decrease was found: from 85% (70-93.5) for children followed up to 12 months of age, to 83% (71-90) when children are followed up to 24 months of age.

RotaTEQ:

Efficacy against RVGE of any severity dropped from 72.7% (65.6–78.4) after first epidemic season, to 62.6% (44.3-75.4) through the second epidemic season (study MERCK 006).

Efficacy against severe RVGE dropped from 98.0% (88.3–100.0) after first epidemic season, to 88.0% (49.4-98.7) through the second epidemic season (study MERCK 006).

MERCK 005 study did not estimate a lower efficacy against RVGE of any severity after the second epidemic season. However, efficacy estimate after 1st epidemic season was calculated for three vaccine titers together ($2.4*10^6$, $7.9*10^6$ and $2.7*10^7$), whereas efficacy after 2nd season was calculated separately for vaccine titers $2.7*10^7$ (76.2%) and $7.9*10^6$ (53.1%).

Efficacy of RotaRIX and RotaTEQ during the *third epidemic season* after vaccination

Efficacy against RVGE of any severity after 3rd season was estimated 69.3% (49-82) and 61% (39-79) for vaccine titers $2.7*10^7$ and $7.9*10^6$ respectively (MERCK 005).

SUMMARY EFFICACY

The efficacy of RotaRIX and RotaTEQ vaccines in reducing rotavirus-related health outcomes, depends on country, severity of GE, and vaccine formulation.

The estimates of most importance for the cost-effectiveness study in Belgium, are the ones resulting from the large trials in developed countries (RotaRIX: Europe (n=3994), RotaTEQ: Finland and USA (n=5673)):

Efficacy against RVGE of any severity

RotaRIX: 87%

RotaTEQ: 72.7%

Efficacy against severe RVGE

RotaRIX: 95.8%

RotaTEQ: 98.0%

Efficacy against hospitalisations

RotaRIX: 100%

RotaTEQ: 95.8%

Efficacy against different serotypes: RVGE cases were predominantly G1, so efficacy estimates against other serotypes are based on a small number of observations. Serotype-specific efficacy estimates are therefore used in univariate sensitivity analysis.

Efficacy after 2nd and 3rd epidemic season is lower than after 1st epidemic se

SAFETY

Overview randomized clinical trials for assessing safety of RIX4414 (RotaRIX) and pentavalent bovine-human reassortant vaccine (RotaTEQ)

RotaRIX - Seven randomized, double-blinded, placebo-controlled trials have been conducted in different countries and in different conditions (GSK 004, 006, 007 and 023, Dennehy et al.[56], Macias et al.[57] and Vesikari et al.[58]). Parents were asked to fill in a diary card with respect to solicited symptoms (diarrhoea, vomiting and fever for all studies; irritability, loss of appetite and cough/runny nose for some studies) for 7 or 15 days after each vaccination. Unsolicited symptoms were recorded for 43 days after each vaccination. Serious adverse effects (including intussusception and death) were followed up for the whole study period (for a maximum of 2 years).

RotaTEQ - Three randomized, double-blinded, placebo-controlled trials have been conducted in different countries and different conditions (MERCK 005, 006 and 007 and a pooled analysis of MERCK 006, 007 and 009[59]). The MERCK 005 study was described by Vesikari et al.[51], and detailed information about adverse effects of this study was reported in Heaton et al.[60], based on a meeting report of Vesikari[61]. Parents were asked to fill in a diary card with respect to solicited symptoms (diarrhoea, vomiting, fever and irritability) for 7 days after each vaccination. Other adverse effects were recorded for 42 days after each vaccination. Serious adverse effects were recorded at least 42 days after each dose, vaccine-related serious adverse effects and deaths until end of study (one year after the first dose).

All reported values are based on ITT analysis unless stated otherwise. The reported relative risks are based on tables obtained confidentially from the ESPID/ESPGHAN expert group (European Society of Pediatric Infectious Diseases/European Society of Pediatric Gastroenterology, Hepatology and Nutrition). These tables will be published in the Journal of Pediatric Gastroenterology and Nutrition (they are currently under revision and conditionally accepted). The relative risks reported in those tables were all calculated on the same manner, only few original articles mentioned relative risks for the different safety measurements.

1. Intussusception

RotaRIX:

Only study GSK 023 was specifically designed to assess the risk of definite intussusception, but cases of intussusception were reported in all studies.

In study GSK 023 a total of 25 cases of definite intussusception were recorded for the entire study period (median duration 100 days after dose 1). Nine cases occurred in vaccine recipients (6 of them within 31 days after any dose) and 16 in placebo recipients (7 of them within 31 days after any dose). There was no significant increased risk of intussusception in the vaccine group compared to the placebo group (RR=0.56% (0.25-1.24), Table A.4). No temporal cluster of intussusception cases after either dose was found.

Table A.4: Risk of definite intussusception among infants from study GSK 023 receiving vaccine (RotaRIX) or placebo (table adapted from Ruiz-Palacios et al.[44]). HRV denotes human rotavirus, CI confidence interval.

Definite intussusception	No. of events HRV vaccine (n=31,673)	Placebo (n=31,552)	Relative Risk* [95% CI)
≤ 31 days after the administration of either vaccine dose§	6	7	0.85 [0.30;2.42]
≤ 31 days after the administration of vaccine dose 1§	1	2	0.50 [0.07;3.80]
≤ 31 days after the administration of vaccine dose 2§	5|	5°	0.99 [0.31;3.21]
Between dose 1 and 30 to 90 days after dose 2	9	16	0.56 [0.25;1.24]

* The relative risk is the risk in the HRV-vaccine group as compared with that in the placebo group.

§ The 31-day postvaccination window included the day of vaccination and the 30-day period after the dose.

| Data were available for 29,616 infants.

° Data were available for 29,465 infants.

In study GSK 004 and Dennehy et al.[56] no cases of intussusception occurred. In Study GSK 007 there was one case of intussusception in a 3-month-old male infant. Another case of intussusception, which was determined to be unrelated to vaccination, was reported in a 14-month-old subject in the placebo group. In Study GSK 006 one case of intussusception occurred 6 months after the second dose of the vaccine with titre $10^{4.7}$ ffu. This case was assessed as not related to RV vaccination. Another study[57] reported fewer cases of intussusception in vaccine group (4/10159) compared to placebo group (14/10010), RR=0.3 (0.1-0.8).

RotaTEQ:

Study MERCK 006 was specifically designed to assess the risk of definite intussusception. A total of 27 cases of intussusception occurred within one year after the first dose of the vaccine. No increased risk of intussusception was found within 42 days after any dose (multiplicity-adjusted relative risk: 1.6 (0.4-6.4) (6 cases in vaccine group and 5 cases in placebo group)), nor within one year after first dose (relative risk: 0.8 (0.4-1.7) (12 cases in vaccine group and 15 cases in the placebo group)). One case of intussusception was reported in study MERCK 005 in a 7-month-old male. Intussusception was diagnosed 9 days after receiving first dose of the low-potency vaccine. No vaccine strains were recovered from stool specimens collected 3 days after vaccinations and at the time of the diagnosis of intussusception. No cases of intussusception were reported in study MERCK 007 (Table II B(ii)).

Post-marketing in the US: The number of intussusception cases reported to date after RotaTEQ administration does not exceed the number expected based on background rates of 18-43 per 100,000 per year for an unvaccinated population of children ages 6 to 35 weeks *(CDC, unpublished data, 14 Feb 2007)*.

2. Adverse effects (solicited and unsolicited symptoms):

RotaRIX (Tables II D-I(i)):

In all studies, the following symptoms were recorded: diarrhoea, vomiting and fever. In studies GSK 004, 006, Vesikari et al.[58] and Dennehy et al.[56] also irritability, loss of appetite and cough/running nose were recorded.

GSK 023 reported that serious adverse events related to gastroenteritis, such as diarrhoea and vomiting were reported in fewer vaccines than placebo recipients. The other studies did not show unambiguous higher incidence rates for all adverse effects in neither the vaccine nor the placebo group:

Diarrhoea – Only GSK 004 reported a higher rate of diarrhoea in the vaccine group compared to the placebo group (RR=1.9 (0.9-3.95). In the other studies[58, 56] no differences in the occurrence of diarrhoea was found.

Vomiting – No differences in rate of fever were reported between the vaccine and placebo group (Vesikari et al.[58], Dennehy et al.[56], GSK 007 and GSK 004).

Fever – The same results as for diarrhoea are found: Only GSK 004 reported a higher rate of fever in the vaccine group compared to the placebo group (RR=1.3 (0.9-1.8). In the other studies (studies Vesikari et al.[58], Dennehy et al.[56] and GSK 007) no difference in rate of fever was found.

Irritability - No differences in rate of irritability were reported between the vaccine and placebo group (studies Vesikari et al.[58], Dennehy et al.[56] and GSK 004).

Loss of appetite - GSK 004 reported a higher rate of loss of appetite in the vaccine group compared to the placebo group (RR=1.4 (1-1.9)). Vesikari et al.[58] found the same for vaccine titre $10^{4.7}$ + Mylanta (RR=2.8 (0.9-10.5)) and vaccine titre $10^{4.1}$ calcium carbonate (RR=2 (0.7-6.2), but found no difference for the other two vaccine titres. Dennehy et al.[56] neither found a difference in rate of loss of appetite.

Regarding unsolicited adverse effects, no data are available for studies GSK 004, 006 and 007. Study GSK 023 reported that serious adverse events related to GE, such as dehydration, and hypovolemic shock, were reported in fewer vaccines than placebo recipients. Dennehy et al.[56] noted similar frequencies of adverse effects in the vaccine and placebo groups: a total of 52.8% (45.9 –59.7) of subjects in the GSK 5.2 group, 49.8% (42.8 –56.7) in the GSK 6.4 group and 44.4% (34.9 –54.3) in the placebo group reported at least one unsolicited symptom in the 43 days after any dose. The most frequently reported nonserious adverse events were upper respiratory tract infection and otitis media.

RotaTEQ (Tables II D,E,G(i)):

Diarrhoea - Dennehy et al.[59] showed a higher risk of diarrhoea (RR=1.14 (1.02-1.3)) in the vaccine group compared to placebo, as well as Heaton et al.[60] for the $2.5*10^6$ pfu vaccine group. This was not the case for the $25*10^6$ pfu and $8*10^6$ pfu vaccine groups. Study MERCK 006 showed no increase in risk of diarrhoea (RR=1 (0.95-1.1)).

Vomiting – Similar results as for diarrhoea were found: Dennehy et al.[59] showed a higher risk of vomiting (RR=1.2 (1.1-1.4)) in the vaccine group compared to placebo, as did Heaton et al 2005 for the $2.5*10^6$ pfu vaccine group. However, this was not the case for the $25*10^6$ pfu and $8*10^6$ pfu vaccine groups. The study MERCK 006 showed no increase in risk of vomiting (RR=0.95 (0.9-1.1)).

Fever - MERCK 007 showed a higher rate of fever (RR=1.5 (1.1-2.1)), MERCK 006 a lower rate of fever (RR=0.95 (0.9-0.99) and Dennehy et al.[59] no difference in the rate of fever in vaccine recipients versus the placebo group. Heaton et al.[60] reported only for the $2.5*10^6$ pfu vaccine group a higher rate of fever. Again, this was not the case for the $25*10^6$ pfu and $8*10^6$ pfu vaccine groups.

Irritability – Heaton et al.[60] reported higher rates of irritability for the $2.5*10^6$ pfu vaccine group. This was not the case for the $25*10^6$ pfu and $8*10^6$ pfu vaccine groups.

3. Serious adverse effects (excluding mortality):

RotaRIX (Table II A(i)):

In study GSK 006 and 023 the number of patients with at least one serious adverse effect was lower in the vaccine group compared to the placebo group (GSK 006: RR=0.8 (0.5-1.1), GSK 023: RR=0.88 (0.81-0.96)). For the GSK 006 study there were 52 subjects (n=538) with at least one serious adverse effect in the vaccine with titre $10^{4.7}$ group, 55 subjects (n=540) in the titre $10^{5.2}$ group, 39 subjects (n=540) in the titre $10^{5.8}$ group and 64 subjects (n=537) in the placebo group. All these serious adverse effects were assessed as not related to the vaccine under study.

By contrast, study GSK 004, 007 and Dennehy et al.[56] reported more subjects with at least one serious adverse event in the vaccine group compared to the placebo group. In study GSK 004 there were 28 out of 265 subjects with an adverse event in the vaccine group compared to 9 out of 255 in the placebo group (RR=1.9 (0.7-5.3)). For both groups events were deemed to be unrelated to vaccination, and were mainly upper respiratory tract infections. Study GSK 007 reports 58/653 (vaccine group) compared to 40/653 (placebo group) with serious adverse events (RR=1.5 (0.98-2)). Four serious adverse events were said to be possibly related to vaccination (all subjects had also received concomitantly administered DTPa-IPV/Hib vaccine). In Dennehy et al.[56], 8 subjects (n=212) from the vaccine titre $10^{5.2}$ group evolved serious adverse events, 7 subjects (n=209) from the vaccine titre $10^{6.4}$ group and 6 subjects (n=108) from the placebo group. Twelve of these 28 cases were due to the respiratory system and 6 of the 28 cases due to the gastrointestinal system. If only taking the final vaccine titre ($10^{6.4}$) into consideration, relative risk becomes 0.6 (0.2-1.7).

Study Vesikari et al.[58] reported one patient with a serious adverse event in the vaccine group (n=30) and no serious adverse effects in placebo group (n=14).

RotaTEQ (Table II A(ii)):

The number of serious adverse effects was greater in the placebo group compared to the vaccine group (studies MERCK 006 and 007). No serious adverse events were reported in the MERCK 005 study.

4. Deaths:

RotaRIX:

In study GSK 023 more patients of the vaccine group died compared to the placebo group (56 compared to 43; RR=1.3 (0.87-1.93)). The death of four vaccine recipients and 2 placebo recipients was related to diarrhoea, but the cause of diarrhoea was not determined. Also relatively more patients from the vaccinated group died due to pneumonia (7 compared to 3 deaths within 31 days after any vaccination (Table II C(i)) and 16 compared to 6 for the whole period.

During study GSK 006, three patients died, one from the placebo group due to generalized visceral congestion, one from the titre $10^{4.7}$ due to sepsis and one from the titre $10^{5.8}$ group due to an automobile accident, all of them assessed as not related to study vaccination

No children died in the studies Vesikari et al.[58], Dennehy et al.[56] and GSK 004.

RotaTEQ:

In the MERCK 006 study, more patients died in the vaccine group compared to the placebo group (24 compared to 20 cases; RR=1.2 (0.7-2.2)). The most common cause of death in both groups was sudden infant death syndrome (7 cases of vaccine group and 8 cases of the placebo group). More detailed information is not given. No deaths were reported in the MERCK 005 study.

5. Faecal shedding of vaccine strains (Table A.5 below)

RotaRIX:

Faecal shedding of vaccine strains during day 7(-9) after each dose was assessed in studies GSK 006, 007, Vesikari et al.[58] and Dennehy et al.[56]. Faecal shedding is substantial and occurs in about half of vaccine recipients after the first dose and in 20-30% of vaccine recipients after the second dose. Dennehy et al.[56] and study GSK 006 report 2 respectively 1 subject who shed vaccine strain 2 months after the first dose. Study GSK 007 reports 11-16% of the patients shedding vaccine strain 45 days after the first dose.

RotaTEQ:

In the MERCK 006 study, faecal shedding of vaccine strains during the four-to-six day period after the administration of the first dose occurred in 12.7% (n=134) of the vaccinees. In the MERCK 005 study, faecal shedding of vaccine strains during the three-to-five day period after administration of the first dose occurred between 1.4-6.3% of the vaccinees. Vaccine shedding was infrequent after the second and third dose of the vaccine.

Table A.5: Percentage of children with faecal shedding of vaccine strain after first, second (and third) dose of RotaRIX and RotaTEQ. Faecal shedding of RotaRIX was assessed during day 7(-9) after each dose, for RotaTEQ this was done during 3-5 or 4-6 day period after first dose.

Reference	vaccine titer	first dose	second dose	third dose
Vesikari et al.[58]	RIX4414 CaCO3 buffer $10^{4.1}$	38%	7 subjects over the three titres	
	RIX4414 CaCO3 buffer $10^{4.7}$	60%		
	RIX4414 CaCO3 buffer $10^{5.8}$	55%		
Dennehy et al.[56]	RIX4414 $10^{5.2}$	47.5%		
	RIX4414 $10^{6.4}$	54.6%		
GSK 006 (all titers together)	RIX4414	35-44%	11-21%	
GSK 007 (all titers together)	RIX4414	76-80%	18-29%	
MERCK 005	PRV $2.69*10^{7}$ pfu	4.1%	shedding infrequent (< 0.6%)	shedding infrequent (< 0.4%)
	PRV $7.92*10^{6}$ pfu	6.3%		
	PRV $2.41*10^{6}$ pfu	1.4%		
MERCK 006	PRV	12.7%	0%	0%

SUMMARY SAFETY

Intussusception and serious adverse events: no increased risk in vaccine compared to placebo group;

Deaths: for both vaccines, a larger number of deaths was reported in the vaccine compared to the placebo group; however, this difference was not statistically significant.

Adverse effects (vomiting, diarrhoea, fever, irritability):

RotaRIX: no difference between vaccine and placebo group

RotaTEQ: largest study showed no difference, but combined with 2 other studies: higher risk of vomiting and diarrhoea in vaccine group compared to placebo group;

Faecal shedding: RotaRIX vaccination results in substantial shedding of vaccine strain, whereas no such shedding is expected or observed with RotaTEQ.

Post-marketing in the US: The number of intussusception cases reported to date after RotaTEQ administration does not exceed the number expected based on background rates of 18-43 per 100,000 per year for an unvaccinated population of children ages 6 to 35 weeks [1].

IMMUNOGENICITY

Comparisons between the immunogenicity levels induced by both vaccines are difficult, because seroconversion rates were defined differently and are measured at different time points (Table A.6). Only one study investigated immunogenicity later than 2 months after administrating last dose.

RotaRIX:

Serum samples were collected before the first dose and one or two months after the second dose. In Vesikari et al.[58], GSK 006 and GSK007, samples were also collected two months after the first dose, and study GSK 004 collected samples at the end of the first and the second epidemic season. Seroconversion was defined as antirotavirus antibody IgA concentration of $\geq$ 20 units/mL in infants initially seronegative for antirotavirus IgA antibody (i.e. before the first dose). Results of the studies are shown in Table A.6. Final titre for the RotaRIX vaccine is $10^{6,4}$ ffu.

RotaTEQ:

Serum samples were collected before the first dose and after the third dose (for study MERCK 005 and 006 approximately 14 days after the third dose, for study MERCK 007 approximately 42 days after the third dose). Seroconversion was defined as an increase in the antibody titre by a factor of 3 or more from the baseline for G1, G2, G3, G4 and P[8] neutralizing antibody titre (MERCK 007 also assesses G6 and P[5] neutralizing antibody titre, because the WC3 parent bovine strain has a G6 serotype and P[5] genotype), and serum anti-rotavirus IgA level. Results of the MERCK 005, 006 and 007 studies are shown in Table A.6. Final titre for the RotaTEQ vaccine is $6.7*10^7$ to $12.4*10^7$ infectious units per dose

Table A.6: Antirotavirus antibody IgA seroconversion rates after vaccination with RotaRIX and RotaTEQ. Final vaccine titres are highlighted.

study	vaccine	dose	2 months after 1st dose/day 2nd dose	14 days after last dose	1 month after last dose	45 days after last dose	2 months after last dose	at 1 year of age/ end first episode	end 2nd episode
GSK 007	RotaRIX	$10^{4,7}$ ffu	75%		76%		72%		
		$10^{5,2}$ ffu	86%		91%		87%		
		$10^{6,1}$ ffu	81%		88%		85%		
GSK 006	RotaRIX	$10^{4,7}$ ffu	38%				61%		
		$10^{5,2}$ ffu	appr. 37%				appr. 62%		
		$10^{5,8}$ ffu	43%				65%		
GSK 004	RotaRIX	$10^{4,7}$ ffu			80%			76%	67%
Dennehy et al.[56]	RotaRIX	$10^{5,2}$ ffu					67,40%		
		$10^{6,4}$ ffu					78,20%		
Vesikari et al.[58]	RotaRIX	$10^{4,1}$ ffu	50%		73%				
		$10^{4,7}$ ffu	72%		84%				
		$10^{5,8}$ ffu	88%		96%				
MERCK 005	RotaTEQ	$2,41*10^{6}$ pfu		93,40% (between 93,4 and 98,7%)					
		$7,92*10^{6}$ pfu							
		$2,69*10^{7}$ pfu		98,70%					
MERCK 006	RotaTEQ	**$6.7*10^{7}$ to $12.4*10^{7}$ infectious units per dose**		95,20%					
MERCK 007	RotaTEQ	$1.1*10^{7}$ infectious units per dose				95,50%			

Overall, the studies showed for both RotaRIX and RotaTEQ increasing seroconversion rates (rotavirus IgA antibody) with increasing vaccine potencies.

For RotaRIX, GSK 004 and GSK 006 showed a higher proportion of infants that developed RVGE in infants that failed to seroconvert compared to the seroconverted infants. However, Vesikari et al.[47] mentioned that rotavirus IgA seroconversion was not an assurance of protection in individual cases. In natural rotavirus infection, only high titers of rotavirus IgA antibody correlate with clinical protection.[62, 63] Such relationships were not explored for RotaTEQ.

However, for RotaTEQ also seroconversion rate of neutralizing antibodies against the different serotypes was assessed. Serologic responses to individual G-serotypes were much lower than anti-rotavirus IgA response, suggesting that protective efficacy is greater than what could be inferred from serum neutralizing antibody responses.

RotaRIX:

Seroconversion rate of anti-rotavirus IgA level increases with increasing vaccine titre and ranges from 73% for GSK vaccine with $10^{4.1}$ ffu, to 96% for GSK vaccine with $10^{5.8}$ ffu (Vesikari et al.[58]) and 88% for GSK vaccine with $10^{6.1}$ ffu (GSK 007), when measured one month after the second dose. For the final titre for the GSK vaccine of $10^{6.4}$ ffu, Dennehy et al.[56]reported a seroconversion rate of 78.2% two months after administration of the second dose. Overall, the seroconversion rates two months after the second dose, or even at the end of the first and second epidemic season are lower than the ones one

month after administration of the second dose of the vaccine. On the other hand, the immune response is higher after the second dose, versus after the first dose.

Some studies also reported geometric mean concentrations (GMC) for groups who got vaccines with different titres. Dennehy et al.[56]reported no difference between vaccine groups; and Vesikari et al.[58] reported higher GMC's in groups vaccinated with vaccine with higher titre. Vesikari et al.[58] also reported an increasing vaccine take for increasing titres of the vaccine, ranging from 74% for GSK vaccine with $10^{4.1}$ ffu, to 96% for GSK vaccine with $10^{5.8}$ ffu (with vaccine take defined as seroconversion and/or vaccine virus shedding in any stool specimen collected).

RotaTEQ:

Seroconversion rate of anti-rotavirus IgA level increases with increasing vaccine titre and ranges from 93.4% to 98.7% for the MERCK 005 study. MERCK 006 found a seroconversion rate of 95.2% for vaccine with $6.7*10^7$ to $12.4*10^7$ infectious units per dose, and MERCK 007 found a seroconversion rate of 95.5% for vaccine with $1.1*10^7$ infectious units per dose.

Clearly, the seroconversion rate of neutralizing antibodies against the G1 serotype depends on vaccine titre. It ranges from 62% (54.2-69.5) for vaccine with $2.41*10^6$ pfu, to 86% (79.5-91.2) for vaccine with $2.69*10^7$ pfu (MERCK 005). MERCK 006 and 007 show seroconversion rates of 75% respectively 56.7%. Seroconversion rates of neutralizing antibodies against the G4 and P[8] serotypes reached 55% respectively 25%. Rate against the G2 serotype is 34% respectively ~15% and against G3 serotype 23% respectively ~8%.

SUMMARY IMMUNOGENICITY

Immunogenicity of the RotaRIX and RotaTEQ will not be directly taken into account in our cost-effectiveness analysis, because:

- No clear relationship between immunogenicity and efficacy of the vaccines was shown.
- Comparison between induced immunity by RotaRIX and RotaTEQ is difficult, because seroconversion rates were defined differently and were measured at different time points.

Immunogenicity was assessed as seroconversion of antirotavirus antibody IgA and serospecific neutralizing antibodies.

Tables I: Efficacy tables for RotaRIX and RotaTEQ.

Tables II: Safety tables for RotaRIX and RotaTEQ.

Tables III: Type-specific efficacy for RotaRIX and RotaTEQ.

The tables intended to put hereafter were obtained confidentially from the ESPID/ESPGHAN expert group (European Society of Pediatric Infectious Diseases/European Society of Pediatric Gastroenterology, Hepatology and Nutrition), but not yet published at the moment of finishing this report. As soon as the tables are published, there will be a link to them. For now, the yet published efficacy estimates are shown (Tables I).

Table. IA(i). Evaluation of efficacy of RIX 4414 (RotaRIX) for the prevention of rotavirus gastroenteritis (RVGE) of any severity – results of randomised, double–blind, placebo controlled trials

Study publication (*abstracts*)	Location (country)	Population (N randomised)	Interventions (experimental *vs* control)	Outcome	Results		RRR (%) (95% CI)	Follow-up period
					Vaccine	Placebo		
1. Vesikari T, 2004	Finland	Healthy infants 6–12 weeks of age N=405	RIX4414 *vs* placebo lower vaccine titre $10^{4.7}$ (final titre $10^{6.5}$)	Any RVGE[c]	7/245	13/123	73 (27–91)	2 weeks post dose 2 – end of 1st epidemic season
					6/241	11/120	73 (20–92)	2nd epidemic season
3. Phua B, 2005	Singapore	Healthy infants 11–17 weeks of age N=2464	RIX4414 (3 different titres) *vs* placebo	Any RVGE[c]	$10^{4.7}$: 2/501 $10^{5.2}$: 0/639 $10^{6.1}$: 0/639	4/642	82 (no CI reported)	2 weeks post dose 2 through 18 months of age
4. Salinas B, 2005	Brazil, Mexico, Venezuela	Healthy infants 6–12 weeks of age N=2155	RIX4414 (3 different titres) *vs* placebo lower vaccine titres (final titre $10^{6.5}$)	Any RVGE[c]	$10^{4.7}$: 21/468 $10^{5.2}$: 22/460 $10^{5.8}$: 5/464	49/454	$10^{4.7}$: 58 (29-76) $10^{5.2}$: 56 (25-75) $10^{5.8}$: 70 (46-84)	2 weeks post dose 2 through 12 months of age

ARR; absolute risk reduction; ATP – according–to–protocol; ITT – intention–to–treat; OPV – oral polio vaccine; MCV – meningococcal conjugate vaccine; PCV – pneumococcal conjugate vaccine; PRV – pentavalent human-bovine reassortant vaccine; RVGE, rotavirus gastroenteritis

Table. IA(ii). Evaluation of efficacy of pentavalent human-bovine reassortant vaccine (RotaTEQ) for the prevention of rotavirus gastroenteritis (RVGE) of any severity – results of randomised, double–blind, placebo controlled trials

Study publication (*abstracts*)	Location (country)	Population (N randomised)	Interventions (experimental *vs* control)	Outcome	Results		RRR (%) (95% CI)	Follow-up period
					Vaccine	Placebo		
5. Vesikari T, 2006 (REST)	Finland, USA	Healthy infants 6–12 weeks of age N=5,673	PRV *vs* placebo	Any RVGE[c]	83/2,207	318/2,305	74.0 (66.8–79.9)	2 weeks post dose 3 through the end of 1st full epidemic season
					150/2834	371/2,839	60 (51.5–67.1)	Any time post dose 1 through the end of 1st full epidemic season
					36/813	88/756	62.6 (44.3–75.4)	2nd epidemic seasons
6. Vesikari T, 2006 (Vaccine)	Finland	Healthy infants 2–8 months of age (median 5) N=1,349	PRV (3 different titres) *vs* placebo	Any RVGE[c]	$2.7x10^7$: 19/276 $7.9x10^6$: 12/237 $2.4x10^6$: 20/253	43/264	$2.7x10^7$: 68.0 (31.1-86.4) $7.9x10^6$: 74.3 (37.9-91.0) $2.4x10^6$: 57.6 (11.8-80.9)	2 weeks post dose 3 through the end of 1st epidemic season
					$2.7x10^7$: 13/303 $7.9x10^6$: 8/264 $2.4x10^6$: 16/280	33/281	$2.7x10^7$: 65.8 (27.7-85.0) $7.9x10^6$: 75.1 (39.9-91.3) $2.4x10^6$: 53.1 (5.3-77.9)	2 weeks post dose 3 through the end of 1st epidemic season
7. Block S, 2007	Finland, USA	Healthy infants 6–13 weeks of age (median 10) N=1,310	PRV *vs* placebo	Any RVGE[c]	15/551	54/564	72.6 (50.6–85.6)	2 weeks post dose 3 through the end of 1st epidemic season (mean 4,6 months)
					27/650	64/660	58 (no CI reported)	Post dose 1 through the end of 1st epidemic season

ARR; absolute risk reduction; ATP – according–to–protocol; ITT – intention–to–treat; OPV – oral polio vaccine; MCV – meningococcal conjugate vaccine; PCV – pneumococcal conjugate vaccine; PRV – pentavalent human-bovine reassortant vaccine; RVGE, rotavirus gastroenteritis

Table IB(i). Evaluation of efficacy of RIX 4414 (RotaRIX) for the prevention of severe rotavirus gastroenteritis (RVGE) – results of randomised, double–blind, placebo controlled trials

Study publication (*abstracts*)	Location (country)	Population (N randomised)	Interventions (experimental *vs* control)	Outcome	Results		RRR (%) (95% CI)	Follow-up period
					Vaccine	Placebo		
1. Vesikari T, 2004	Finland	Healthy infants 6–12 weeks of age N=405	RIX4414 *vs* placebo lower vaccine titre $10^{4.7}$ (final titre $10^{6.5}$)	Severe RVGE (≥11 Vesikari score)	1/245	5/123	90 (10–100)	Two weeks post dose 2 – end of 1st epidemic season
					2/241	6/120	83 (7–98)	2nd epidemic season (full year)
3. Ruiz-Palacios G, 2006	Latin America	Healthy infants 6–13 weeks of age N=20,169	RIX4414 (final titre) *vs* placebo	Severe RVGE (hospitalisation or rehydration in medical facility)	12/9,009	77/8,858	84.7 (71.1–92.4)	2 weeks post dose 2 through 12 months of age
					18/10,159	94/10,010	81.3 (68.4–95.3)	Post dose 1 through 12 months of age
5. Salinas B, 2005	Brazil, Mexico, Venezuela	Healthy infants 6–12 weeks of age N=2155	RIX4414 (3 different titres) *vs* placebo lower vaccine titres (final titre $10^{6.5}$)	Severe RVGE (≥11 Vesikari score)	**$10^{4.7}$:** 12/468 **$10^{5.2}$:** 10/460 **$10^{5.8}$:** 5/464	34/454	**$10^{4.7}$: 66** (32-84) **$10^{5.2}$: 71** (40-87) **$10^{5.8}$: 86** (63-96)	2 weeks post dose 2, 12 months of age
6. Phua B, 2005	Singapore	Healthy infants 11–17 weeks of age N=2464	RIX4414	Hospitalisation RVGE	**$10^{4.7}$:** 0/501 **$10^{5.2}$:** 0/639 **$10^{6.1}$:** 0/639	1/642	–	2 weeks post dose 2, from 18 months of age

ARR; absolute risk reduction; ATP – according–to–protocol; ITT – intention–to–treat; OPV – oral polio vaccine; MCV – meningococcal conjugate vaccine; PCV – pneumococcal conjugate vaccine; PRV – pentavalent human-bovine reassortant vaccine; RVGE, rotavirus gastroenteritis

Table IB(ii). Evaluation of efficacy of pentavalent human-bovine reassortant vaccine (RotaTEQ) for the prevention of severe rotavirus gastroenteritis (RVGE) – results of randomised, double–blind, placebo controlled trials

Study publication (*abstracts*)	Location (country)	Population (N randomised)	Interventions (experimental *vs* control)	Outcome	Results		RRR (%) (95% CI)	Follow-up period
					Vaccine	Placebo		
7. Vesikari T, 2006	Finland, USA	Healthy infants 6–12 weeks of age N=5,673	PRV *vs* placebo	Severe RVGE (>16 Clark score)	1/2,207	51/2,305	98.0 (88.3–100.0)	2 weeks post third dose through end of the first full epidemic season
					2/813	17/756	88 (49.4–98.7)	2nd epidemic seasons
				Office visits for RVGE	13/2834	98/2839	86 (73.9–92.5)	2 weeks post third dose through end of the first full epidemic season
8. Vesikari T, 2006 (Vaccine)	Finland	Healthy infants 2–8 months of age (median 5) N=1,349	PRV (3 different titres) *vs* placebo	Severe RVGE (>16 Clark score)	$2.7x10^7$: 0/276 $7.9x10^6$: 0/237 $2.4x10^6$: 0/253	8/264	100 (no CI reported)	2 weeks post dose 3 through the end of 1st epidemic season
9. Block S, 2007	Finland, USA	Healthy infants 6–13 weeks of age (median 10) N=1,310	PRV *vs* placebo	Severe RVGE (>16 Clark score)	0/551	6/564	100 (13–100)	2 weeks post dose 3 through the end of 1st epidemic season

ARR; absolute risk reduction; ATP – according–to–protocol; ITT – intention–to–treat; OPV – oral polio vaccine; MCV – meningococcal conjugate vaccine; PCV – pneumococcal conjugate vaccine; PRV – pentavalent human-bovine reassortant vaccine; RVGE, rotavirus gastroenteritis

Table IC(i). Evaluation of efficacy of RIX 4414 (RotaRIX) for the prevention of hospitalisation or emergency department visits for rotavirus gastroenteritis (RVGE) – results of randomised, double–blind, placebo controlled trials

Study publication (*abstracts*)	Location (country)	Population (N randomised)	Interventions (experimental *vs* control)	Outcome	Results		RRR (%) (95% CI)	Follow-up period
					Vaccine	Placebo		
2. Ruiz-Palacios G, 2006	Latin America, Finland	Healthy infants 6–13 weeks of age N=20,169	RIX4414 *vs* placebo	Hospitalisation RVGE (≥1 day in hospital)	9/9,009	59/8,858	85 (91.2–96.6)	2 weeks post dose 2 through 12 months of age
4. Phua B, 2005	Singapore	Healthy infants 11–17 weeks of age N=2464	RIX4414 *vs* placebo	Hospitalisation RVGE	**$10^{4.7}$:** 0/501 **$10^{5.2}$:** 0/639 **$10^{6.1}$:** 0/639	1/642	–	2 weeks post dose 2, from 18 months of age
5. Salinas B, 2005	Brazil, Mexico, Venezuela	Healthy infants 6–12 weeks of age N=2155	RIX4414 (3 different titres) *vs* placebo lower vaccine titres (final titre $10^{6.5}$)	Hospitalizations RVGE	9/1395	14/454	79 (48–92)	2 weeks post dose 2, 12 months of age

ARR; absolute risk reduction; ATP – according–to–protocol; ITT – intention–to–treat; OPV – oral polio vaccine; MCV – meningococcal conjugate vaccine; PCV – pneumococcal conjugate vaccine; PRV – pentavalent human-bovine reassortant vaccine; RVGE, rotavirus gastroenteritis

Table IC(ii). Evaluation of efficacy of pentavalent human-bovine reassortant vaccine (RotaTEQ) for the prevention of hospitalisation or emergency department visits for rotavirus gastroenteritis (RVGE) – results of randomised, double–blind, placebo controlled trials

Study publication (*abstracts*)	Location (country)	Population (N randomised)	Interventions (experimental *vs* control)	Outcome	Results		RRR (%) (95% CI)	Follow-up period
					Vaccine	Placebo		
6. Vesikari T, 2006	Mostly USA and Europe (88%)	Healthy infants 6–12 weeks of age N=69,274	PRV *vs* placebo	Hospitalisation RVGE	6/28,646	138/28,488	95.8 (90.5–98.2)	2 weeks post third dose up to 2 years
				ED–RVGE	13/28,646	191/28,488	93.7 (89–96.5)	2 weeks post third dose up to 2 years
				Hospitalisation/ ED–RVGE	20/28,646	357/28,488	94.5 (91.2–96.6)	2 weeks post third dose up to 2 years

ARR; absolute risk reduction; ATP – according–to–protocol; ED, emergency department; ITT – intention–to–treat; OPV – oral polio vaccine; MCV – meningococcal conjugate vaccine; PCV – pneumococcal conjugate vaccine; PRV – pentavalent human-bovine reassortant vaccine; RVGE, rotavirus gastroenteritis

APPENDIX B: ECONOMIC EVALUATIONS OF ROTAVIRUS VACCINATION PROGRAM OPTIONS

We summarize two cost-utility analyses (also account for the effect on quality of life of preventing episodes of RVGE) in developed countries, i.e. a study performed in England/Wales[3] and Australia (Newall et al., *forthcoming*). Methods and results of both studies are compared.

At the time of writing, two other cost-effectiveness analyses were published.[4, 5] They are not implemented in the text below, but they are included in the overview table at the end of this Appendix B. It is likely that between the time of finishing the writing of this report and publishing it, new cost-effectiveness analyses will be published.

Methods

Modelling

Both studies investigated if routine infant immunisation with two likely vaccinate candidates RotaTEQ and RotaRIX, can be cost-effective from the perspective of the health care payer and society (i.e. work loss taken into account). Therefore they used a model following a hypothetical cohort of children over the first 5 years of life. Newall et al. (*forthcoming*) used one-month cycles over the entire analytical horizon, Jit and Edmunds[3] used one-month cycles for the first year of age and one-year cycles thereafter. Newall et al. (*forthcoming*) discounted costs and benefits at a rate of 5%, Jit and Edmunds[3] discounted costs and benefits at a rate of 3,5% for the first 30 years, and at 3% thereafter.

Health outcomes due to rotavirus (Table B.1)

The models quantified the proportion of individuals in specific outcomes of disease, i.e. hospital admission, emergency department visit (EDV), visit of general practitioner (GP) and RV-related deaths. Jit and Edmunds[3] also included nosocomial infections and calls to NHS Direct. For both studies, incidences for the different health care outcomes were estimated in other studies: Newall et al.[64] (Australia) and Harris et al.[25](England/Wales).

For Newall et al. (*forthcoming*), no annual incidences per 1000 children under 5 were reported. Therefore we calculated the number of children under 5 years of age between 1st July 2000 and 30 June 2002 from Newall et al. (*forthcoming*), i.e. 1,276,396 children. We used this as denominator to calculate annual incidences of number of hospitalizations, ED visits and GP consultations. The numerators for the different health care outcomes were obtained from Newall et al. (*forthcoming*), unless stated otherwise.

Table B.1: Annual incidence of health care outcomes due to rotavirus, per 1000 children under 5 years.

	Australia	England/Wales
hospital admissions	3.093 / 7.835 [1]	4.49
nosocomial infections		0.14
ED visits	17.32	9.3
GP consultations	89.94	28.4 / 44.3 [2]
calls to NHS Direct		10.2 / 11.8 [3]
deaths	0.000313	0.0055

[1] Newall et al.[64]/ Newall et al. (*forthcoming*)

[2] from RCGP consultation rates / from GPRD consultation rates[25]

[3] Jit and Edmunds[3] / Harris et al.[25]

Vaccine efficacy (Table at the end of this Appendix B)

Efficacy estimates used for RotaRIX and RotaTEQ should not be regarded as directly comparable, because they are based on different case definitions and obtained from different countries. Efficacy estimates for RotaRIX were based on a study in Latin American countries and Finland[44], whereas estimates for RotaTEQ were based on a study in USA and Finland[40]. However, Newall et al. (*forthcoming*) also used efficacy estimates for RotaRIX based on a yet unpublished European study (Vesikari et al., *forthcoming*). No serotype-specific efficacy estimates are available for the European study.

All used efficacy estimates were based on ATP analysis. For RotaRIX, only ITT based estimates are available for efficacy against RVGE of any severity (Vesikari et al., *forthcoming*) and efficacy against severe RVGE [44] and (Vesikari et al., *forthcoming*). For RotaTEQ, ITT based estimates are available for efficacy against RVGE of any severity, and prevention of RVGE-related hospitalizations and EDV.[40]

For RotaRIX, Jit and Edmunds[3] used for efficacy against EDV and GP the same estimate as for hospitalizations, whereas Newall et al. (*forthcoming*) adjusted the efficacy according to the proportions observed in the RotaTEQ trials (efficacy hospitalizations compared to efficacy EDV, efficacy hospitalizations compared to efficacy GP). Also different estimates were used for efficacy against GP visits in Newall et al. (*forthcoming*) and Jit and Edmunds[3]. Newall et al. (*forthcoming*) used the published estimate for office and clinic visits, whereas Jit and Edmunds[3] used the estimate against RVGE of any severity (which is lower than the estimate used by Newall et al. (*forthcoming*)).

Newall et al. (*forthcoming*) did not adjust for serotype-specific efficacy estimates. For both vaccines in the base-case they assumed serotype coverage to be equal to all typeable rotavirus in Australia (92%). They assumed that vaccines would not be effective against the 8% of rotavirus specimens tested over the last 5 years that were found to be non-typeable. In worst case scenario, serotype coverage was assumed to be 83% (non-responsive or mixed serotypes excluded, which peaked in 2001/2002 at 17%), and for best case scenario 100% (assuming non-reactive samples are actually standard G types).

Jit and Edmunds[3] adjusted vaccine efficacy for the genotype distribution in UK (assessed from 315 samples from 6 centres between January and June 2006). For RotaRIX, the genotype specific efficacy estimate against severe RVGE due to G1 P[8] and G2 P[4] was used, and a pooled estimate for G3 P[8], G4 P[8] and G9 P[8] (Ruiz-Palacios et al 2006). If other genotype appeared with also P[8], the pooled estimate for G3 P[8], G4 P[8] and G9 P[8] was used, otherwise the estimate for G2 P[4] was used. For RotaTEQ, genotype specific efficacy estimates against RVGE of any severity and for the prevention of hospitalizations and EDV were available for G1, G2, G3, G4, G9 and G12.(Vesikari et al 2006a). Jit and Edmunds[3] did not use the G12 efficacy estimate because it was based on only one case, and used instead the G9 estimate.

Newall et al. (*forthcoming*) also looked at efficacy against all-cause GE –related hospitalizations (after the first dose for RotaTEQ).

Partial protection and waning

Both studies took partial vaccination into account. Newall et al. (*forthcoming*) gave the RotaTEQ vaccine 10% efficacy of full vaccination from the first dose, and 50% of the efficacy of full vaccination of the second dose. For RotaRIX, they used data from the phase III trials on the efficacy for the period between dose one and two (against severe RVGE: 62.5% (16-83)). Jit and Edmunds[3] altered the efficacy of partial doses up to the point where partial immunisation affords no protection.

Jit and Edmunds[3] adjusted for waning of the vaccine efficacy, i.e. in base case the vaccine was assumed to be fully effective from first dose, without waning protection within the ages considered in the model. In sensitivity analysis, they used figures for the decrease in RotaTEQ vaccine efficacy between the first and second season as maximum possible annual decrease due to waning protection.

Vaccine coverage (Table B.2)

Vaccine coverage rates were based on estimates for vaccines to be delivered on similar schedules.

Table B.2: Vaccine coverage used in Newall et al. (*forthcoming*) and Jit and Edmunds[3] for RotaRIX and RotaTEQ.

	Vaccine coverage
Newall et al. (*forthcoming*)	
1 dose RotaRIX	5%
1 dose RotaTEQ	2.5%
2 doses RotaTEQ	2.5%
fully immunised	90%
Jit and Edmunds[3]	
1 dose RotaTEQ	0,06%
2 doses RotaTEQ, 1 dose RotaRIX	0,13%
fully immunised	95%

Impact on quality of life

Both studies used the same Canadian survey(Sénécal et al 2006) for estimates on impact of RV episode on the quality of life of children and health carers. Newall et al. (*forthcoming*) used one primary care giver at base case, but looked in sensitivity analysis at a scenario with two or no caregivers per RV episode. Jit and Edmunds[3] only looked at the scenario with 2 caregivers.

Costs (Table B.3)

Both studies estimated costs according to health care system in their country. Costs from Newall et al. (*forthcoming*) were inflated from 2004 to 2006 australian dollars (based on Consumer Price Index, Australian Bureau of Statistics), costs from Jit and Edmunds[3] from 2005 to 2006 pounds (based on harmonized indices of consumer prices). Australian dollars and British pounds were then converted to euros according to Purchasing Power Parities (OECD) (information obtained from http://www.oecd.org/department/0,2688,en_2649_34357_1_1_1_1_1,00.html, accessed 28 February 2007).

Table B.3: Health care costs and indirect economic costs related to rotavirus gastroenteritis, used in Newall et al. (*forthcoming*) and Jit and Edmunds[3].

	Newall et al. (*forthcoming*)	Jit and Edmunds[3]	Newall et al. (*forthcoming*)	Jit and Edmunds[3]
health care costs				
hospitalization	$1890	£611.71	€1290.61	€895.01
ED consultation	$320	£56.44	€218.52	€82.58
GP consultation	$38	£25.63	€25.95	€37.50
GP prescription		£1.89	€0	€2.77
Call to NHS Direct		£15.11		€22.11
1 dose of vaccine	$A80 (RotaRIX)/ $A60 (RotaTEQ)	£35 (RotaRIX)/ £25 (RotaTEQ)	€54.63 (RotaRIX)/ €40.97 (RotaTEQ)	€51.21 (RotaRIX)/ €36.58 (RotaTEQ)
vaccine administration cost	$2.67(RotaRIX)/$2(RotaTEQ)	£5 per dose	€1.82	€7.32 per dose
indirect economic costs (work loss)				
per hospital case	$668	£43.33	€456.15	€63.40
per EDV	$446		€604.56	
per GP	$271	£43.33	€185.06	€63.40
per NHS Direct case		£20.02		€29.29

Sensitivity analysis

Both studies performed univariate sensitivity analysis to investigate the effect on predicted cost per QALY gained, but in a different manner. Jit and Edmunds[3] varied each parameter over the 95% confidence interval of the range of values in its distribution. Newall et al. (*forthcoming*) tested for each parameter a range of values that were considered plausible values (best case and worst case), based on level of uncertainty in the data. Additionally, Newall et al. (*forthcoming*) performed two-way sensitivity analysis and both studies performed a probabilistic sensitivity analysis.

Results (Table B.4)

First of all, there was a large influence of using for RotaRIX the European efficacy estimates instead of the Latin American efficacy estimates: in base case analysis the cost per QALY gained decreases from $60,778 (Latin American estimates) to $44,008 (European estimates) (Newall et al. (*forthcoming*)).

Furthermore, Newall et al. (*forthcoming*) evaluated both vaccines to be possibly cost-effective, depending largely on the application of QOL utilities and the perspective used (health care provider or society). From the health care payer perspective without application of QOL utilities, the complete vaccination needs to cost approximately under $170 (base case vaccine price RotaRIX: 2 doses*$80=$160; RotaTEQ: 3 doses*$60=$120). When quality of life impact is applied to the child only, the completed vaccination would need to be priced at under $120 (approximately) to fall under the $70,000 threshold. In the societal perspective (when work loss is included) both vaccines are bordering on what is considered cost-effective at base case vaccine prices. Other influential parameters were efficacy against hospitalizations and GP visits, and the number of deaths attributable to rotavirus.

Jit and Edmunds[3] evaluated both vaccines not to be cost-effective, for a large range of all considered parameter values. The threshold of £30,000 would be reached in base case, for RotaRIX vaccine price of £19 and RotaTEQ vaccine price of £10 (base case vaccine price RotaRIX: £35; base case vaccine price RotaTEQ: £25). The adjustment for vaccine efficacy for the genotype distribution in UK had no effect on the efficacy estimate of RotaRIX, but resulted in slightly lower efficacy estimates for RotaTEQ. An important

parameter affecting the cost-effectiveness was the number of deaths attributable to rotavirus, a parameter very difficult to estimate. Other influential parameters were found to be QALY's lost by care givers and the cost of the vaccine. Also, the efficacy against non-hospitalizations was found to be influential for RotaTEQ.

Table B.4. Costs per QALY gained for RotaRIX and RotaTEQ vaccination compared to no vaccination in Australia (Newall et al., *forthcoming*) and England/Wales[3]. The maximal threshold for Newall et al. (*forthcoming*) was taken $70,000/QALY gained (€47,800/QALY gained), for Jit and Edmunds[3] £30,000/QALY gained (€43,894/QALY gained).

		health care provider perspective (base case)	societal perspective	health care provider perspective (base case)	societal perspective
Australia	RotaRIX (Latin American efficacy estimates)	$60,778	dominating (cost-saving)	€41,503	dominating (cost-saving)
	RotaRIX (European efficacy estimates)	$44,008		€30,051	
	RotaTEQ	$68,387	dominating (cost-saving)	€46,699	dominating (cost-saving)
England/Wales	RotaRIX (Latin American efficacy estimates)	£61,000	£54,500	€89,251	€79,741
	RotaTEQ	£79,900	£74,000	€116,904	€108,272

Summary

The implementation of rotavirus vaccine is likely to be found more attractive in Australia (Newall et al., *forthcoming*) compared to England/Wales[3], because of the higher estimated burden, together with higher estimated costs (direct and indirect) per RVGE case. Moreover, Jit and Edmunds[3] showed a larger impact of number of deaths, likely because they estimated the annual incidence of RVGE- related deaths higher than Newall et al. (*forthcoming*).

Table (Appendix B): Economic evaluations of rotavirus vaccination program options

reference	Newall et al., *forthcoming*	Jit and Edmunds[3]	Widdowson et al.[5]	Lorgelly et al.[4]
GENERAL				
country	Australia	England/Wales	USA	UK
vaccines	RotaTEQ and RotaRIX	RotaTEQ and RotaRIX	RotaTEQ	mean of RotaTEQ and RotaRIX
perspective	health care payer and society	health care payer	health care payer and society	health care payer and society
model	cohort	cohort	cohort	cohort
follow up	first 5 years of life	first 5 years of life	first 5 years of life	first 5 years of life
	one-month cycles	first year: one-month age bands, one-year age bands thereafter		assume all events occur at age 2
birth cohort	1,276,396	606,166	4,010,000	632
sensitivity analysis		univariate: varied over 95% CI; multivariate:Monte Carlo sampling (Latin hypercube method)	tornado graphs, separately loss of earnings (because almost half of the costs)	univariate and treshold
DISCOUNT RATE				
discount rate costs	5%	3,5% a year for the first 30 years, 3% thereafter	3%	3.50%
discount rate benefits	5%	3,5% a year for the first 30 years, 3% thereafter	3%	(life years gained: 3.5%)
ANNUAL INCIDENCE CHILDREN UNDER 5				
any RVGE			0.7500	0.7000
hospitalization	0.00781	0.0045	0.0167	0.0200
nosocomial infection		0.0001		
outpatient visit			0.0092	
EDV consultation	0.01732	0.0093	0.0533	0.0190
GP visit	0.08994	0.0284	0.0965	0.0960
NHS Direct call		0.0102		
no medical care required			0.5685	
deaths	3.13E-07	5.50E-06	7.70E-06	1.00E-05
COSTS medical				

inflated to	nearest 2005 Australian dollar	2004 pounds sterling	2004 US dollars	2005/2006 pounds sterling
hospitalization	$1890	£611,71	$2,962	£589
nosocomial infection		£611,71		
outpatient visit			$200	
EDV consultation	$320	£56,44	$332	£77
GP visit	$38	£25,63	$63	£22
NHS Direct call		£15,11		£19
death				£6,981
GP prescription		£1,89		
medication			$22	£1.07
over-the-counter medication				£5.84
COSTS non medical				
work loss per hospitalization	$668	£43,33	$236	£608
work loss per nosocomial infection		£43,33		
work loss outpatient visit			$153	
work loss per EDV consultation	$446		$236	£268
work loss per GP visit	$271	£43,33		£268
work loss per NHS Direct call		£20,02		£268
work loss death child			$1,180	included but value not given
child care costs (all episodes)			$9	
other non medical costs (all episodes except death)			$52	
lifetime productivity cost of child death			$1,167,789	£23,600 per year
QALY LOSS				
QALY loss child	0.00186	0.00186		
QALY loss caregiver	0.0022	0.0022		
VACCINE EFFICACY ROTARIX				
any illness				73%
mild/moderate gastroenteritis				

deaths	85% (Latin America) /100% (Europe)	85%		92%
hospitalisations	85% (Latin America) /100% (Europe)	85%		92%
outpatient hospital visits				
EDV consultations	83,1% (Latin America) /97,8% (Europe)	85%		92%
GP visits	76,3% (Latin America)/89,8% (Europe)	85%		92%
nosocomial infections		85%		
NHS direct calls		85%		
serotype specific		85.20%		
serotype coverage	92% (83-100)			
partial protection	62.50%	full protection from first dose		
vaccine waning				
VACCINE EFFICACY ROTATEQ				
any illness				73%
mild/moderate gastroenteritis			65%	
deaths	95.80%	96%	90%	92%
hospitalisations	95.80%	96%	90%	92%
outpatient hospital visits			85%	
EDV consultations	93.70%	93.70%	90%	92%
GP visits	86%	72.70%	85%	92%
nosocomial infections		96%		
NHS direct calls		72.70%		
serotype specific		66,9% (severe) 94,0% (non-severe)		
serotype coverage	92%			
partial protection	10% of efficacy full vaccination after first dose, 50% after second dose	full protection from first dose	for both 1 or 2 doses: half the efficacy of full vaccination (3 doses)	
vaccine waning				
VACCINE COSTS				
cost/dose RotaRIX	$80	£35		£30
cost/dose RotaTEQ	$60	£25	$63	£20
administration cost/dose	$2.67 (RotaRIX)/ $2(RotaTEQ)	£5 (£1 in table)	$10	

extra cost on total vaccination cost per child for treatment of ISS			$0.10	
extra cost on total vaccination cost per child for outpatient diagnostic evaluation ruling out ISS			$0.15	
VACCINE COVERAGE				
only one dose RotaRIX	5%	0.13%		
two doses RotaRIX	90%	95%		
only one dose RotaTEQ	2.50%	0.06%		
only two doses RotaTEQ	2.50%	0.13%		
three doses RotaTEQ	90%	95%	70%	91%
RESULTS				
Cost/QALY gained, health care payer, RotaRIX	$60,778 (Latin America efficacy estimates)/ $44,008 (European efficacy estimates)	£61,000		
Cost/QALY gained, health care payer, RotaTEQ	$68,387	£61,000		
Cost/QALY gained, society, RotaRIX	dominating	£54,500		
Cost/QALY gained, society, RotaTEQ	dominating	£74,000		
Cost/episode saved: health care payer			$366	£60
Cost/episode saved: society			$138	dominating
Cost/serious episode saved: health care payer			$3,024	
Cost/serious episode saved: society			$2,636	
Cost/hospitalisation saved				£2,527
Cost/life year saved: health care payer			$470,729	£177,212

Cost/life year saved: society			$197,190	
Cost/child in the population: health care payer				£42
Cost/child in the population: society				dominating
break-even cost of vaccine: society			$12	
break-even cost of vaccine: health care payer			$42	
influential variables	QOL lost by care givers, cost of vaccine, estimation of hospitalization, efficacy against GPV, (coverage, partial vacc effic, number of deaths)	QALYs lost by carers, cost of vaccine, RotaTEQ: effic against non-hospitalized cases	cost of hospitalisations, EDV, extra child care, work loss	vaccine efficiency against severe illness, probability of in-patient stay, length of hospital stay, incidence of ratovirus, cost of an in-patient stay
influential variables: society				days off work, foregone earnings, vaccine efficiency against any illness, incidence of rotavirus, discount rate

APPENDIX C: DATA REQUEST MKG-MFG

1. Primaire selectiecriteria MKG-MFG verblijven

a. Gastro-enteritiden: **ICD-9-CM codes 001.* tot en met 009.***

i. de infectieuze: deze omvatten volgende (door ons zelf af te lijnen) subgroepen:

1. Rotavirus infecties: code 008.61
2. Andere virale enteritiden: codes 008.62 tot en met 008.69
3. Bacteriële enteritiden: codes 001.* tot en met 008.5
4. Restgroep infectieuze enteritiden: codes 008.8 tot en met 009.3

ii. de overige niet-infectieuze vormen van gastro-enteritis en colitis: codes 558.*

b. zowel in **hoofddiagnose** als in **nevendiagnose**.

c. **gekoppelde**, zowel als **niet-gekoppelde MKG-verblijven.**

d. **alle types verblijven met uitzondering van de types F en M** (eerste en tussentijdse MKG-registraties)

e. **registratiejaren 2003 + 2004**

f. **voor de <1-jarigen** worden bijkomend een aantal gegevens van dataset <pathbirth> opgevraagd, voor zoverre deze verblijven retraceerbaar zijn (zie verder)

2. Gegevensprecisie (i.v.m. reductie van het risico op indirecte persoonsidentificatie):

a. gegevens op **verblijfsniveau** maar met **ad hoc hercodering** van:

i. het patiëntpseudoniem H2 (indien beschikbaar)

ii. het ziekenhuispatiëntnummer

Voor beide kan een simpele persoonsunieke hernummering volstaan, bijv. 1, 2, … etc. voor de H2 en z1, z2, z3,…. voor de ziekenhuispatiëntnummers (na concatenatie ziekenhuisnummer & ziekenhuispatiëntnummer). Er zijn GEEN decoderingstabellen vereist.

b. **leeftijd** & **geslacht** patiënt + veld <**indicator leeftijd**>

c. domicilie patiënt: gereduceerd tot de **provincie woonplaats** (geen NIS-code noch postcode!)

d. geen ziekenhuisverblijfsnummers, noch ziekenhuisnummers: niet relevant voor het onderzoek

e. veld <**verwezen door**>: integraal

f. veld <**type opname**>: integraal

g. **ziekenhuismortaliteit**: extractie uit de velden <bestemming na ontslag> (waarde: 8) en <type ontslag> (waarden 3 en 4); overige waarden zijn niet relevant voor het onderzoek

3. Opgevraagde datasets en hun aggregatieniveau

a. MFG

i. dataset <Verblijf> - recordtype 1

1. jaar en maand van (her)opname
2. jaar en maand van ontslag
3. geslacht
4. alle overige velden niet vereist

ii. dataset <Prestaties> - recordtype 7:

1. aggregatie nomenclatuurcodes in twee subgroepen:
    a. medische beeldvorming
    b. overige prestaties
2. gevraagde aggregatiegegevens: subtotalen <aantal verstrekkingen> en <ZIV-uitgaven> voor beide subgroepen
3. overige velden niet vereist (plaats + datum van verstrekking, noch identificatie zorgverlener)

iii. dataset <Implant> - recordtype 8:

1. gevraagde aggregatiegegevens: totalisaties van <aantal verstrekkingen> en <ZIV-uitgaven>
2. overige velden niet vereist (plaats + datum van verstrekking, noch identificatie zorgverlener)

iv. dataset <BC_MN > - recordtype 9

1. Gevraagde aggregatiegegevens: subtotalen <aantal verstrekkingen> en <ZIV-uitgaven> per <subgroep klinische biologie>
2. overige velden niet vereist (plaats + datum van verstrekking)

v. dataset <Verpleegdagen> - recordtype 3

1. gevraagde aggregatiegegevens: totalisaties van aantal prestaties en bedrag
2. alle overige velden niet vereist

vi. dataset <BPMRI> - recordtype 4

1. gevraagde aggregatiegegevens: totalisaties van aantal gefactureerde eenheden en ZIV-bedrag
2. alle overige velden niet vereist

vii. dataset <Pharma> - recordtype 6

1. gevraagde aggregatiegegevens: totalisaties van aantal geleverde eenheden en vergoed bedrag
2. Codes farmaceutische specialiteiten of nomenclatuurcode van de relatieve verstrekking evenals pseudocode van de vergoedings-categorie zowel als plaats en datum van verstrekking niet vereist, noch het persoonlijk aandeel patiënt.

b. MKG

i. dataset <stayhosp>

Enkel volgende variabelen (of afgeleiden) worden aangevraagd:

a. statistische periode - jaar

b. type verblijf
c. opnamejaar en – maand
d. ontslagmaand
e. totale verblijfsduur in dagen
f. leeftijd (jaren) en geslacht
g. provincie van domicilie (i.p.v. postcode en NIS-code)
h. type opname
i. verwezen door
j. ziekenhuismortaliteit (waarden 1 of 0) i.p.v. de velden <bestemming na ontslag> en <type ontslag>
k. gehercodeerd patiëntnummer ziekenhuis

ii. dataset <stayxtra>

Enkel volgende variabelen worden aangevraagd:

a. APRDRG (versie 15)
b. graad van ernst
c. hosptype 2
d. aantal aangestaste systemen
e. aantal dagen IZ voor ganse verblijf

iii. dataset <stayindx>

1. code bedindex
2. berekende verblijfsduur in bedindex (dagen)

iv. dataset <diagnose>

1. volgnummer specialisme
2. ICD-9-CM diagnosecode
3. hoofd- of nevendiagnose
4. zekerheidsgraad

v. dataset <procicd9>

1. diagnosecode
2. procedurecode
3. interval opname-uitvoering (dagen)

vi. dataset <patbirth>

Voor alle patiënten < 1 jaar uit de primaire selectie, van wie het 'geboorteverblijf ' kan teruggevonden worden via hun pseudoniem H2 of hun ziekenhuispatiëntnummer wordt volgende gegevens aangevraagd:

1. ICD-9-CM code van de geboorte
2. geboortegewicht, teruggebracht tot volgende categoriën:
   a. < 500 gr.
   b. 500-749 gr
   c. 750-999 gr.
   d. 1000-1249 gr.

e. 1250-1499 gr.
f. 1500-1749 gr.
g. 1750-1999 gr.
h. 2000-2499 gr.
i. > 2500 gr.

3. Apgarscores 1 en 5 min.
4. weken zwangerschap
5. prenatale verblijfsduur moeder
6. registratiejaar van het verblijf van de geboorte of eerste verblijf in het ziekenhuis voor elders geborenen

vii. datasets <stayunit>, <stayspec> en <procrizi> zijn NIET vereist!

4. Besluit

Het beoogde gegevensdetail is voldoende 'versluierd' opdat het risico op indirecte persoonsidentificatie als quasi zero zou kunnen beschouwd worden: er worden geen ziekenhuisspecificaties noch enige decoderingstabellen aangevraagd en de domicillie-precisie wordt gereduceerd tot het niveau provincie. Daarenboven worden voor alle datasets (met uitzondering van de ICD-9-CM coderingen) de gegevens geaggregeerd aangevraagd. Al deze elementen samen sluiten een toevallige contextuele identificatie van de patiënt virtueel uit, zodat hier van feitelijk anonieme gegevens mag gesproken worden.

Brussel, 31/01/2007

Dr. Stefaan Van de Sande

Arts-expert & arts-toezichthouder

Federaal Kenniscentrum voor de gezondheidszorg

Wetstraat 62

1040 Brussel

APPENDIX D: CM QUESTIONNAIRE

CM QUESTIONNAIRE

DEEL I: ALGEMEEN

Vragen die moeten worden gesteld aan iedereen (dus zowel de mensen die ambulant werden behandeld als de gehospitaliseerden).

Kosten

Vermeld enkel de categorieën waarin kosten zijn gemaakt op het invulblad (tab 2 van EXCEL-formulier).

Van ieder van deze categorieën wordt het aantal eenheden, de eigen bijdrage (per eenheid en/of totaal), de RIZIV-bijdrage (per eenheid en/of totaal) en/of de totale kost gevraagd.

Categorie		**Eenheid**
MEDISCHE KOSTEN		
	Consultatie huisarts:	
1	Raadpleging op kabinet	Aantal
2	Huisbezoek	Aantal
3	Raadpleging spoedgevallen (zonder hospitalisatie)	Aantal
4	Consultatie specialist/pediater ambulant	Aantal
5 6 7 8	Consultaties overige gezondheidsberoepen ambulant: diëtist verpleegkundige op thuisbezoek bezoek praktijk verpleegkundige andere	Aantal
9 10 11	Ambulante technische onderzoeken aanvragen labo beeldvorming andere	Aantal aanvragen
12 13 14	Ambulante medicatie ORS (oplossing om oraal vocht toe te dienen) antibiotica andere	Aantal verpakkingen
15	Terugbetaalde ambulante verzorgingsproducten	Aantal verpakkingen
NIET-MEDISCHE OF PERSOONLIJKE KOSTEN		
16	Transport van/naar de dokter, hospitaal, … (met auto, bus, taxi, …)	Aantal km (… euro/km)
17 18	Niet terugbetaalde ambulante verzorgingsproducten *extra* luiers andere (bv. ontsmettingsmiddelen, zalven, …)	Aantal verpakkingen
19	Ambulante speciale voeding (bijvoeding, voedingssupplementen, sondevoeding, …)	Aantal verpakkingen
20	Hulpverlening aan huis (extra hulp van betaalde oppas maar egen verpleegkundige)	Aantal dagen

Bijkomende info

Vermeld het antwoord bij iedere categorie op het invulblad (tab 3 van EXCEL-formulier).

Categorie	
21	Wat is de hoedanigheid van de geënquêteerde? 1. Moeder van het kind 2. Vader van het kind 3. Voogd van het kind 4. Andere
22	Opleidingsniveau (hoogste niveau van studies beëindigd door de moeder van het kind): 1. Geen enkele 2. Basisonderwijs (lagere school) 3. Beroepsonderwijs 4. Lager technisch onderwijs 5. Lager secundair onderwijs 6. Hoger technisch onderwijs 7. Hoger secundair onderwijs 8. Hoger onderwijs buiten de universiteit 9. Universitair onderwijs 10. Andere 11. Niet gekend
23	Opleidingsniveau (hoogste niveau van studies beëindigd door de vader van het kind): 1. Geen enkele 2. Basisonderwijs (lagere school) 3. Beroepsonderwijs 4. Lager technisch onderwijs 5. Lager secundair onderwijs 6. Hoger technisch onderwijs 7. Hoger secundair onderwijs 8. Hoger onderwijs buiten de universiteit 9. Universitair onderwijs 10. Andere 11. Niet gekend
24	Hoeveel telefonische consultaties hebt u in verband met deze infectie met een arts gehad? (Aantal keer)
25	Is uw kind ooit ernstig ziek geweest? 1. Ja 2. Neen
26	Hoe frequent is uw kind in het jaar voorafgaand aan de infectie (tijdsinterval [infectiedatum - 1 jaar, infectiedatum]) naar de dokter geweest? (Aantal keer)
27	Hoeveel keer had uw kind voor deze periode van braken/diarree reeds andere episodes van braken/diarree sinds zijn/haar geboorte? (Aantal keer)
28	Hoeveel dagen is uw kind ziek geweest tijdens de periode van diarree/braken ten gevolge van rotavirus? (Aantal dagen)
29 30 31 32 33	Beantwoord de 13 onderstaande vragen over de periode van infectie bij uw kind met 1. Helemaal niet 2. Een beetje 3. Gemiddeld 4. Veel 5. Heel veel Maakte dit u bezorgd? Maakte dit u meer gestresseerd dan anders?

34 35 36 37 38 39 40 41	Maakte dit u meer ongeduldig dan anders? Maakte dit u geërgerd? Had dit een invloed op uw stemming? Maakte dit dat de kwaliteit van uw slaap achteruitgegaan is? Maakte dit dat u minder tijd voor andere familieleden had? Maakte dit dat u uw vrijetijdsactiviteiten heeft moeten verminderen? Maakte dit dat uw dagelijks leven verstoord werd door last-minute veranderingen? Maakte dit dat u het moeilijk had met het maken van plannen? Voelde u zich machteloos? Had zijn/haar infectie een invloed op uw gezondheid? Was dit een bron van spanning en misverstanden binnen de familie?
42	Welk niveau van stress ervaarde u tijdens de episodes van braken/diarree bij uw kind? Gradeer van 1 (geen stress) tot 10 (extreme stress).
43	Onbetaalde oppas: Beroep van diegene die voor het zieke kind heeft gezorgd (slechts 1 keuze mogelijk - kies meest relevante): 1. Geen 2. Arbeider 3. Bediende 4. Middenkader 5. Hoger kader 6. Zelfstandige 7. Niet gekend
44	Onbetaalde oppas: Hoeveel dagen werkverlet heeft deze persoon hierdoor gehad? (Aantal dagen - nauwkeurigheid is een halve dag)

DEEL II: GEHOSPITALISEERDE PATIENTEN

Vragen die enkel moeten worden gesteld aan gehospitaliseerde patiënten.

Andere info

Categorie	
45	Wat was de reden van opname in het ziekenhuis?
46	Op welke dag van de opname is het kind beginnen braken/kreeg het kind diarree? (=0 indien het kind reeds braakte/diarree had bij opname)
47	Hoeveel dagen heeft uw kind op intensieve zorgen verbleven? (=0 indien het kind niet op intensieve zorgen heeft gelegen)

APPENDIX E: QUESTIONS TO CLINICIANS ABOUT CAUSE OF DEATH OF PATIENTS WITH ROTAVIRUS

I. LETTER TO THE CLINICIAN

(an english version can be find below)

Geachte,

Wij voeren een studie uit omtrent de evaluatie van rotavirusvaccinatie in België (in opdracht van het Federaal Kenniscentrum voor de Gezondheidszorg). Hiervoor is het onder meer belangrijk na te gaan hoeveel kindjes er sterven ten gevolge van een rotavirus infectie.

Op basis van MKG gegevens weten we welke kindjes er stierven sinds 2004 met rotavirus als hoofddiagnose en als nevendiagnose, maar niet of rotavirus bijdroeg aan het overlijden. Omdat één sterfgeval meer of minder ten gevolge van rotavirus infectie een sterke invloed kan hebben op een al dan niet positieve evaluatie van rotavirusvaccinatie, willen we voor elk sterfgeval nauwkeurig nagaan of rotavirus mee bepalend was voor het overlijden.

Daarom zouden we u willen vragen of u de hoofd- en nevendiagnoses van elk van de 14 sterfgevallen even na kan gaan, en aan kan duiden in de tabel onderaan deze mail of u denkt dat het overlijden had kunnen vermeden worden indien het kind geen rotavirus infectie had gehad (ja/nee/niet met zekerheid te bepalen).

In bijgevoegd Excel bestand ('diagnoses') vindt u voor elk sterfgeval de hoofd- en nevendiagnose van hospitalisatie (ICD9 code en de definitie van deze code). Het gaat om 3 kindjes met RVGE als hoofddiagnose en 11 kindjes met RVGE als nevendiagnose.

Daar één sterfgeval meer of minder ten gevolge van rotavirus infectie een sterke invloed kan hebben op de al dan niet positieve evaluatie van rotavirus vaccin, hopen we dat u even tijd kan vrijmaken. Het zal niet meer dan een kwartier van uw tijd in beslag nemen, we hopen dan ook dat u snel de ingevulde tabel kan terugsturen (indien mogelijk, vóór zaterdag 7 april). Uw antwoord wordt uiteraard anoniem behandeld.

Alvast bedankt,

Met vriendelijke groeten,

Pierre Van Damme

Dear,

Currently we are doing a study concerning the evaluation of rotavirus vaccination in Belgium. For this purpose, it is very important to know how many children die due to a rotavirus infection. Based on MKG data, we have a list of children who died from 2004 onwards, with rotavirus (RVGE) as primary and secondary diagnosis. However, we do not know if rotavirus was the cause of death. Because one more death due to rotavirus infection can impact strongly on the outcome of rotavirus vaccination evaluation, we would like to determine accurately for each child if rotavirus contributed to his/her death.

For this reason, we would like to ask if you could read through the diagnoses of each of the 14 deceased children, and point out (in the table at the end of this e- mail) if it is in your opinion that the child would not have died if he/she was not infected by rotavirus.

In the attached Excel file ('diagnoses'), you can find for each deceased child the primary and secondary diagnosis during hospitalisation (ICD9 codes and the definitions of these codes). There are 3 children with RVGE as primary diagnosis and 11 children with RVGE as secondary diagnosis.

Because one more death due to rotavirus infection can impact strongly on the outcome of rotavirus vaccination evaluation, we hope you can find a little time (not more than 15 minutes) to fill in the table below and to send it back quickly to us (if possible, before April 7th). Your answer will be handled anonymously.

Thank you very much in advance,

Kind regards,

Pierre Van Damme

Invultabel/ Table to complete

Op basis van de hoofd- en neven diagnoses, denkt u dat het overlijden van het kind vermeden had kunnen worden indien het kind niet geïnfecteerd was met rotavirus?

Based on the primary and secondary diagnoses, do you think the child would not have died if he/she was not infected by rotavirus?

3 deceased patients with RVGE as main diagnosis

	yes: without the rotavirus infection, the child would not have died	**no:** even without the rotavirus infection, the child would have died	**I do not know**
patient 1 patient 2 patient 3			

11 deceased patients with RVGE as secondary diagnosis

	yes: without the rotavirus infection, the child would not have died	**no:** even without the rotavirus infection, the child would have died	**I do not know**
patient 4 patient 5 patient 6 patient 7 patient 8 patient 9 patient 10 patient 11 patient 12 patient 13 patient 14			

II. LIST OF DECEASED PATIENTS WITH THEIR DIAGNOSIS

I. Background on the data

Via MKG (Minimale Klinische Gegevens) hebben wij een lijst gekregen van alle patiënten die gestorven zijn met rotavirus gastroenteritis (RVGE) als hoofd- of nevendiagnose. Voor elk van deze patiënten is de leeftijd gegeven, het aantal dagen dat hij/zij in het ziekenhuis verbleef, en alle hoofd- en nevendiagnoses in de vorm van ICD9 codes. Wij hebben vervolgens voor elk kind de definities van de ICD9 codes opgezocht om zo per kind een volledige beschrijving van de diagnose te verkrijgen (i.p.v. enkel codes).

In dit Excel bestand vindt u dus voor elk sterfgeval de leeftijd van het kind, het aantal dagen dat hij/zij in het ziekenhuis verbleef, en de hoofd- en nevendiagnose van hospitalisatie (zowel de ICD9 codes als de definities van deze codes). Het gaat om 3 kindjes met RVGE als hoofddiagnose en 11 kindjes met RVGE als nevendiagnose.

We obtained a list of all patients who died with rotavirus gastroenteritis as primary or secondary diagnosis from the MKG. For each of these patients the following was reported: age, the duration of hospital stay (in days), and all primary and secondary diagnoses as ICD9 codes. We searched for each child the definitions of the ICD9 codes, in order to get for each child a complete description of his/her diagnosis (instead of only codes).

Thus, in this Excel file you can find for each deceased child, his/her age, duration of stay in the hospital, and the primary and secondary diagnosis of hospitalisation (ICD9 codes as wel as the definition of these codes). There are 3 children with RVGE as primary diagnosis and 11 children with RVGE as secondary diagnosis.

II. Diagnoses of the patients

DIAGNOSIS OF 3 PATIENTS WHO DIED WITH RVGE AS PRIMARY DIAGNOSIS

	ICD9 code	definition ICD9 code
patient 1	(2 days in hospital, 2 years old at hospital admission)	
primary diagnosis:	00861	rotavirus
secondary diagnosis:	4280	428.0 Congestive heart failure, unspecified Congestive heart disease Right heart failure (secondary to left heart failure) *Excludes:* *fluid overload NOS (276.6)*
	5728	572.8 Other sequelae of chronic liver disease
	586	586 Renal failure, unspecified Includes: Uremia NOS *Excludes:* *following labor and delivery (669.3)* *posttraumatic renal failure (958.5)*

		that complicating: *abortion (634-638 with .3, 639.3)* *ectopic or molar pregnancy (639.3)* *uremia:* *extrarenal (788.9)* *prerenal (788.9)* *with any condition classifiable to 401 (403.0-403.9 with fifth-digit 1)*
	78031	780.31 Febrile convulsions (simple), unspecified Febrile seizures NOS
	78550	785.50 Shock, unspecified Failure of peripheral circulation
patient 2	(0 days in hospital, younger than 28 days at hospital admission)	
primary diagnosis:	00861	rotavirus
secondary diagnosis:	2765	276.5 Volume depletion *Excludes:* *hypovolemic shock:* *postoperative (998.0)* *traumatic (958.4)*
	7999	799.9 Other unknown and unspecified cause Undiagnosed disease, not specified as to site or system involved Unknown cause of morbidity or mortality
	9331	933.1 Larynx Asphyxia due to foreign body Choking due to: food (regurgitated) phlegm
	938	938 Foreign body in digestive system, unspecified Alimentary tract NOS Swallowed foreign body
patient 3	(0 days in hospital, 2 years old at hospital admission)	
primary diagnosis:	00861	rotavirus
secondary diagnosis:	78559	785.59 Other Shock: hypovolemic *Excludes:* *shock (due to):* *anesthetic (995.4)* *anaphylactic (995.0)* *due to serum (999.4)* *electric (994.8)* *following abortion (639.5)* *lightning (994.0)* *obstetrical (669.1)* *postoperative (998.0)* *traumatic (958.4)*

DIAGNOSIS OF 11 PATIENTS WHO DIED WITH RVGE AS SECONDARY DIAGNOSIS

	ICD9 code	definition ICD9 code
patient 4		(25 days in hospital, between 28 days and one year old at hospital admission)
primary diagnosis:	59010	590.1 Acute pyelonephritis Acute pyelitis Acute pyonephrosis 590.10 Without lesion of renal medullary necrosis
secondary diagnosis:	00861	rotavirus
	0416	041.6 Proteus (mirabilis) (morganii)
	1944	194 Malignant neoplasm of other endocrine glands and related structures 194.4 Pineal gland
	V452	V45.2 Presence of cerebrospinal fluid drainage device Cerebral ventricle (communicating) shunt, valve, or device in situ *Excludes:* *malfunction (996.2)*
patient 5		(45 days in hospital, between 28 days and one year old at hospital admission)
primary diagnosis:	75651	756.51 Osteogenesis imperfecta Fragilitas ossium Osteopsathyrosis
secondary diagnosis:	DDDD	geen ICD9-cm code werd aangeduid
	00861	rotavirus
	486	486 Pneumonia, organism unspecified *Excludes:* *hypostatic or passive pneumonia (514)* *influenza with pneumonia, any form (487.0)* *inhalation or aspiration pneumonia due to foreign materials (507.0-507.8)* *pneumonitis due to fumes and vapors (506.0)*
patient 6		(31 days in hospital, between 28 days and one year old at hospital admission)
primary diagnosis:	20500	205 Myeloid leukemia Includes: leukemia: granulocytic myeloblastic myelocytic myelogenous myelomonocytic myelosclerotic

myelosis

secondary diagnosis: 27 secondary diagnoses were specified, only a selection of them are reported hereafter:

00861 rotavirus

07999 <u>079.9 Unspecified viral and chlamydial infections</u>
Excludes:
viremia NOS (790.8)

1960 196 Secondary and unspecified malignant neoplasm of lymph nodes
196.0 Lymph nodes of head, face, and neck
Cervical
Cervicofacial
Scalene
Supraclavicular

42291 422.91 Idiopathic myocarditis
Myocarditis (acute or subacute):
Fiedler's
giant cell
isolated (diffuse) (granulomatous)
nonspecific granulomatous

4275 427.5 Cardiac arrest
Cardiorespiratory arrest

485 485 Bronchopneumonia, organism unspecified
Bronchopneumonia:
hemorrhagic
terminal
Pleurobronchopneumonia
Pneumonia:
lobular
segmental
Excludes:
bronchiolitis (acute) (466.11- 466.19)
chronic (491.8)
lipoid pneumonia (507.1)

7455 745.5 Ostium secundum type atrial septal defect
Defect:
atrium secundum
fossa ovalis
Lutembacher's syndrome
Patent or persistent:
foramen ovale
ostium secundum

78609 786.09 Other
Respiratory:
distress
insufficiency
Excludes:

		respiratory distress: *following trauma and surgery (518.5)* *newborn (770.89)* *syndrome (newborn) (769)* *adult (518.5)* *respiratory failure (518.81, 518.83-518.84)* *newborn (770.84)*
patient 7	(55 days in hospital, between 28 days and one year old at hospital admission)	
primary diagnosis:	3350	335.0 Werdnig-Hoffmann disease Infantile spinal muscular atrophy Progressive muscular atrophy of infancy
secondary diagnosis:	00861	rotavirus
	30759	307.59 Other Feeding disorder of infancy or early childhood of nonorganic origin Infantile feeding disturbances of nonorganic origin Loss of appetite of nonorganic origin
	3449	344.9 Paralysis, unspecified
	78609	786.0 Dyspnea and respiratory abnormalities 786.09 Other Respiratory: distress insufficiency *Excludes:* *respiratory distress:* *following trauma and surgery (518.5)* *newborn (770.89)* *syndrome (newborn) (769)* *adult (518.5)* *respiratory failure (518.81, 518.83-518.84)* *newborn (770.84)*
	7872	787.2 Dysphagia Difficulty in swallowing
	7907	790.7 Bacteremia *Excludes:* *bacteremia of newborn (771.83)* *septicemia (038)* Use additional code to identify organism (041
patient 8	(21 days in hospital, between 28 days and one year old at hospital admission)	
primary diagnosis:	33521	335.21 Progressive muscular atrophy Duchenne-Aran muscular atrophy Progressive muscular atrophy (pure)
secondary diagnosis:	00861	rotavirus
	4659	465.9 Unspecified site

		Acute URI NOS Upper respiratory infection (acute)
	4824	482.4 Pneumonia due to Staphylococcus
	5128	512.8 Other spontaneous pneumothorax Pneumothorax: NOS acute chronic *Excludes:* *pneumothorax:* *congenital (770.2)* *traumatic (860.0-860.1, 860.4-860.5)* *tuberculous, current disease (011.7)*
	7872	787.2 Dysphagia Difficulty in swallowing
	7991	799.1 Respiratory arrest Cardiorespiratory failure *Excludes:* *cardiac arrest (427.5)* *failure of peripheral circulation (785.50)* *respiratory distress:* *NOS (786.09)* *acute (518.82)* *following trauma or surgery (518.5)* *newborn (770.89)* *syndrome (newborn) (769)* *adult (following trauma or surgery) (518.5)* *other (518.82)* *respiratory failure (518.81, 518.83-518.84)* *newborn (770.84)* *respiratory insufficiency (786.09)* *acute (518.82)*
patient 9	(160 days in hospital, between 28 days and one year old at hospital admission)	
primary diagnosis:	4254	425.4 Other primary cardiomyopathies Cardiomyopathy: NOS congestive constrictive familial hypertrophic idiopathic nonobstructive obstructive restrictive Cardiovascular collagenosis
	4280	428.0 Congestive heart failure, unspecified Congestive heart disease Right heart failure (secondary to left heart failure) *Excludes:*

		fluid overload NOS (276.6)
	99683	996.8 Complications of transplanted organ Transplant failure or rejection Use additional code to identify nature of complication, such as: Cytomegalovirus [CMV] infection (078.5) 996.83 Heart
secondary diagnosis:	rotavirus as secondary diagnosis, other secondary diagnoses not reported	
patient 10	(28 days in hospital, between 28 days and one year old at hospital admission)	
primary diagnosis:	4829	482.9 Bacterial pneumonia unspecified
secondary diagnosis:	00861	rotavirus
	3350	335.0 Werdnig-Hoffmann disease Infantile spinal muscular atrophy Progressive muscular atrophy of infancy
	5180	518.0 Pulmonary collapse Atelectasis Collapse of lung Middle lobe syndrome *Excludes:* *atelectasis:* *congenital (partial) (770.5)* *primary (770.4)* *tuberculous, current disease (011.8)*
	51881	518.81 Acute respiratory failure Respiratory failure NOS *Excludes:* *acute and chronic respiratory failure (518.84)* *acute respiratory distress (518.82)* *chronic respiratory failure (518.83)* *respiratory arrest (799.1)* *respiratory failure, newborn (770.84)*
	V197	V19.7 Consanguinity
patient 11	(11 days in hospital, between 28 days and one year old at hospital admission)	
primary diagnosis:	51881	518.81 Acute respiratory failure Respiratory failure NOS *Excludes:* *acute and chronic respiratory failure (518.84)* *acute respiratory distress (518.82)* *chronic respiratory failure (518.83)* *respiratory arrest (799.1)* *respiratory failure, newborn (770.84)*
secondary diagnosis:	00861	rotavirus

03810 038.10 Staphylococcal septicemia, unspecified

2866 286.6 Defibrination syndrome
Afibrinogenemia, acquired
Consumption coagulopathy
Diffuse or disseminated intravascular coagulation [DIC syndrome]
Fibrinolytic hemorrhage, acquired
Hemorrhagic fibrinogenolysis
Pathologic fibrinolysis
Purpura:
fibrinolytic
fulminans
Excludes:
that complicating:
abortion (634-638 with .1, 639.1)
pregnancy or the puerperium (641.3, 666.3)
disseminated intravascular coagulation in newborn (776.2)

7483 748.3 Other anomalies of larynx, trachea, and bronchus
Absence or agenesis of:
bronchus
larynx
trachea
Anomaly (of):
cricoid cartilage
epiglottis
thyroid cartilage
tracheal cartilage
Atresia (of):
epiglottis
glottis
larynx
trachea
Cleft thyroid, cartilage, congenital
Congenital:
dilation, trachea
stenosis:
larynx
trachea
tracheocele
Diverticulum:
bronchus
trachea
Fissure of epiglottis
Laryngocele
Posterior cleft of cricoid cartilage (congenital)
Rudimentary tracheal bronchus
Stridor, laryngeal, congenital

7485 748.5 Agenesis, hypoplasia, and dysplasia of lung
Absence of lung (fissures) (lobe)
Aplasia of lung
Hypoplasia of lung (lobe)
Sequestration of lung

	22809 5191 75560 7564 78559 7895 DDDD	
patient 12	(23 days in hospital, 3 years old at hospital admission)	
primary diagnosis:	51882	518.82 Other pulmonary insufficiency, not elsewhere classified Acute respiratory distress Acute respiratory insufficiency Adult respiratory distress syndrome NEC *Excludes:* *adult respiratory distress syndrome associated with trauma or surgery (518.5)* *pulmonary insufficiency following trauma or surgery (518.5)* *respiratory distress:* *NOS (786.09)* *newborn (770.89)* *syndrome, newborn (769)* *shock lung (518.5)*
	5819	581.9 Nephrotic syndrome with unspecified pathological lesion in kidney Glomerulonephritis with edema NOS Nephritis: nephrotic NOS with edema NOS Nephrosis NOS Renal disease with edema NOS
secondary diagnosis:	25 secondary diagnoses were specified, only a selection of them are reported hereafter:	
	00861	rotavirus
	0419	041.9 Bacterial infection, unspecified
	2738	273.8 Other disorders of plasma protein metabolism Abnormality of transport protein Bisalbuminemia
	2761	276.1 Hyposmolality and/or hyponatremia Sodium [Na] deficiency
	27903	279.03 Other selective immunoglobulin deficiencies Selective deficiency of IgG
	40599	405 Secondary hypertension
	41511	415.11 Iatrogenic pulmonary embolism and infarction
	5184	518.4 Acute edema of lung, unspecified Acute pulmonary edema NOS Pulmonary edema, postoperative

		Excludes: *pulmonary edema:* *acute, with mention of heart disease or failure (428.1)* *chronic or unspecified (514)* *due to external agents (506.0-508.9)*
	78559	785.59 Other Shock: hypovolemic
patient 13	(176 days in hospital, less than 28 days old at hospital admission)	
primary diagnosis:	7452	745.2 Tetralogy of Fallot Fallot's pentalogy *Ventricular septal defect with pulmonary stenosis or atresia, dextraposition of aorta, and hypertrophy of right ventricle* *Excludes:* *Fallot's triad (746.09)*
	V5849	V58.49 Other specified aftercare following surgery Change or removal of drains
secondary diagnosis:	106 secondary diagnoses were specified, only a selection of them are reported hereafter:	
	00861	rotavirus
	3459	345.9 Epilepsy, unspecified
	3481	348.1 Anoxic brain damage
	3488	348.8 Other conditions of brain Cerebral: calcification fungus
	4168	416.8 Other chronic pulmonary heart diseases Pulmonary hypertension, secondary
	4275	427.5 Cardiac arrest Cardiorespiratory arrest
	5180	518.0 Pulmonary collapse Atelectasis Collapse of lung Middle lobe syndrome *Excludes:* *atelectasis:* *congenital (partial) (770.5)* *primary (770.4)* *tuberculous, current disease (011.8)*
	5182	518.2 Compensatory emphysema
	51881	518.81 Acute respiratory failure Respiratory failure NOS *Excludes:* *acute and chronic respiratory failure (518.84)* *acute respiratory distress (518.82)* *chronic respiratory failure (518.83)* *respiratory arrest (799.1)* *respiratory failure, newborn (770.84)*
patient 14	(25 days in hospital, 1 year old at hospital admission)	
primary diagnosis:	7798	779.8 Other specified conditions originating in the perinatal

period
which can be ONE of the following:

779.81 Neonatal bradycardia
Excludes:
abnormality in fetal heart rate or rhythm complicating labor and delivery (763.81-763.83)
bradycardia due to birth asphyxia (768.5-768.9)
779.82 Neonatal tachycardia
Excludes:
abnormality in fetal heart rate or rhythm complicating labor and delivery (763.81-763.83)
779.83 Delayed separation of umbilical cord
779.84 Meconium staining
Excludes:
meconium aspiration (770.11, 770.12)
meconium passage during delivery (763.84)
779.85 Cardiac arrest of newborn
779.89
Other
specified
conditions
originating
in the
perinatal
period
Use additional code to specify condition

secondary diagnosis: 00861 rotavirus

3332 333.2 Myoclonus
Familial essential myoclonus
Progressive myoclonic epilepsy
Unverricht-Lundborg disease
Use additional E code to identify drug, if drug-induced

7283 728.3 Other specific muscle disorders
Arthrogryposis
Immobility syndrome (paraplegic)
Excludes:
arthrogryposis multiplex congenita (754.89)
stiff-man syndrome (333.91)

7708 770.8 Other respiratory problems after birth
Excludes:
mixed metabolic and respiratory acidosis of newborn (775.81)

7808 780.8 Generalized hyperhidrosis
Diaphoresis
Excessive sweating
Secondary hyperhidrosis
Excludes:
focal (localized) (primary) (secondary) hyperhidrosis (705.21-705.22)
Frey's syndrome (705.22)

7832 783.2 Abnormal loss of weight and underweight

	Use additional code to identify Body Mass Index (BMI), if known (V85.0-V85.54)
7991	799.1 Respiratory arrest Cardiorespiratory failure *Excludes:* *cardiac arrest (427.5)* *failure of peripheral circulation (785.50)* *respiratory distress:* *NOS (786.09)* *acute (518.82)* *following trauma or surgery (518.5)* *newborn (770.89)* *syndrome (newborn) (769)* *adult (following trauma or surgery) (518.5)* *other (518.82)* *respiratory failure (518.81, 518.83-518.84)* *newborn (770.84)* *respiratory insufficiency (786.09)* *acute (518.82)*

Thanks!

APPENDIX F: PARAMETER ESTIMATES (AND DISTRIBUTIONS) BASELINE ANALYSIS

Table (Appendix F): Parameter estimates (and distributions) base line analysis
NA= not applicable
VE= vaccine efficacy

Health care outcome	Parameter name	Parameter estimate	Distribution	Source
ANNUAL INCIDENCE (for children under 7 years of age)				
Hospitalizations	age-specific incidence	annual number for all children under 7 years * age-specific proportion		
	annual number for all children under 7 years	4648 (stdev: 246; LL:0; UL:birth cohort)	Truncated Normal	MKG, averaged over 4 seasons
	proportion age 0	1-sum(proportions age 1-6)		
	proportion age 1	36.71% (90%range: 35.30-38.13)	Beta	Carenet
	proportion age 2	13.04% (90%range: 12.06-14.04)	Beta	Carenet
	proportion age 3	5.50% (90%range: 4.84-6.18)	Beta	Carenet
	proportion age 4	1.73% (90%range: 1.36-2.13)	Beta	Carenet
	proportion age 5	1.28% (90%range: 0.97-1.63)	Beta	Carenet
	proportion age 6	0.003% (90%range: 0.002-0.005)	Beta	Carenet
Nosocomial infections	age-specific incidence	annual number for all children under 7 years * age-specific proportion		
	annual number for all children under 7 years	annual number for all children under 7 years, RVGE any diagnosis*proportion nosocomial		
	annual number for all children under 7 years, RVGE any diagnosis	7243 (stdev: 435; LL:0; UL:birth cohort)	Truncated Normal	MKG, averaged over 4 seasons
	proportion nosocomial	14% (90%range: 11-17)	Beta	Raes et al.[20]
	proportion age 0	1-sum(proportions age 1-6)		
	proportion age 1	36.71% (90%range: 35.30-38.13)	Beta	Carenet
	proportion age 2	13.04% (90%range: 12.06-14.04)	Beta	Carenet
	proportion age 3	5.50% (90%range: 4.84-6.18)	Beta	Carenet
	proportion age 4	1.73% (90%range: 1.36-2.13)	Beta	Carenet
	proportion age 5	1.28% (90%range: 0.97-1.63)	Beta	Carenet

	proportion age 6	0.003% (90%range: 0.002-0.005)	Beta	Carenet
Outpatient visits	incidence	7 (stdev: 4; LL: 0; UL: birth cohort)	Truncated Normal	MKG, averaged over 4 seasons
GP visits RV+	age-specific incidence	annual number for all children under 7 years * age-specific proportion		
	annual number for all children under 7 years	number of sentinel GP consultations RV+ (6 months) extrapolated to annual incidence for all Belgian children under 7 years		
	number of sentinel GP consultations RV+	55 (stdev: 15; LL: 0; UL: birth cohort)	Truncated Normal	sentinel GPs
	age-specific proportion age 0	1-sum(proportions age 1-6)		
	age 1	0.324 (90%range: 0.319-0.329)	Beta	WIV sentinel labs
	age 2	0.091 (90%range: 0.088-0.094)	Beta	WIV sentinel labs
	age 3	0.032 (90%range: 0.030-0.034)	Beta	WIV sentinel labs
	age 4	0.014 (90%range: 0.012-0.015)	Beta	WIV sentinel labs
	age 5	0.005 (90%range: 0.004-0.006)	Beta	WIV sentinel labs
	age 6	0.003 (90%range: 0.002-0.004)	Beta	WIV sentinel labs
Ped visits RV+	age-specific incidence	age-specific annual number of GP visits divided by proportion at least one GP visit (i.e. 1-proportion Ped visit) from all ambulant visits, multiplied by proportion Ped visits		
	proportion Ped visits			
	age 0	31% (90%range: 20-43)	Beta	CM survey
	age 1	18% (90%range: 9-30)	Beta	CM survey
	age 2	15% (90%range: 5-28)	Beta	CM data + our assumption
	age 3	(1-sum proportions age0-2)/4		our assumption
	age 4	(1-sum proportions age0-2)/4		our assumption
	age 5	(1-sum proportions age0-2)/4		our assumption
	age 6	(1-sum proportions age0-2)/4		our assumption

GP visits RV not tested	age-specific incidence	(proportion GP visits for AGE attributable to RVGE - proportion GP visits RV+) * age-specific numbef of sentinel GP visits for AGE extrapolated to incidence for all Belgian children under 7 years		
	number of sentinel GP visits for *AGE* age			
	0	84	NA	sentinel GPs
	age 1	390	NA	sentinel GPs
	age 2	380	NA	sentinel GPs
	age 3	290	NA	sentinel GPs
	age 4	258	NA	sentinel GPs
	age 5	170	NA	sentinel GPs
	age 6	166	NA	sentinel GPs
	proportion GP visits for AGE attributable to RVGE	22%	Triangular	Regression analysis + Harris et al., 2007; Lorgelly et al., 2007; Widdowson et al., 2007
No medical care	age-specific incidence	(age-specific proportion symptomatic infections * total birth cohort) minus number of children for each age group for whom medical care is sought		
	age-specific proportion of symptomatic RVGE infections	random pick of one of 3 beta distributions: 27% (90%range: 19-34) 25% (90%range: 19-30) 4% (90%range: 2-8)	Beta	Gurwith et al.[26]; Velazquez et al.[28]; Rodriguez et al.[27]
	age 0			
	age 1	random pick of one of 3 beta distributions: 25% (90%range: 17-35) 11% (90%range: 7-15) 25% (90%range: 15-36)	Beta	Gurwith et al.[26]; Velazquez et al.[28]; Rodriguez et al.[27]
	age 2	7% (90%range: 1-16)	Beta	Rodriguez et al.[27]
	age 3	4% (90%range: 0.2-11)	Beta	Rodriguez et al.[27]
	age 4	4% (90%range: 0.2-11)	Beta	Rodriguez et al.[27]
	age 5	2%	NA	our assumption
	age 6	2%	NA	our assumption
Deaths	age-specific incidence	deaths a year equally distributed over the three youngest age groups		Jit et al.[29]

	incidence	0.6 (90%range: 0.007-2.649)	beta	MKG + Questionnaire paediatric clinicians
COSTS (euros 2006)				
Hospitalizations	hospital stay			
Hospitalizations	cost hospital stay	732 € (90%range: 439-1094)	Gamma	Carenet(NHS+remgeld+suppl)
	costs other than hospital stay	84 € (90%range: 8-216)	Gamma	cm survey (NHS+remgeld+suppl)
Nosocomial infections	cost/day in hospital	210 € (90%range: 119-317)	Gamma	Carenet(NHS+remgeld+suppl)
	number of extra days in hospital due to RVGE	4.4 (min:1.7 ;max:5.9)	Triangular	Gleizes et al.[22]
Outpatient visits		129 € (90%range: 65-219)	Gamma	cm survey: ambulant costs for patients with at least one GP visit
GP visits RV+		129 € (90%range: 65-219)	Gamma	cm survey: ambulant costs for patients with at least one GP visit
Ped visits RV+		147 € (90%range: 61-331)	InvGauss	cm survey: ambulant costs for patients with only a Ped visit
GP visits RV not tested		54 € (90%range: 35-73)	Lognormal	cm survey
No medical care		17 € (stdev: 8; 90%range: 5-29)	Normal	cm survey
Death		cfr. cost for hospitalization		
WORK LOSS				
	number of half days caregiver stay home from work (for hospitalized case)	5 (min: 0; max: 14)	Triangular	cm survey
	number of half days caregiver stay home from work (for ambulatory case)	3 (min: 0; max: 8)	Triangular	cm survey
	productivity loss (measured as loss in salary)/day for hospitalized child	155.90 €	NA	'Het absenteïsme in België 2005', ZebraZone European Research & Service Center, 2005
	productivity loss/day for ambulatory case	160.62 €	NA	'Het absenteïsme in België 2005', ZebraZone European Research &

			Service Center, 2005
Hospitalizations	number of half days (hospital)/2 * productivity loss/day for hospitalized child		
Nosocomial infections	number of half days (hospital)/2 * productivity loss/day for hospitalized child		
Outpatient visits	number of half days (ambulatory)/2 * productivity loss/day for ambulatory case		
GP visits RV+	number of half days (ambulatory)/2 * productivity loss/day for ambulatory case		
Ped visits RV+	number of half days (ambulatory)/2 * productivity loss/day for ambulatory case		
GP visits RV not tested	number of half days (ambulatory)/2 * productivity loss/day for ambulatory case		
No medical care	number of half days (ambulatory)/2 * productivity loss/day for ambulatory case/2		
Death	number of half days (hospital)/2 * productivity loss/day for hospitalized child		
QALY LOSS			
Child-medical care	0.0022 (95%C.I.: 0.001682-0.002717)	Beta	Sénécal et al.[38]: HUI-2
Caregiver-medical care	0.001839 (95%C.I.: 0.000927-0.002751)	Beta	Sénécal et al.[38]: EQ-5ED
Child-no medical care	QALY loss child-medical care divided by 2	Triangular (min=zero and max=QALY loss caregiver-medical care)	our assumption
Caregiver-no medical care	QALY loss caregiver-medical care divided by 2	Triangular (min=zero and max=QALY loss caregiver-medical care)	our assumption
VACCINE EFFICACY			
ROTARIX			

Hospitalizations		100% (95%C.I.: 82-100)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against hospitalizations
Nosocomial infections		100% (95%C.I.: 82-100)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against hospitalizations
Outpatient visits		87% (95%C.I.: 80-92)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against RVGE of any severity
GP visits RV+		87% (95%C.I.: 80-92)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against RVGE of any severity
Ped visits RV+		87% (95%C.I.: 80-92)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against RVGE of any severity
GP visits RV not tested		87% (95%C.I.: 80-92)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against RVGE of any severity
no medical care		87% (95%C.I.: 80-92)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against RVGE of any severity
Deaths		96% (95%C.I.: 90-98)	Normal (Log 1-VE)	Vesikari forthcoming (Europe): efficacy against severe RVGE
Waning rate		efficacy after 2nd season/efficacy after 1st season (if efficacy after 2nd season > efficacy after 1st season, waning rate=1)		
	efficacy after 2nd season against severe RVGE (Latin America)	81% (95%C.I.: 71-87)	Normal (Log 1-VE)	Velazquez[65]
	efficacy after 2nd season against hospitalizations (Latin America)	83% (95%C.I.: 71-90)	Normal (Log 1-VE)	Velazquez[65]
	efficacy after 1st season against severe RVGE (Latin America)	85% (95%C.I.: 71-92)	Normal (Log 1-VE)	Ruiz-Palacios et al.[44]
	efficacy after 1st season against hospitalizations (Latin America)	85% (95%C.I.: 70-94)	Normal (Log 1-VE)	Ruiz-Palacios et al.[44]

Partial protection	efficacy after 1st dose	90% (95%C.I.: 9-100)	Normal (Log 1-VE)	De Vos[42]: efficacy against hospitalizations
ROTATEQ				
Hospitalizations		96% (95%C.I.: 91-98)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against hospitalizations and EDV
Nosocomial infections		96% (95%C.I.: 91-98)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against hospitalizations and EDV
Outpatient visits		73% (95%C.I.: 66-78)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against RVGE of any severity
GP visits RV+		73% (95%C.I.: 66-78)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against RVGE of any severity
Ped visits RV+		73% (95%C.I.: 66-78)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against RVGE of any severity
GP visits RV not tested		73% (95%C.I.: 66-78)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against RVGE of any severity
No medical care		73% (95%C.I.: 66-78)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against RVGE of any severity
Deaths		98% (95%C.I.: 88-100)	Normal (Log 1-VE)	Vesikari et al.[40] (Finland and USA): efficacy against severe RVGE
Waning rate		efficacy after 2nd season/efficacy after 1st season (if efficacy after 2nd season > efficacy after 1st season, waning rate=1)		
	efficacy after 2nd season against RVGE of any severity	63% (95%C.I.: 44-75)	Normal (Log 1-VE)	Vesikari et al.[40]
	efficacy after 2nd season against severe RVGE	88% (95%C.I.: 49-99)	Normal (Log 1-VE)	Vesikari et al.[40]

Partial protection	efficacy against hospitalizations and EDVs after 1st dose	83% (95%C.I.: 38-97)		Vesikari et al.[43]
	efficacy against RV of any severity after 1st dose	38% (95%C.I.: <0-70)		Vesikari et al.[43]
	efficacy against hospitalizations and EDVs after 2nd dose	81% (95%C.I.: 50-94)		Vesikari et al.[43]
	efficacy against RV of any severity after 2nd dose	39% (95%C.I.: <0-78)		Vesikari et al.[43]
DISCOUNT RATE				
Costs		3%	NA	'KCE report voorlopige richtlijnen farmacoeconomische evaluatie'
Effects		1.5%	NA	'KCE report voorlopige richtlijnen farmacoeconomische evaluatie'
VACCINE COST				
RotaRIX/dose	factory price minus 10%	56 €	NA	'Aanvraag tot opname aan de Commissie Tegemoetkoming Geneesmiddelen'
RotaTEQ/dose	factory price minus 10%	37 €	NA	'Aanvraag tot opname aan de Commissie Tegemoetkoming Geneesmiddelen'
Administration		5 €	NA	our assumption
VACCINE COVERAGE				
2 months of age		98.0%	NA	Theeten, Hoppenbrouwers et al.[39]; Swennen, Vaxinfo 2005
3 months of age		98.0%	NA	Theeten, Hoppenbrouwers et al.[39]; Swennen, Vaxinfo 2005
4 months of age		97.5%	NA	Theeten, Hoppenbrouwers et al.[39]; Swennen, Vaxinfo 2005

APPENDIX G: PRODUCT INSERTS ROTARIX AND ROTATEQ

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rotarix, powder and solvent for **oral** suspension
Rotavirus vaccine, live

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (1 ml) contains:

Human rotavirus RIX4414 strain (live attenuated)* not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for **oral** suspension.
The powder is white.
The solvent is a turbid liquid with a slow settling white deposit and a colourless supernatant.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rotarix is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastro-enteritis due to rotavirus infection (see section 4.2).

In clinical trials, efficacy was demonstrated against gastro-enteritis due to rotavirus of types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] (see sections 4.4 and 5.1).

The use of Rotarix should be based on official recommendations.

4.2 Posology and method of administration

Posology

The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.

In clinical trials, spitting or regurgitation of the vaccine has rarely been observed and, under such circumstances, a replacement dose was not given. However, in the unlikely event that an infant spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

It is recommended that infants who receive a first dose of Rotarix complete the 2-dose regimen with Rotarix. There are no data on safety, immunogenicity or efficacy when Rotarix is administered for the first dose and another rotavirus vaccine is administered for the second dose or vice versa.

Method of administration

Rotarix is for **oral** use only.

Rotarix should under no circumstances be injected.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity after previous administration of rotavirus vaccines.

Previous history of intussusception.

Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception.

Infants who have known or suspected immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of Rotarix. However, in the absence of sufficient data, administration of Rotarix to asymptomatic HIV subjects is not recommended.

Administration of Rotarix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication for immunisation.

The administration of Rotarix should be postponed in subjects suffering from diarrhoea or vomiting.

4.4 Special warnings and precautions for use

It is good clinical practice that vaccination should be preceded by a review of the medical history especially with regard to the contraindications and by a clinical examination.

The vaccine contains 9 mg of sucrose as an excipient. This amount is too low to cause adverse events in patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

There are no data on the safety and efficacy of Rotarix in infants with gastrointestinal illnesses or growth retardation. Administration of Rotarix may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Excretion of the vaccine virus in the stools is known to occur after vaccination with peak excretion around the 7th day. Viral antigen particles detected by ELISA were found in 50% of stools after the first dose and 4% of stools after the second dose. When these stools were tested for the presence of live vaccine strain, only 17% were positive.

Cases of transmission of this excreted vaccine virus to seronegative contacts of vaccinees have been observed without causing any clinical symptom.

Rotarix should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or individuals receiving immunosuppressive therapy.

Contacts of recent vaccinees should observe personal hygiene (e.g. wash their hands after changing child's nappies).

Limited data in 140 premature children indicate that Rotarix can be given to premature children, however a lower immune response may be observed and the level of clinical protection remains unknown.

A protective immune response may not be elicited in all vaccinees (see section 5.1).

In clinical trials, efficacy was demonstrated against gastro-enteritis due to rotavirus of types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]. The extent of protection that Rotarix might provide against other serotypes is unknown. Clinical studies from which efficacy data were derived were conducted in Europe and Central and South America (see section 5.1).

Rotarix does not protect against gastro-enteritis due to other pathogens than rotavirus.

No data are available on the use of Rotarix for post-exposure prophylaxis.

Rotarix should under no circumstances be injected.

4.5 Interaction with other medicinal products and other forms of interaction

Rotarix can be given concomitantly with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTPa-HBV-IPV/Hib)]: diphtheria-tetanus-whole cell pertussis vaccine (DTPw), diphtheria-tetanus-acellular pertussis vaccine (DTPa), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccine. Clinical studies demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Concominant administration of Rotarix and oral polio vaccine (OPV) does not affect the immune response to the polio antigens. Although concomitant administration of OPV may slightly reduce the immune response to rotavirus vaccine there is currently no evidence that clinical protection against severe rotavirus gastro-enteritis would be affected. The immune response to Rotarix is unaffected when OPV is administered two weeks apart from Rotarix.

There are no restrictions on the infant's consumption of food or liquid, either before or after vaccination.

4.6 Pregnancy and lactation

Rotarix is not intended for use in adults. Thus human data on use during pregnancy or lactation are not available and animal reproduction studies have not been performed.

Based on evidence generated in clinical trials, breast-feeding does not reduce the protection against rotavirus gastro-enteritis afforded by Rotarix. Therefore, breast-feeding may be continued during the vaccination schedule.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

In a total of eleven placebo-controlled clinical trials, approximately 77800 doses of Rotarix were administered to approximately 40200 infants.

In two clinical trials (Finland), Rotarix was administered alone (administration of routine paediatric vaccines was staggered). The incidence of diarrhoea, vomiting, loss of appetite, fever and irritability was not different in the group receiving Rotarix when compared to the group receiving placebo. No increase in the incidence or severity of these reactions was seen with the second dose.

In the remaining nine trials (Europe, Canada, USA, Latin America, Singapore, South-Africa), Rotarix was co-administered with routine paediatric vaccines (see section 4.5). The adverse reaction profile observed in these subjects was similar to the adverse reaction profile observed in subjects receiving the same paediatric vaccines and placebo.

Adverse reactions are listed below per system organ class and frequency.

Frequencies are reported as:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000, <1/1,000)

Infections and infestations
Rare: upper respiratory tract infection

Psychiatric disorders
Very common: irritability
Uncommon: crying, sleep disorder

Nervous system disorders
Uncommon: somnolence

Respiratory, thoracic and mediastinal disorders
Rare: hoarseness, rhinorrhoea

Gastrointestinal disorders
Very common: loss of appetite
Common: diarrhoea, vomiting, flatulence, abdominal pain, regurgitation of food
Uncommon: constipation

Skin and subcutaneous tissue disorders
Rare: dermatitis, rash

Musculoskeletal and connective tissue disorders
Rare: muscle cramp

General disorders and administration site conditions
Common: fever, fatigue

The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63225 subjects were enrolled. This trial gave evidence of no increased risk of intussusception in the Rotarix group when compared with the placebo group as shown in the table below.

Intussusception within 31 days after administration of:	Rotarix N=31673	Placebo N=31552	Relative risk (95% CI)
First dose	1	2	0.50 (0.07;3.80)
Second dose	5	5	0.99 (0.31;3.21)

CI: confidence interval

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: viral vaccines, ATC code: J07BH01

Protective efficacy

Clinical studies have been conducted in Europe and Latin America to evaluate the protective efficacy of Rotarix against any and severe rotavirus gastro-enteritis.

A clinical study performed in Europe evaluated Rotarix given according to different European schedules (2, 3 months; 2, 4 months; 3, 4 months; 3, 5 months) in 4000 subjects. Severity of gastro-enteritis was defined according to the Vesikari 20-point scale which evaluates the full clinical picture of rotavirus gastro-enteritis by taking into account the severity and duration of diarrhoea and vomiting, the severity of fever and dehydration as well as the need for treatment.

After two doses of Rotarix, the protective vaccine efficacy during the first year of life was 87.1% (95% CI: 79.6;92.1) against any rotavirus gastro-enteritis, 95.8% (95% CI: 89.6;98.7) against severe rotavirus gastro-enteritis (Vesikari score ≥11), 91.8% (95% CI: 84;96.3) against rotavirus gastro-enteritis requiring medical attention and 100% (95% CI: 81.8;100) against hospitalisation due to rotavirus gastro-enteritis. Vaccine efficacy during the first year of life progressively increased with increasing disease severity, reaching 100% (95% CI: 84.7;100) for Vesikari scores ≥17.

The type specific vaccine efficacy is presented in the table below:

Type	**Rotavirus gastro-enteritis of any severity**		**Severe rotavirus gastro-enteritis**	
	Rotarix N=2572; Placebo N=1302 (§)			
	Efficacy (%)	**95% CI**	**Efficacy (%)**	**95% CI**
G1P[8]	95.6*	87.9;98.8	96.4*	85.7;99.6
G3P[8]	89.9*	9.5;99.8	100.0*	44.8;100.0
G4P[8]	88.3*	57.5;97.9	100.0*	64.9;100.0
G9P[8]	75.6*	51.1;88.5	94.7*	77.9;99.4
Strains with P[8] genotype	88.2*	80.8;93.0	96.5*	90.6;99.1

(§) ATP cohort for efficacy
* Statistically significant ($p < 0.05$)

A clinical study performed in Latin America evaluated Rotarix in more than 20000 subjects. Severity of gastro-enteritis was defined according to WHO criteria. The protective vaccine efficacy against severe rotavirus gastro-enteritis requiring hospitalisation and/or rehydration therapy in a medical facility and the type specific vaccine efficacy after two doses of Rotarix are presented in the table below:

Type	**Severe rotavirus gastro-enteritis (1st year of life) Rotarix N=8858; Placebo N=9009(§)**		**Severe rotavirus gastro-enteritis (2nd year of life) Rotarix N=7175; Placebo N=7062 (§)**	
	Efficacy (%)	**95% CI**	**Efficacy (%)**	**95% CI**
All RVGE	84.7*	71.7;92.4	79.0*	66.4;87.4
G1P[8]	91.8*	74.1;98.4	72.4*	34.5;89.9
G3P[8]	87.7*	8.3;99.7	71.9	-47.7;97.1
G4P[8]	50.8#	-844;99.2	63.1*	0.7;88.2
G9P[8]	90.6*	61.7;98.9	87.7*	72.9;95.3
Strains with P[8] genotype	90.9*	79.2;96.8	79.5*	67.0;87.9

(§)ATP cohort for efficacy
* Statistically significant ($p < 0.05$)
# The numbers of cases, on which the estimates of efficacy against G4P[8] were based, were very small (1 case in the Rotarix group and 2 cases in the placebo group).

A pooled analysis of five efficacy studies*, showed a 71.4% (95% CI:20.1;91.1) efficacy against severe rotavirus gastro-enteritis (Vesikari score ≥11) caused by rotavirus G2P[4] type during the first year of life.

* In these studies, the point estimates and confidence intervals were respectively: 100% (95% CI: -1858.0;100), 100% (95% CI: 21.1;100), 45.4% (95% CI: -81.5;86.6), 74.7 (95% CI :-386.2;99.6). No point estimate was available for the remaining study.

Immune response

The immunologic mechanism by which Rotarix protects against rotavirus gastro-enteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastro-enteritis has not been established. The following table shows the percentage of subjects with serum anti-rotavirus IgA antibody titers ≥ 20U/ml (by ELISA) one to two months after the second dose of vaccine or placebo as observed in different studies.

Schedule	**Studies conducted in**	**Vaccine**			**Placebo**		
		N	**% ≥ 20U/ml**	**95% CI**	**N**	**% ≥ 20U/ml**	**95% CI**
2, 3 months	France, Germany	239	82.8	77.5;87.4	127	8.7	4.4;15.0
2, 4 months	Spain	186	85.5	79.6;90.2	89	12.4	6.3;21.0
3, 5 months	Finland, Italy	180	94.4	90.0;97.3	114	3.5	1.0;8.7
3, 4 months	Czech Republic	182	84.6	78.5;89.5	90	2.2	0.3;7.8
2, 3 to 4 months	Latin America; 11 countries	393	77.9%	73.8;81.6	341	15.1%	11.7;19.0

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Dextran
Sorbitol
Amino acids
Dulbecco's Modified Eagle Medium (DMEM)

Solvent
Calcium carbonate
Xanthan gum
Sterile water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution:
After the reconstitution, the vaccine should be administered immediately.

However, experimental data have shown that the reconstituted vaccine is stable when stored for 24 hours at ambient temperature (18-25°C). These data are not recommendations for storage.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Store in the original package, in order to protect from light.

In case of temporary storage of the powder and the solvent outside the refrigerator, experimental data have shown that the powder as well as the solvent are stable when stored at temperatures up to 37°C for 1 week. These data are not recommendations for storage.

For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

1 dose of powder in a glass container (type I glass) with a stopper (rubber butyl)
1 ml of solvent in an **oral** applicator (type I glass) with a plunger stopper and a protective tip cap (rubber butyl).
Transfer adapter for reconstitution (1/dose)
in the following pack sizes:
- pack size of 1 glass container of powder plus 1 **oral** applicator of solvent
- pack size of 5 glass containers of powder plus 5 **oral** applicators of solvent
- pack size of 10 glass containers of powder plus 10 **oral** applicators of solvent
- pack size of 25 glass containers of powder plus 25 **oral** applicators of solvent

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

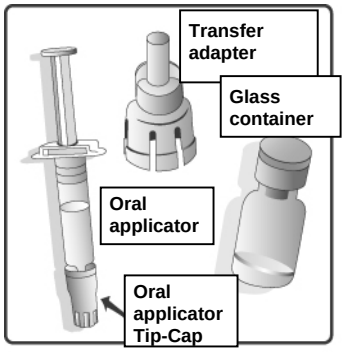
A white deposit and clear supernatant is observed upon storage of the **oral** applicator containing the solvent. The solvent should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to reconstitution.
The reconstituted vaccine is slightly more turbid than the solvent and is milky white in appearance.
The reconstituted vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

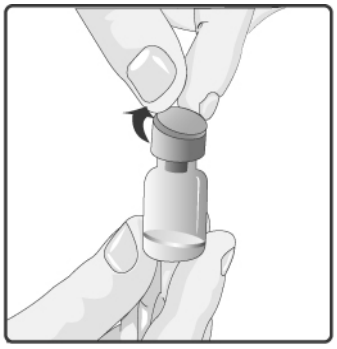
Instructions for reconstitution and administration of the vaccine:

1. Remove the plastic cover from the glass container containing the powder.
2. Connect the transfer adapter onto the glass container by pushing it downwards until the transfer adapter is properly and securely placed.

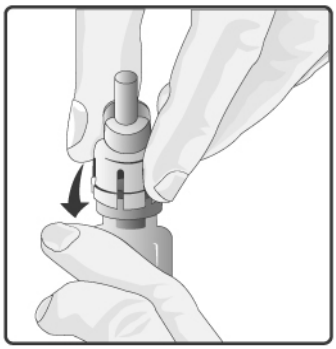
3. Shake the **oral** applicator containing the solvent vigorously. The shaken suspension will appear as a turbid liquid with a slow settling white deposit.
4. Remove the protective tip cap from the **oral** applicator.
5. Connect the **oral** applicator into the transfer adapter by pushing it firmly on this device.
6. Transfer the entire content of the **oral** applicator into the glass container containing the powder.
7. With the **oral** applicator still attached, shake the glass container and examine it for complete suspension of the powder. The reconstituted vaccine will appear more turbid than the solvent alone. This appearance is normal.
8. Withdraw the entire mixture back into the **oral** applicator.
9. Remove the **oral** applicator from the transfer adapter.
10. This vaccine is for **oral administration only**. The child should be seated in a reclining position. Administer the entire content of the **oral** applicator **orally** (by administering the entire content of the **oral** applicator on the inside of the cheek).
11. **Do not inject.**

If the reconstituted vaccine is to be stored temporarily before administration, replace the protective tip cap on the **oral** applicator. The **oral** applicator containing the reconstituted vaccine should be shaken gently again before **oral** administration. **Do not inject**.

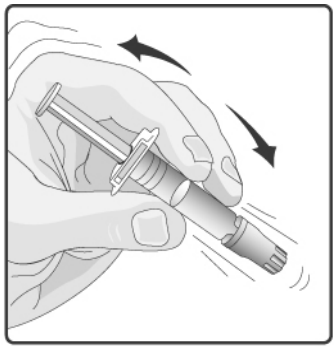




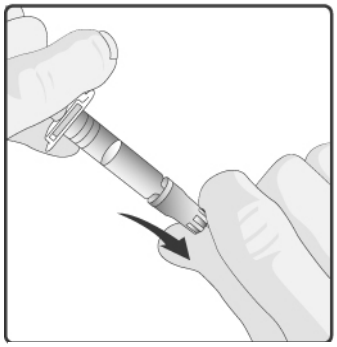
1. Remove the plastic cover from the glass container containing the powder



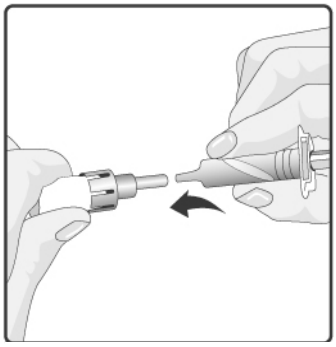
2. Connect the transfer adapter onto the glass container by pushing it downwards until the transfer adapter is properly and securely placed



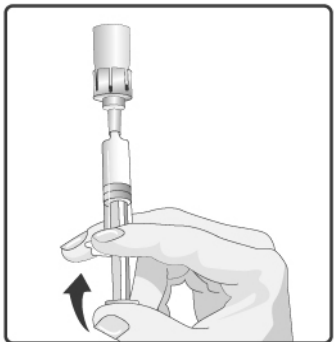
3. Shake the oral applicator containing the solvent vigorously. The shaken suspension will appear as a turbid liquid with a slow settling white deposit



4. Remove the protective tip cap from the oral applicator

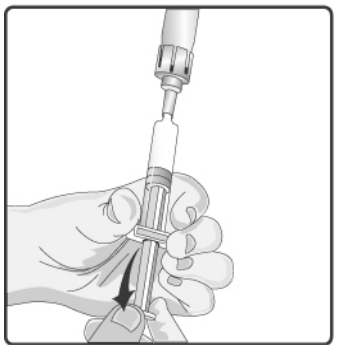


5. Connect the oral applicator into the transfer adapter by pushing it firmly on this device

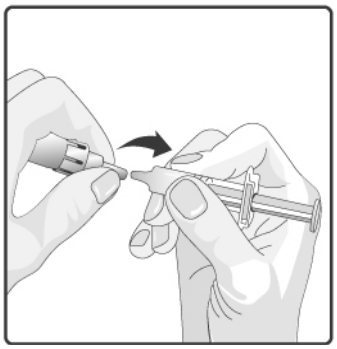


6. Transfer the entire content of the oral applicator into the glass container containing the powder

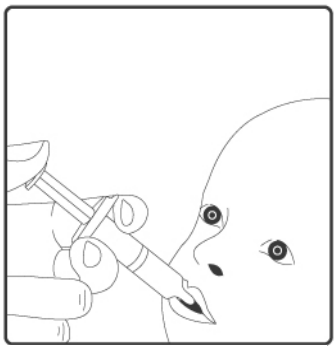
7. With the oral applicator still attached, shake the glass container and examine it for complete suspension of the powder. The reconstituted vaccine will appear more turbid than the solvent alone. This appearance is normal



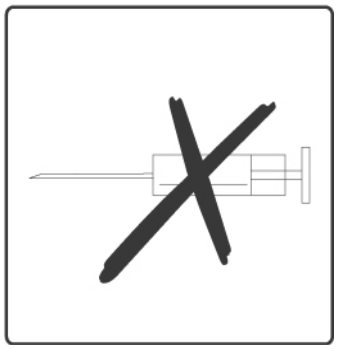
8. Withdraw the entire mixture back into the oral applicator



9. Remove the oral applicator from the transfer adapter



10. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer the entire content of the oral applicator orally (by administering the entire content of the oral applicator on the inside of the cheek)



11. **Do not inject.**

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/330/001
EU/1/05/330/002
EU/1/05/330/003
EU/1/05/330/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/06

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
1330 Rixensart
Belgium

Name and address of the manufacturer(s) responsible for batch release

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
1330 Rixensart
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not aplicable.

- **OTHER CONDITIONS**

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK SIZE OF 1 GLASS CONTAINER WITH 1 ORAL APPLICATOR AND 1 TRANSFER ADAPTER

1. NAME OF THE MEDICINAL PRODUCT

Rotarix, powder and solvent for **oral** suspension
Rotavirus vaccine, live

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (1 ml) contains:

Human rotavirus RIX4414 strain (live attenuated)* not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

3. LIST OF EXCIPIENTS

Powder: sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM)
Solvent: calcium carbonate, xanthan gum, sterile water

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for **oral** suspension
glass container: powder
oral applicator: solvent
transfer adapter
1 dose (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral administration
Do not inject!
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/330/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK SIZE OF 5 GLASS CONTAINERS WITH 5 ORAL APPLICATORS AND 5 TRANSFER ADAPTERS

1. NAME OF THE MEDICINAL PRODUCT

Rotarix, powder and solvent for **oral** suspension
Rotavirus vaccine, live

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (1 ml) contains:

Human rotavirus RIX4414 strain (live attenuated)* not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

3. LIST OF EXCIPIENTS

Powder: sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM)
Solvent: calcium carbonate, xanthan gum, sterile water

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for **oral** suspension
glass container: powder
oral applicator: solvent
transfer adapter
5 x 1 dose
1 dose (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral administration
Do not inject!
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/330/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK SIZE OF 10 GLASS CONTAINERS WITH 10 ORAL APPLICATORS AND 10 TRANSFER ADAPTERS

1. NAME OF THE MEDICINAL PRODUCT

Rotarix, powder and solvent for **oral** suspension
Rotavirus vaccine, live

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (1 ml) contains:

Human rotavirus RIX4414 strain (live attenuated)* not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

3. LIST OF EXCIPIENTS

Powder: sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM)
Solvent: calcium carbonate, xanthan gum, sterile water

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for **oral** suspension
glass container: powder
oral applicator: solvent
transfer adapter
10 x 1 dose
1 dose (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral administration
Do not inject!
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/330/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK SIZE OF 25 GLASS CONTAINERS WITH 25 ORAL APPLICATORS AND 25 TRANSFER ADAPTERS

1. NAME OF THE MEDICINAL PRODUCT

Rotarix, powder and solvent for **oral** suspension
Rotavirus vaccine, live

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (1 ml) contains:

Human rotavirus RIX4414 strain (live attenuated)* not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

3. LIST OF EXCIPIENTS

Powder: sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM)
Solvent: calcium carbonate, xanthan gum, sterile water

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for **oral** suspension
glass container: powder
oral applicator: solvent
transfer adapter
25 x 1 dose
1 dose (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral administration
Do not inject!
Shake before use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/330/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS
ORAL APPLICATOR WITH SOLVENT FOR RECONSTITUTION WITH POWDER

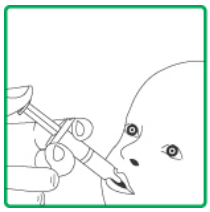
1. NAME OF THE MEDICINAL PRODUCT

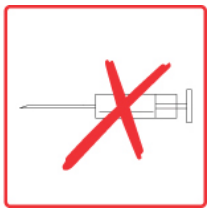
2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER





MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
GLASS CONTAINER WITH POWDER TO BE RECONSTITUTED WITH SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rotarix
Powder for **oral** suspension
Rotavirus vaccine, live
Oral administration

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
ORAL APPLICATOR WITH SOLVENT FOR RECONSTITUTION WITH POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rotarix
Solvent for **oral** suspension
Rotavirus vaccine, live
Oral administration

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (1 ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Rotarix, powder and solvent for oral suspension
Rotavirus vaccine, live

Read all of this leaflet carefully before your child receives this vaccine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ROTARIX IS AND WHAT IT IS USED FOR

Pharmaco-therapeutic group: viral vaccines, ATC code: J07BH01

Rotarix is a viral vaccine, containing live, attenuated human rotavirus, that helps to protect your child against gastro-enteritis (diarrhoea and vomiting) caused by rotavirus infection.

Rotavirus infection is the most common cause of severe diarrhoea in infants and young children. Rotavirus is easily spread from hand-to-mouth due to contact with stools from an infected person. Most children with rotavirus diarrhoea recover on their own. However, some children become very ill with severe vomiting, diarrhoea and life-threatening loss of fluids that requires hospitalisation. Rotavirus infections are responsible for hundreds of thousands of deaths worldwide every year especially in developing countries, where nutrition and health care are not optimal.

When a person is given the vaccine, the immune system (the body's natural defences) will make antibodies against the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus.

As with all vaccines, Rotarix may not completely protect all people who are vaccinated against the rotavirus infections it is intended to prevent.

2. BEFORE YOUR CHILD RECEIVES ROTARIX

Rotarix should not be given:
- if your child has previously had any allergic reaction to rotavirus vaccines or any component contained in Rotarix. The active substances and other ingredients in Rotarix are listed at the end of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- if your child has previously had intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment).
- if your child was born with a malformation of the gastrointestinal system that would predispose for intussusception.
- if your child has any disease which reduces his/her resistance to infection.

- if your child has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- if your child has diarrhoea or is vomiting. It might be necessary to postpone the vaccination until recovery.

Take special care with Rotarix
Excretion of the live vaccine virus in the stools of vaccinated children is known to occur after vaccination, especially around the 7th day. Persons in contact with recent vaccinated children should wash their hands after changing the child's nappies.
Rotarix should be given with caution to children in close contacts with individuals having any disease or receiving any medicine which may reduce his/her resistance to infection.
A lower immune response (reduced ability of the body to respond to the vaccine) may be observed when Rotarix is given to premature children.
Rotarix should be given with caution to children with disorders of the stomach or intestines or children with growth retardation.

Using other vaccines
Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Rotarix may be given at the same time your child receives other normally recommended vaccines, such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, oral or inactivated polio, hepatitis B vaccines as well as pneumococcal and meningococcal serogroup C conjugate vaccines.

Using Rotarix with food and drink
There are no restrictions on your child's consumption of food or liquids, either before or after vaccination.

Breast-feeding
Based on evidence generated in clinical trials, breast-feeding does not reduce the protection against rotavirus gastro-enteritis afforded by Rotarix. Therefore, breast-feeding may be continued during the vaccination schedule.

Important information about some of the ingredients of Rotarix
If you have been told by your doctor that the child being vaccinated has an intolerance to some sugars, contact your doctor before using this vaccine.

3. HOW ROTARIX IS GIVEN

The doctor or nurse will administer the recommended dose of Rotarix to your child. The vaccine (1 ml liquid) will be given **orally**. Under no circumstance should this vaccine be administered by injection.

Your child will receive two doses of the vaccine. Each dose will be given on a separate occasion with an interval of at least 4 weeks between the two doses. The first dose may be given from the age of 6 weeks. The two doses of the vaccine must have been given by the age of 24 weeks, although they should preferably have been given before 16 weeks of age.

In case your child spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

When Rotarix is given to your child for the first dose, it is recommended that your child also receives Rotarix (and not another rotavirus vaccine) for the second dose.

It is important that you follow the instructions of your doctor or nurse regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Rotarix can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Rotarix were as follows:

- Very common (side effects which may occur in equal or more than 1 per 10 doses of vaccine):
  - loss of appetite
  - irritability

- Common (side effects which may occur in less than 1 per 10 but equal or more than 1 per 100 doses of vaccine):
  - fever, fatigue
  - diarrhoea, vomiting, regurgitation of food, flatulence, abdominal pain

- Uncommon (side effects which may occur in less than 1 per 100 but equal or more than 1 per 1,000 doses of vaccine):
  - crying
  - sleep disorder, sleepiness
  - constipation

- Rare (side effects which may occur in less than 1 per 1,000 but equal or more than 1 per 10,000 doses of vaccine):
  - upper respiratory tract infection, hoarseness, runny nose
  - dermatitis, rash
  - muscle cramp

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ROTARIX

Keep out of the reach and sight of children.

Do not use Rotarix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

After reconstitution, the vaccine contained in the **oral** applicator should be administered promptly. If the reconstituted vaccine is not used within 24 hours, it should be discarded.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Rotarix contains

- The active substances are:

  Human rotavirus RIX4414 strain (live attenuated)* not less than $10^{6.0}$ $CCID_{50}$

*Produced on Vero cells

- The other ingredients in Rotarix are:
  Powder: sucrose, dextran, sorbitol, amino acids, Dulbecco's Modified Eagle Medium (DMEM)
  Solvent: calcium carbonate, xanthan gum, sterile water

What Rotarix looks like and contents of the pack

Powder and solvent for **oral** suspension

Rotarix is supplied as a whitish powder in a single dose glass container and a separate **oral** applicator of solvent which contains a slow settling white deposit and a colourless supernatant. There is also a transfer adapter which allows easy transfer of the solvent into the glass container containing the powder for mixing the different components of the vaccine.

Both components must be mixed together before your child receives the vaccine. The mixed vaccine will appear more turbid than the solvent alone.

Rotarix is available in a pack of 1, 5, 10 or 25.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.eu.int/.

The following information is intended for medical or healthcare professionals only:

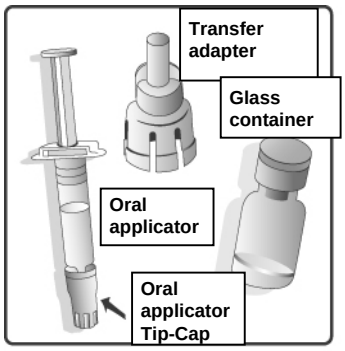
A white deposit and clear supernatant is observed upon storage of the **oral** applicator containing the solvent. The solvent should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to reconstitution.

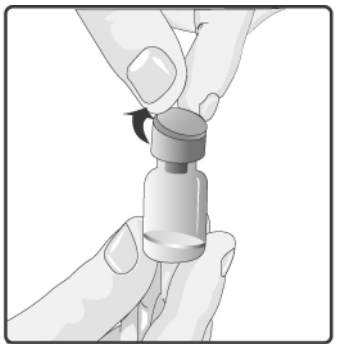
The reconstituted vaccine is slightly more turbid than the solvent and is milky white in appearance.
The reconstituted vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

Instructions for reconstitution and administration of the vaccine:

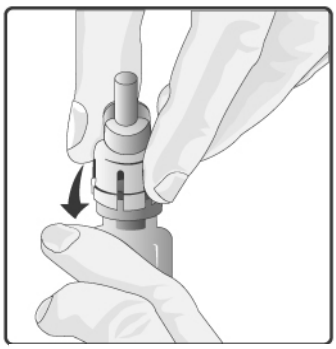
1. Remove the plastic cover from the glass container containing the powder.
2. Connect the transfer adapter onto the glass container by pushing it downwards until the transfer adapter is properly and securely placed.
3. Shake the **oral** applicator containing the solvent vigorously. The shaken suspension will appear as a turbid liquid with a slow settling white deposit.
4. Remove the protective tip cap from the **oral** applicator.
5. Connect the **oral** applicator into the transfer adapter by pushing it firmly on this device.
6. Transfer the entire content of the **oral** applicator into the glass container containing the powder.
7. With the **oral** applicator still attached, shake the glass container and examine it for complete suspension of the powder. The reconstituted vaccine will appear more turbid than the solvent alone. This appearance is normal.
8. Withdraw the entire mixture back into the **oral** applicator.
9. Remove the **oral** applicator from the transfer adapter.
10. This vaccine is for **oral administration only**. The child should be seated in a reclining position. Administer the entire content of the **oral** applicator **orally** (by administering the entire content of the **oral** applicator on the inside of the cheek).
11. **Do not inject.**

If the reconstituted vaccine is to be stored temporarily before administration, replace the protective tip cap on the **oral** applicator. The **oral** applicator containing the reconstituted vaccine should be shaken gently again before **oral** administration. **Do not inject.**

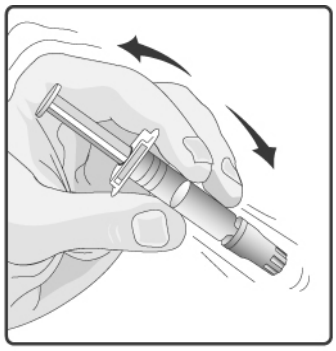




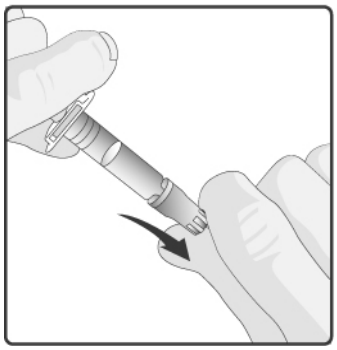
1. Remove the plastic cover from the glass container containing the powder



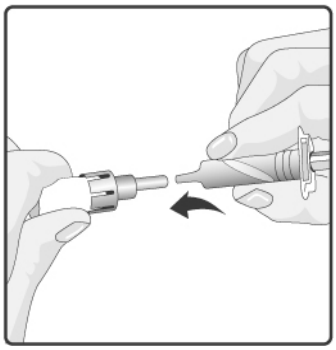
2. Connect the transfer adapter onto the glass container by pushing it downwards until the transfer adapter is properly and securely placed



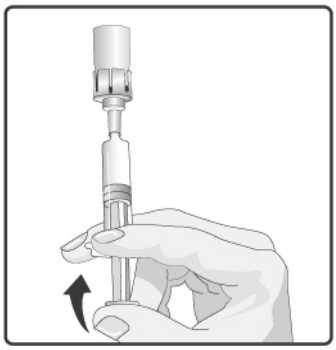
3. Shake the oral applicator containing the solvent vigorously. The shaken suspension will appear as a turbid liquid with a slow settling white deposit



4. Remove the protective tip cap from the oral applicator

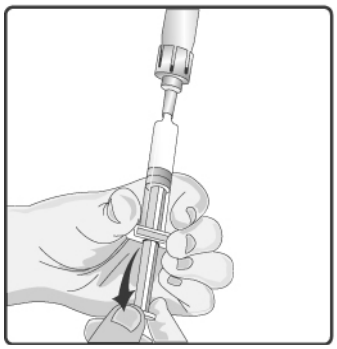


5. Connect the oral applicator into the transfer adapter by pushing it firmly on this device

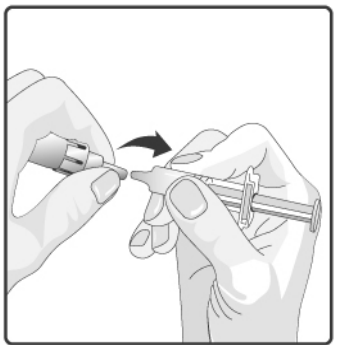


6. Transfer the entire content of the oral applicator into the glass container containing the powder

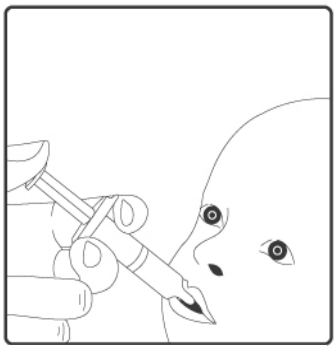
7. With the oral applicator still attached, shake the glass container and examine it for complete suspension of the powder. The reconstituted vaccine will appear more turbid than the solvent alone. This appearance is normal



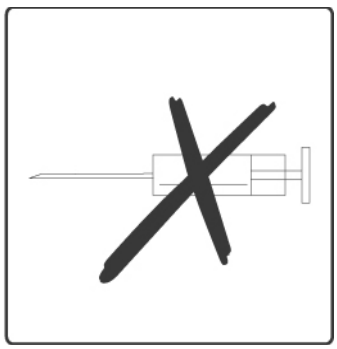
8. Withdraw the entire mixture back into the oral applicator



9. Remove the oral applicator from the transfer adapter



10. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer the entire content of the oral applicator orally (by administering the entire content of the oral applicator on the inside of the cheek)



11. Do not inject.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RotaTeq, oral solution

Rotavirus vaccine (live, oral)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 2-ml dose contains:

rotavirus serotype* G1	not less than 2.2 x 10^6 IU[1, 2]
rotavirus serotype* G2	not less than 2.8 x 10^6 IU[1, 2]
rotavirus serotype* G3	not less than 2.2 x 10^6 IU[1, 2]
rotavirus serotype* G4	not less than 2.0 x 10^6 IU[1, 2]
rotavirus serotype* P1[8]	not less than 2.3 x 10^6 IU[1, 2]

* human-bovine rotavirus reassortants (live), produced in Vero cells.

[1] Infectious Units
[2] As lower confidence limit (p = 0.95)

Excipient:
This product contains sucrose 1080 mg (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution

Pale yellow clear liquid that may have a pink tint

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RotaTeq is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastroenteritis due to rotavirus infection (see section 4.2).

In clinical trials, efficacy was demonstrated against gastroenteritis due to rotavirus of serotypes G1P1[8], G2P[4], G3P1[8], G4P1[8], and G9P1[8]. See sections 4.4 and 5.1.

The use of RotaTeq should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology
Three doses of RotaTeq should be administered.

The first dose may be administered from the age of six weeks and no later than the age of 12 weeks.

There should be intervals of at least 4 weeks between doses.

It is preferable that all three doses should be administered before the age of 20-22 weeks.

All three doses should be given by the age of 26 weeks.

As no data exist regarding the interchangeability of RotaTeq with another rotavirus vaccine, it is recommended that infants who receive RotaTeq for the first immunisation against rotavirus should receive this same vaccine for the subsequent doses.

If it is observed or strongly suspected that an incomplete dose has been swallowed (e.g., infant spits or regurgitates the vaccine), a single replacement dose may be given at the same vaccination visit, however, this has not been studied in clinical trials. If the problem recurs, additional replacement doses should not be given.

No further doses are recommended after completion of the 3-dose series (see sections 4.4 and 5.1 regarding available information on persistence of protection).

Method of administration
For oral administration only.

RotaTeq SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

RotaTeq may be given without regard to food, liquid, or breast milk.

See section 6.6 for administration instructions.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity after previous administration of rotavirus vaccines.

Previous history of intussusception.

Subjects with congenital malformation of the gastrointestinal tract that could predispose to intussusception.

Infants who have known or suspected immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of RotaTeq. However, in the absence of sufficient data, administration of RotaTeq to asymptomatic HIV subjects is not recommended.

Administration of RotaTeq should be postponed in infants suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication for immunisation.

The administration of RotaTeq should be postponed in subjects suffering from acute diarrhoea or vomiting.

4.4 Special warnings and precautions for use

No safety or efficacy data are available regarding administration of RotaTeq to immunocompromised infants, infants infected with HIV or infants who have received a blood transfusion or immunoglobulins within 42 days of dosing.

In trials, RotaTeq was shed in the stools of 8.9 % of vaccine recipients almost exclusively in the week after dose 1 and in only one vaccine recipient (0.3 %) after dose 3. Peak excretion occured within 7 days of dosing. It is theoretically possible that transmission of vaccine virus may occur to seronegative contacts. RotaTeq should be administered with caution to individuals with close contacts who are immunodeficient (e.g., individuals with malignancies or who are otherwise

immunocompromised or individuals receiving immunosuppressive therapy). Also, those caring for recent vaccinees should observe careful hygiene especially when handling excreta.

Limited data in 1007 premature infants indicate RotaTeq can be given to premature infants. However the level of clinical protection remains unknown.

Safety or efficacy data are not available for infants with active gastrointestinal illnesses (including chronic diarrhoea) or growth retardation. Administration of RotaTeq may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

The level of protection provided by RotaTeq is based on the completion of all 3 doses. As with any vaccine, vaccination with RotaTeq may not result in complete protection in all recipients. RotaTeq does not protect against gastroenteritis due to other pathogens than rotavirus.

Clinical trials of efficacy against rotavirus gastroenteritis were performed in Europe, the United States, Latin America, and Asia. During these trials, the most common circulating serotype was G1P1[8], while G2P[4], G3P1[8], G4P1[8], and G9P1[8] were identified less often. The extent of protection that RotaTeq might provide against other serotypes and in other populations is unknown.

The duration of protection after completion of the 3-dose series has not been studied beyond the second season after completion of vaccination (see section 5.1).

No clinical data are available on the use of RotaTeq for post-exposure prophylaxis.

RotaTeq contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical studies that involved co-administration of RotaTeq with a range of other routine infant vaccines at 2, 4 and 6 months of age demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected. Therefore, RotaTeq can be given concomitantly with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTaP-HBV-IPV/Hib)]: diphtheria-tetanus-acellular pertussis vaccine (DTaP), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV) and pneumococcal conjugate vaccine.

The concomitant administration of RotaTeq and oral polio vaccine (OPV) has not been studied. RotaTeq should not be administered within two weeks of a dose of OPV.

4.6 Pregnancy and lactation

RotaTeq is intended for use in infants only. Thus human data on use during pregnancy or lactation are not available and animal reproduction studies have not been performed.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

In a subset of infants from 3 placebo-controlled clinical trials (n=6,130 recipients of RotaTeq and 5,560 placebo recipients), RotaTeq was evaluated for all adverse events within 42 days of vaccination with or without concomitant use of other paediatric vaccines. Overall, 47 % of infants given RotaTeq experienced an adverse reaction compared with 45.8 % of infants given placebo. The most commonly reported adverse reactions that occurred more frequently with vaccine than with placebo were pyrexia (20.9 %), diarrhoea (17.6 %) and vomiting (10.1 %).

Adverse reactions more common in the vaccine group are listed below per system organ class and frequency. Based on pooled data from 3 clinical trials in which 6,130 infants received RotaTeq and 5,560 received placebo the adverse reactions listed occurred with excess incidences in RotaTeq recipients compared to placebo recipients of between 0.2 % and 2.5 %.

Frequencies are reported as:
Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000);

Infections and infestations
Common: Upper respiratory tract infection
Uncommon: nasopharyngitis

Gastrointestinal disorders
Very common: Diarrhoea, Vomiting

Uncommon: Abdominal pain upper

Skin and subcutaneous tissue disorders
Uncommon: Rash

General disorders and administration site conditions
Very common: Pyrexia

Serious adverse reactions were assessed in all participants (36,150 recipients of RotaTeq and 35,536 placebo recipients) of 3 clinical trials. The overall frequency of these serious adverse reactions was 0.1 % among recipients of RotaTeq and 0.2 % among placebo recipients.

Otitis media and bronchospasm were reported in significantly more vaccine than placebo recipients overall; however, among cases that were considered to be vaccine-related in the opinion of the study investigator, the incidence of otitis media (0.3 %) and bronchospasm (< 0.1 %) was the same for vaccine and placebo recipients.

Intussusception
The risk of intussusception has been evaluated in a placebo-controlled study in infants. During the combined 42-day periods following each dose, there were 6 cases of intussusception in 34,837 recipients of RotaTeq compared with 5 cases in 34,788 placebo recipients. The 95% CI for the relative risk were 0.4, 6.4. There was no clustering of cases among recipients of RotaTeq at any time period after any dose.

4.9 Overdose

There are no data with regard to overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **viral vaccines**
ATC code: **Not yet assigned**.

Efficacy
The protective efficacy of RotaTeq was evaluated in two ways in the placebo-controlled Rotavirus Efficacy and Safety Trial (REST):

1. In 5,673 vaccinated infants (2,834 in the vaccine group) protective efficacy was measured as a reduction in the incidence of rotavirus (RV) gastroenteritis caused by vaccine serotypes (G1-G4) that occurred at least 14 days after the third dose of vaccine through the first full rotavirus season after vaccination.

2. In 68,038 vaccinated infants (34,035 in the vaccine group) protective efficacy was measured as a reduction in the rate of hospitalisations and emergency department visits for RV gastroenteritis from 14 days for up to a maximum of two years after the third dose.

The results of these analyses are presented in the following table.

Reduction in incidence of RV gastroenteritis through one full season post-vaccination (RotaTeq n=2,834) (% [95 % CI])						
		Serotype				
Severe* disease (G1-G4)	Any severity (G1-G4)	G1	G2	G3	G4	G9
98.0 % [88.3, 100.0]†	74.0 % [66.8, 79.9]†	74.9 % [67.3, 80.9]†	63.4 % [2.6, 88.2]†	82.7 % [<0, 99.6]	48.1 % [<0, 91.6]	65.4 % [<0, 99.3]
Reduction in hospitalisations/emergency department visits for RV gastroenteritis for up to 2 years post-vaccination (RotaTeq n=34,035) (% [95% CI]						
G1-G4		G1	G2	G3	G4	G9
94.5 % [91.2, 96.6]†		95.1 % [91.6, 97.1]†	87.6 % [<0, 98.5]	93.4 % [49.4, 99.1]†	89.1 % [52.0, 97.5]†	100 % [67.4, 100]†

* Severe defined as a score > 16/24 using a validated clinical scoring system based on the intensity and duration of symptoms (fever, vomiting, diarrhoea and behavioural changes)
† Statistically significant

The evidence for protection against G2P[4], G3P1[8], G4P1[8] and G9P1[8] rotavirus is less than that for G1P1[8]. In this regard, it should be noted that the numbers of cases on which the estimates of efficacy against G2P[4] were based were very small. The efficacy observed against G2P[4] most likely resulted from the G2 component of the vaccine.

The reduction in incidence of RV gastroenteritis caused by G1-G4 during the second rotavirus season after vaccination was 88.0 % [95 % CI 49.4, 98.7] for severe disease and 62.6 % [95 % CI 44.3, 75.4] for disease of any severity.

Immunogenicity
The immunological mechanism by which RotaTeq protects against rotavirus gastroenteritis is not completely understood. No immunological correlate of protection has currently been identified for rotavirus vaccines. In phase III studies between 92.5 % and 100 % of recipients of RotaTeq achieved a significant rise in serum anti-rotavirus IgA after a three-dose regimen. The vaccine induces an immune

response (i.e., appearance of serum neutralising antibody) to the five human-rotavirus proteins expressed on the reassortants (G1, G2, G3, G4 and P1[8]).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

A single and repeated dose oral toxicity study in mice suggests no special hazard to humans. The dose administered to mice was approximately 2.79 X 10^8 infectious units per kg (about 14-fold the projected infant dose).

RotaTeq is unlikely to pose any environmental risk.

See section 6.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide
Polysorbate 80
Culture media (containing inorganic salts, amino acids and vitamins)
Purified water

6.2 Incompatibilities

The vaccine must not be mixed with other medicinal products.

6.3 Shelf life

2 years

RotaTeq should be administered promptly after removal from refrigeration.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Keep the dosing tube in the outer carton in order to protect from light.

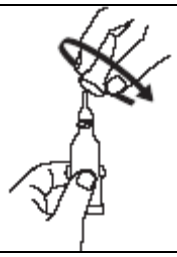
6.5 Nature and contents of container

2 ml solution in a pre-filled squeezable tube (LDPE), with a twist-off cap (HDPE) in a protective bag, pack size of 1 or in a pack of 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The vaccine is to be administered orally without mixing with any other vaccines or solutions. Do not dilute.

<table>
<tr><td colspan="2">To administer the vaccine:</td></tr>
<tr><td>  </td><td>Tear open the protective bag and remove the dosing tube.</td></tr>
<tr><td>  </td><td>Clear the fluid from the dispensing tip by holding tube vertically and tapping the twist-off cap.</td></tr>
<tr><td>  </td><td>Open the dosing tube in 2 easy motions:
1. Puncture the dispensing tip by screwing cap clockwise until it becomes tight.</td></tr>
<tr><td>  </td><td>2. Remove cap by turning it counterclockwise.</td></tr>
<tr><td>  </td><td>Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty. (A residual drop may remain in the tip of the tube.)</td></tr>
<tr><td></td><td>Discard the empty tube and cap in approved biological waste containers according to local regulations.</td></tr>
</table>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Pasteur MSD, SNC
8, rue Jonas Salk
F-69007 LYON
France

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Name of Company:	Merck & Co., Inc
Address:	Sumneytown Pike – PO Box 4 – West Point – Pennsylvania 19486
Country:	United States of America
Telephone:	+1 215 652 5603

Name and address of the manufacturer responsible for batch release

Name of Company:	Merck Sharp and Dohme BV
Address:	Waarderweg 39, 2031 BN Haarlem, P.O. Box 581, 2003 PC Haarlem
Country:	the Netherlands
Telephone:	+31 23 5153153
Telefax:	+31 23 5148000

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not aplicable.

- **OTHER CONDITIONS**

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

RotaTeq – Pack size of 1 single-dose(2ml) Tube
RotaTeq – Pack size of 10 single-dose(2ml) Tubes

1. NAME OF THE MEDICINAL PRODUCT

RotaTeq, oral solution
Rotavirus vaccine (live, oral)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 2 ml dose contains rotavirus serotype*:

G1	$\geq 2.2 \times 10^6$ IU[1]
G2	$\geq 2.8 \times 10^6$ IU[1]
G3	$\geq 2.2 \times 10^6$ IU[1]
G4	$\geq 2.0 \times 10^6$ IU[1]
P1[8]	$\geq 2.3 \times 10^6$ IU[1]

* human-bovine rotavirus reassortants (live), produced in Vero cell.

[1]Infectious Units

3. LIST OF EXCIPIENTS

Sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

2 ml oral solution in a tube
pack size of 1 tube
pack size of 10 tubes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR ORAL USE ONLY
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Keep the dosing tube in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Please read the package leaflet for disposal of medicines no longer required

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Pasteur MSD, SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 pack of 1 tube
EU/0/00/000/002 pack of 10 tubes

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Text for the protective bag

1. NAME OF THE MEDICINAL PRODUCT

RotaTeq, oral solution
Rotavirus vaccine, (live, oral)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Pasteur MSD, SNC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1 dose

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

tube label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RotaTeq
Oral solution
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (2 ml)

6. OTHER

SANOFI PASTEUR MSD, SNC

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

RotaTeq, oral solution
Rotavirus vaccine (live oral)

Read all of this leaflet before your child is vaccinated.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor/health care professional.
- This vaccine has been prescribed for your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor/health care professional.

In this leaflet:

1. WHAT RotaTeq IS AND WHAT IT IS USED FOR

Type of Medicine: vaccine against a virus

RotaTeq is an oral vaccine that helps protect infants and young children against gastroenteritis (diarrhoea and vomiting) caused by rotavirus infection. The vaccine contains five types of live rotavirus strains. When an infant is given the vaccine, the immune system (the body's natural defences) will make antibodies against the most commonly occurring types of rotavirus. These antibodies help protect against gastroenteritis caused by these types of rotavirus.

2. BEFORE YOUR CHILD RECEIVES RotaTeq

Do not use RotaTeq if:

- your child is allergic to any of the components of the vaccine (see section 6).
- your child developed an allergic reaction after receiving a dose of RotaTeq or other rotavirus vaccine.
- your child has previously had intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment).
- your child was born with a malformation of the gastrointestinal system that might predispose for intussusception.
- your child has any disease which reduces his/her resistance to infection.
- your child has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- your child has diarrhoea or is vomiting. It might be necessary to postpone the vaccination until recovery.

Take special care with RotaTeq:
Inform your doctor/health care professional if your child:
- has received a blood transfusion or immunoglobulins within the last 6 weeks.

- has a close contact such as a household member who has a weakened immune system, e.g., a person with cancer or who is taking medicines that may weaken the immune system.
- has any disorder of the gastrointestinal system.
- has not been gaining weight and growing as expected.
- was born prematurely because the level of protection is unknown.

As always, please take care to wash your hands thoroughly after changing soiled nappies.

Also see **Important information about some of the ingredients of RotaTeq** below.

As with other vaccines, RotaTeq may not completely protect all children who are vaccinated even after all three doses have been given. Currently, protection has not been studied beyond 2 years after completing a full course of vaccination.

If your child has already been infected with rotavirus but is not yet ill when vaccinated, RotaTeq may not be able to prevent the illness.

RotaTeq does not protect against diarrhoea and vomiting due to causes other than rotavirus.

Using other medicines and other vaccines:

RotaTeq may be given at the same time as your child receives other normally recommended vaccinations, such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated polio, hepatitis B and pneumococcal conjugate vaccines.
If your child needs to receive polio vaccine by mouth, there should be a gap of 2 weeks between giving any dose of RotaTeq and any dose of oral polio vaccine.

Please tell your doctor/health care professional if your child is taking or has recently taken any other medicine, including medicines obtained without a prescription.

Taking RotaTeq with food and drink:

There are no restrictions on taking food or liquid, including breast milk, either before or after vaccination with RotaTeq.

Important information about some of the ingredients of RotaTeq:

RotaTeq contains sucrose. If you have been told that your child has an intolerance to some sugars, inform your doctor/health care professional before the vaccine is administered.

3. HOW RotaTeq IS GIVEN

RotaTeq IS FOR ORAL USE ONLY.

A doctor or nurse will administer the recommended doses of RotaTeq to your child. The vaccine (2 ml of liquid per dose) will be given by gently squeezing the tube and delivering the vaccine into your child's mouth. The vaccine can be given without regard to food, liquid, or breast milk. In case your child spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

Under no circumstance should this vaccine be administered by injection.

The first dose of RotaTeq may be given from the age of 6 weeks and should be given before 12 weeks of age (about 3 months).

Your child will receive 3 doses of RotaTeq given at least four weeks apart. It is important that your child receives all 3 doses of the vaccine for protection against rotavirus. It is preferred that all three doses should be given by the age of 20-22 weeks and at latest all three doses should be given by the age of 26 weeks.

When RotaTeq is given to your child for the first dose, it is recommended that your child also receives RotaTeq (and not another rotavirus vaccine) to complete the vaccination course.

If you forget an appointment for RotaTeq:

It is important that you follow the instructions of your doctor/health care professional regarding your child's return visits for the follow-up doses. If you forget or are not able to go back to your doctor/health care professional at the scheduled time, ask him or her for advice.

4. POSSIBLE SIDE EFFECTS

Like all medicines, RotaTeq can cause side effects, although not everybody gets them.

The following side effects were reported with the use of RotaTeq:
Very common (occurs in more than 1 in 10 infants): fever, diarrhoea, vomiting.
Common (occurs in more than 1 in 100 infants): infections of the upper respiratory system.
Uncommon (occurs in less than 1 in 100 infants): stomach pains, runny nose and sore throat, ear infection, rash.
Rare (occurs in less than 1 in 1000 infants): bronchospasm (wheezing or coughing).

Ask your doctor/health care professional if you want more information about side effects for RotaTeq.

If any of the side effects gets serious, or if you noticed any side effects not listed in this leaflet, please tell your doctor/health care professional. If the condition persists or worsens, seek medical attention.

5. HOW TO STORE RotaTeq

Keep out of the reach and sight of children.

Store in a refrigerator (2 °C to 8 °C). Keep the dosing tube in the outer carton in order to protect from light.

Do not use any of the dosing tubes of RotaTeq after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What RotaTeq contains

The active substances in RotaTeq are 5 human-bovine reassortant rotavirus strains:

G1	2.2 X 10^6 Infectious Units
G2	2.8 X 10^6 Infectious Units
G3	2.2 X 10^6 Infectious Units
G4	2.0 X 10^6 Infectious Units
P1[8]	2.3 X 10^6 Infectious Units

The other ingredients in RotaTeq are: sucrose, sodium citrate, sodium dihydrate phosphate monohydrate, sodium hydroxide, polysorbate 80, culture media (containing inorganic salts, amino acids and vitamins), and purified water.

What RotaTeq looks like and contents of the pack

Oral solution

This vaccine is contained in a single-dose tube and is a pale yellow clear liquid that may have a pink tint.

RotaTeq is available in pack size of 1, 10. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8, rue Jonas Salk, F-69007 Lyon, France

Manufacturer Responsible for Batch Release: Merck Sharp and Dohme, B.V., Waarderweg, 39, NL-2003 PC Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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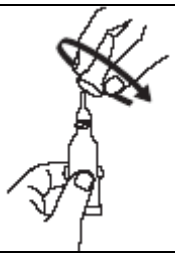
This leaflet was last approved in:

The following information is intended for medical or health care professionals only:

Instructions

To administer the vaccine:	
	Tear open the protective bag and remove the dosing tube.
	Clear the fluid from the dispensing tip by holding tube vertically and tapping the twist-off cap.
	Open the dosing tube in 2 easy motions: 1. Puncture the dispensing tip by screwing cap **clockwise** until it becomes tight.
	2. Remove cap by turning it **counterclockwise**.
	Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty. (A residual drop may remain in the tip of the tube.)
	Discard the empty tube and cap in approved biological waste containers according to local regulations.

Any unused product or waste material should be disposed of in accordance with local requirements.

See also section 3. HOW RotaTeq IS GIVEN.

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All KCE reports are available with a French or Dutch executive summary. The scientific summary is often in English.