Epidemiology of Rotavirus Hospitalizations and Implications for Vaccination Strategies

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Epidemiologie van Rotavirus gerelateerde Ziekenhuisopnames en Implicaties voor Vaccinatie Strategiën
(met een samenvatting in het Nederlands)

Proefschrift

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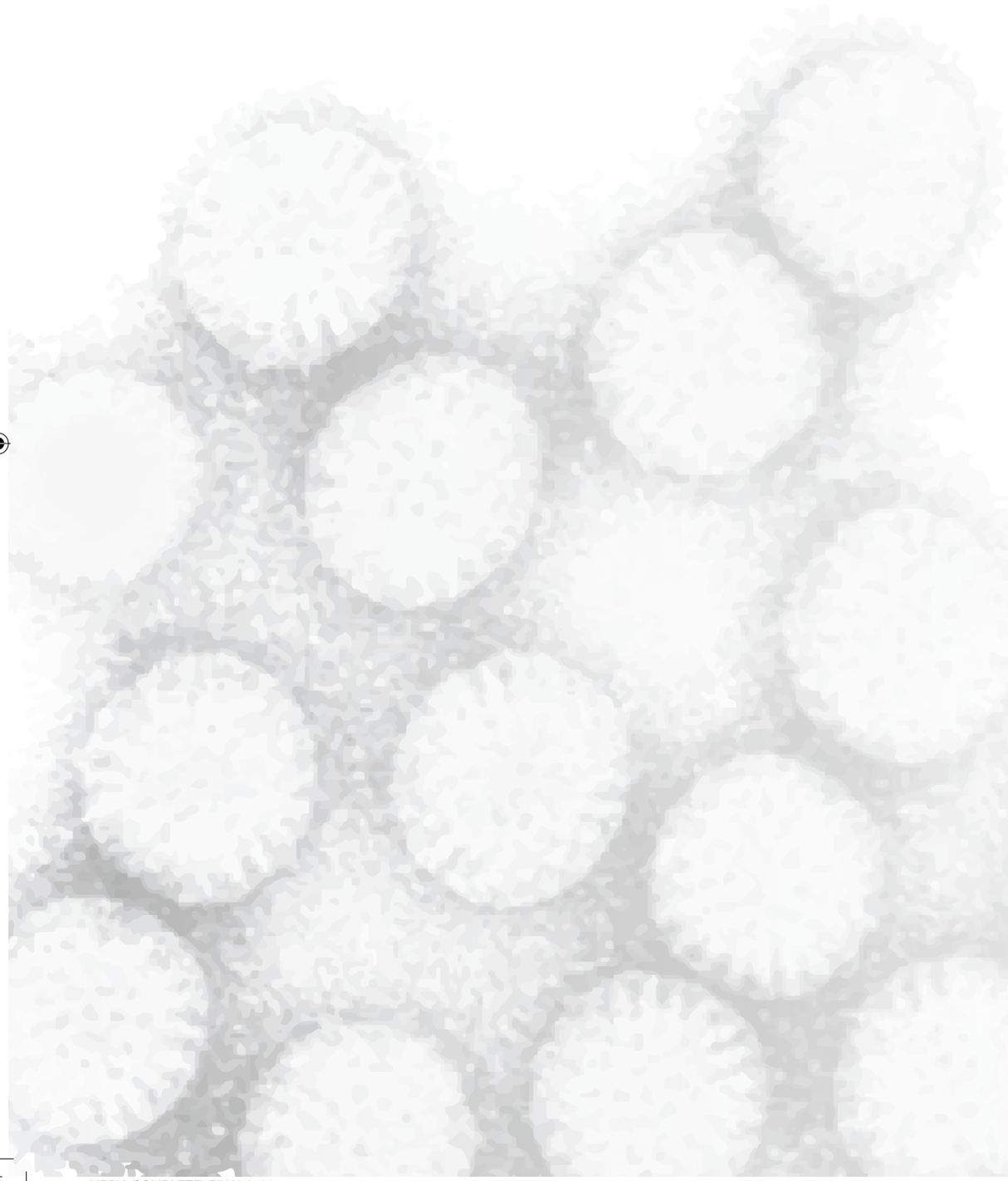

Chapter 1

General Introduction

P Bruijning-Verhagen, C Quach, MJM Bonten

Rotavirus

Epidemiology

Without vaccination, rotavirus (RV) is the most common cause of severe acute gastroenteritis (GE) among young children. As a globally endemic infection, nearly every child gets infected at least once before the age of 5 years.[1] Although a self-limiting disease, the high incidence and young age of first infection makes RV an important cause of morbidity and mortality. Among young infants, severe diarrhea quickly results in dehydration because adequate fluid replacement in the home setting often fails, resulting in doctor visits, hospital admissions or - in the absence of adequate medical care - even deaths. RV can easily be transmitted from an infected hospitalized patient to other, susceptible, hospitalized patients, which makes it also an important nosocomial pathogen.

Before vaccines became available, RV was responsible for > 100 million GE episodes globally, 25 million outpatient visits, 2 million hospitalizations and 420,000-494,000 deaths per year, the latter occurring mainly in developing countries where it represents 37% of all deaths due to diarrhea among children <5 years of age.[2;3]
Vaccination is considered to be the most effective public health strategy to prevent RV disease and to reduce the global RV disease burden.[4]

Transmission

RV is highly contagious and is mainly transmitted via the direct or indirect contact (fecal-oral) route. A dose as small as 100 virus particles is sufficient to cause infection, while symptomatic patients may shed as much as 10^{10} RV virus particles per gram of stool.[5] The virus can survive on hands and retains its infectivity for several hours.[6] Because of prolonged virus survival (up to 60 days) on inanimate surfaces, such as toys and door-handles, these serve as important sources of transmission.[7;8]
In temperate climates, RV transmission occurs mostly between late fall and spring. Prior to universal vaccination programs, the seasonal epidemic pattern of RV followed a unique South-West to North-East sequence in both North-America and Western Europe.[9;10] Annual epidemic peaks occurred in January in the South West of these continents and reached the North East by April and May. Shifts in this seasonal pattern have been observed after implementation of universal RV vaccination.[11]

Disease characteristics

The clinical features of RVGE are non-specific and similar to those caused by other gastrointestinal pathogens. However, RVGE tends to be more severe.[12-15] Following an incubation period of 1-3 days, the illness usually has an abrupt onset. Diarrhea, vomiting and fever are the most common symptoms.[16] Gastrointestinal symptoms typically resolve within 3 to 8 days. The rate of RVGE is highest in children younger than two years of age.[17;18]
In newborns, the infection is usually mild or asymptomatic, possibly due to the presence of transitory maternally-acquired immunity.[19;20]

Virology

Rotavirus is a double-stranded RNA virus. Two proteins that form the outer viral capsid, VP4 (P protein) and VP7 (G protein), represent prime targets for the immune system to mount a neutralizing antibody response. These proteins are key antigens used to characterize strains. Many different G and P genotypes have been identified in strains that cause human infection. Worldwide, five strains are most commonly detected; P[8]G1; P[4]G2; P[8]G3; P[8]G4; P[8]G9. [21-23] In Europe and North America, P[8]G1 is the predominant serotype accounting for

almost 80% of all infections.[24] In developing countries, the diversity of unusual strains is greater and more strains circulate concurrently at any time.[22]

Rotavirus vaccination

History

Studies on the natural history of RV have demonstrated the protective immunity induced by early infections. First infections are generally symptomatic, but few children have severe disease on re-infection. The protective effect increases with subsequent infections. After the second infection, symptomatic disease is uncommon.[1;25] These findings provided the scientific rationale for the development of live oral RV vaccines that mimic natural infection thereby inducing protective immunity. The first RV vaccine (RotaShield®; Wyeth-Lederle) was licensed in 1998 in the US and was recommended for routine immunization of all children. This vaccine was however withdrawn from the market in 1999 after reports of intussusception among vaccine recipients.[26] A small but significantly increased risk of intussusception, an unexpected complication, in the first 2 weeks after the administration of the first vaccine dose was observed.[27;28] Most of the cases of intussusceptions occurred in children who were older than 3 months at the time of immunization.

Current RV vaccines

A new generation of live oral RV vaccines has since been developed: RotaTeq® (Merck and Co, Inc), a pentavalent human-bovine reassortant vaccine with gene components of the 4 most common human RV strains (G1, G2, G3, G4 and P[8]) was first licensed in Europe June 2006 and in Canada in August of the same year. Rotarix® (Glaxo- SmithKline Biologicals), a monovalent live-attenuated vaccine prepared from the single most common human strain P[8]G1 was first licensed in Europe February 2006 and in Canada June 2008. Both are administered as an oral liquid as two (Rotarix®) or three (RotaTeq®) infant doses. In large safety trials that included > 70,000 participants each, the observed risk of intussusception was no greater for either RV vaccine compared to placebo recipients.[29;30]

Vaccine efficacy

Vaccine efficacy for either vaccine was assessed for different geographic populations. High vaccine efficacy was observed in Europe and US where vaccination reduced RV related hospitalizations by 94-96% compared to placebo during 2 years of follow-up.[31-33] Slightly lower vaccine efficacy was observed in Latin-American and Asian studies and the lowest efficacy was observed in studies conducted in African countries where protection against severe RVGE was only 40-60%.[34-37] The differences in vaccine performance have been attributed to higher local RV strain diversity in developing countries, altered host-immune responses, and interference by maternal immunity.

Implementation of RV vaccination

The decision on whether to implement a safe and effective vaccine depends on many factors including the estimated disease and economic burden, expected health gains from vaccination and vaccination costs. This can be formally assessed in cost-effectiveness analysis in which the projected monetary costs of vaccination are compared to the estimated health effects and cost savings (i.e. cost-effectiveness of the intervention).
Since licensure, several developed and developing countries have implemented universal RV vaccination. The impact on RV related hospitalizations in developed countries has been impressive with 60-95% reductions compared to pre-vaccine years.[38-48] In developing

countries, smaller reductions in number of RV hospitalizations were observed but effects on diarrhea related mortality in children under five have been substantial.[48-50]
Despite good vaccine performance, cost-effectiveness of universal RV vaccination in developed countries, where RV mortality is low, has remained controversial limiting its implementation in many countries, especially in Western Europe where only 4 countries currently have funded RV vaccination programs.[51]
Cost-effectiveness of RV vaccination depends mostly on vaccine price, mortality rate and the number of RV hospitalizations, defined as hospital admissions for community-acquired RVGE and hospitalizations complicated by nosocomial RV infections.[52-54] Because different RV hospitalization rates and mortality risks have been reported for healthy children compared to children with prematurity, low birth weight and underlying chronic illnesses, targeted vaccination of high-risk groups could be considered as a low cost alternative, but has not been evaluated thus far.[55-60]
Accurate and up-to-date local incidence and cost estimates of RV hospitalizations are essential for cost-effectiveness analysis of RV vaccination in developed countries. In addition identification of potential risk factors for RV hospitalizations can help determine optimal vaccination strategies.

This thesis focuses on the epidemiology of RV hospitalizations in two countries, Canada and the Netherlands. In Canada, RV vaccination was still under consideration at the start of this thesis project, but has recently been implemented in several provinces. In the Netherlands, RV vaccination is currently considered for inclusion in national immunization program but has not been implemented thus far.

Aims of this thesis

This thesis aims to quantify RV disease burden caused by RV hospitalizations in developed countries, in particular Canada and the Netherlands and to identify risk factors for RV hospitalizations. This thesis further aims to identify an optimal vaccination strategy for RV in developed countries based on cost-effectiveness analysis of different vaccination strategies. In addition, this thesis aims to provide better insight in specific features of severe RVGE among susceptible populations such as premature and low-birth weight infants, children with complex chronic conditions and immunocompromised patients.

Outline of this thesis

Chapter 2 discusses available epidemiologic data on RV disease burden in Canada (Part 1) and the Netherlands (Part 2) with specific focus on RV hospitalizations.

Chapter 3 describes a systematic review and meta-analysis on the incidence of nosocomial RV infections in high-income countries of Europe and North America.

Chapter 4 reports results from an observational study on nosocomial RV infections in a large Canadian tertiary-care hospital.

Chapter 5 describes an epidemiological study on RV hospitalizations in the Netherlands assessing national disease burden and impact on pediatric wards of seasonal RV epidemics.

Chapter 6 reports additional findings from the epidemiological study on the implications of high-risk conditions for RV hospitalization, healthcare costs and mortality. Next, the cost-effectiveness of two different RV vaccination strategies is assessed; universal vaccination and targeted vaccination of high-risk infants.

Chapter 7 focuses on RV infections among immunocompromised patients, both children and adults, describing RV disease course, complications and interventions. In addition, RV contribution to acute GE among adults and immunocompromised patients in particular is estimated relative to other gastrointestinal pathogens.

Chapter 8 discusses the findings and implications of this thesis and sets future research priorities.

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Chapter 2

Epidemiology of Rotavirus Gastroenteritis in Canada and The Netherlands

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Introduction

In order to reliably estimate the potential impact of RV vaccination, accurate figures on RV disease burden are required. Total disease burden is determined by disease incidence, severity and mortality and direct and indirect consequences of disease such as healthcare usage and work-loss. This review summarizes and appraises the available epidemiological data on RV gastroenteritis in Canada and the Netherlands prior to implementation of RV vaccination. Part 1 reviews studies related to RV in Canada. In addition, important issues specific to RV epidemiology are discussed and methodological concepts commonly used in RV observational studies are explained. Part 2 discusses available epidemiological data from the Netherlands.

Part 1: Rotavirus Epidemiology in Canada prior to vaccination

RV prevalence among all-cause gastroenteritis

The relative contribution of RV to all-cause GE episodes illustrates the importance of RV as a gastrointestinal pathogen. RV is the leading cause of dehydrating GE worldwide in young children.[1] RV prevalence among all-cause GE episodes was studied among child-care attendees in the Toronto region during the 1998 RV season.[2] A total of 211 out of 461 child-care attendees aged 0-4 years (46%) experienced an episode of GE during the study period. RV was identified in 18% (33 cases). Peak RV prevalence occurred in April when 45% of all GE episodes among children < 3 years old were RV positive. Because RV tends to be more severe compared to other causes of infectious GE at young age, the proportion of GE episodes attributable to RV rises with subsequent levels of healthcare.[3-7] In the same study RV contribution to GE related outpatient visits was 28% with a peak up to 63% in April and May, but only 31% of GE patients presenting at an outpatient facility were tested for RV. In another Canadian study of children < 3 years old who presented with symptoms of GE at one of 59 pediatric practices across Canada between January and June 2005 found that 186 of 336 children (55%) had a stool sample positive for RV (96% of recruited children tested).[6]

RV prevalence among hospitalizations for GE was assessed in a prospective hospital-based surveillance study performed by Ford-Jones et al. among children aged 0 to 35 months admitted for GE in one of 18 hospitals in the Toronto metropolitan region. RV was identified in 41% of children undergoing stool testing (representing 64% of all GE patients) during the months of November through June with peak prevalence of 77% occurring in April.[8] Another prospective study assessed RV prevalence among GE hospitalizations in 7 Quebec hospitals including children < 5 years between December 1999 and May 2000.[9] With 27 - 94% of GE patients tested, RV was identified in 52-78% across the different centers, but untested patients were significantly older, had shorter hospital-stays and were less likely to receive IV fluids suggesting that RV prevalence among untested patients may have been lower. Observations reported from the US are comparable to those in Canada: Fifty to 70% of GE hospitalizations during peak epidemic months are associated with RV and year-round prevalence is between 34% to 48%.[5;10-12]

These studies confirm the importance of RV in seasonal GE peaks and RV contribution to all-cause GE hospitalizations has been well described for RV epidemic months. Yet, none of the Canadian studies collected data during the low epidemic months, when other infectious causes of GE are relatively more important. Therefore, the year-round contribution of RV is not exactly known. Furthermore, in all studies variable proportions of GE episodes were not tested for RV and limited or no data were provided to compare tested and untested patient characteristics, which may affect the validity of reported results.

RV incidence

The national burden of RVGE is usually assessed by applying age-specific infection rates to population census data thereby generating estimated numbers of symptomatic RV infections. Similarly, incidence rates for RV related healthcare encounters are used to estimate numbers of outpatient visits and hospitalizations.

Global incidence for children < 2 years old was recently estimated in a meta-analysis that included studies from different geographic regions. Using a random effects model and including only studies with low risk of bias, the global incidence rate was estimated to be 0.31 (95% Confidence Interval [CI]: 0.19; 0.50) symptomatic RV infections per child-year and

0.24 (95% CI: 0.17; 0.34) when excluding the extremely high value of 0.84 reported for Mayan Indians in Guatemala.[13] The incidence of RVGE was generally similar between developing and developed countries. Apparently, basic improvements in water supply, sanitation, hygiene, nutrition and education do not necessarily reduce the incidence of infection.[13]

In Canada, the rate of RV infection for children < 2 years old was assessed in a population-based surveillance study in Winnipeg by Gurwith et al. between 1976 and 1979.[14] A total of 104 newborns were enrolled and followed until 24 months of age. Stool and serum samples were collected from each child at regular visits and whenever GE occurred. RV incidence rates for age groups 6-11 months, 12-17 months and 18-23 months were 0.047 (95% CI: 0.030; 0.069), 0.031 (95% CI: 0.015; 0.057) and 0.026 (95% CI: 0.009; 0.061) per child-month, respectively. This amounts to incidence rates (IR) of 0.56, 0.37 and 0.31 per child-year. RVGE was uncommon before six months of age (IR: 0.003 per child-month). Among all GE episodes observed during the study period, RV was identified in 23%. RVGE incidence was also studied by Ford-Jones et al. among 461 child-care attendees in 1998.[2] For ages 0-23 months the IR was 0.011(95% CI: 0.007; 0.016) per child-month, based on observations between November and June. Assuming no additional RV cases during the remaining low epidemic months of the year, the yearly IR would be 0.09, which is lower than the estimate from the Winnipeg study, but includes children 0-6 months old. Furthermore, Gurwith et al. used more lenient criteria for the definition of GE. Overall, the data are in the same range as those reported in the meta-analysis on RV incidence, with highest rates for ages of 6 -23 months. RV incidence data for older age groups are scarce.

Incidence of RV related hospitalizations

The main reason to consider implementation of RV vaccination in developed countries, where RV mortality is generally low, is the high number of hospitalizations due to RVGE among young infants occurring each year during the epidemic months. RV hospitalizations are also responsible for most of RV related healthcare costs.[15]

Contrary to RV infection rates, the incidence rate of RV related hospitalizations may vary substantially across regions of the world due to differences in healthcare access and practice as well as issues such as nutritional status, concomitant infections and general health of the pediatric population. National estimates of RV hospitalization incidence are therefore critical to policy makers and determine to a large extent results of cost-effectiveness analyses.[16]

Prospective surveillance studies where each GE episode is identified on hospital admission through systematic testing for RV are considered most sensitive to capture all community-acquired RV hospitalizations. Being labor intensive, active surveillance studies are usually confined to a limited number of hospitals and short observation periods, which affects generalizability given the high regional and year-to-year variability in intensity of RV epidemics.

Retrospective studies on RV hospitalization rates use hospital discharge data with or without additional RV laboratory records. Diarrhea related hospitalizations are identified based on assigned International Classification of Disease (ICD) discharge codes. Because these indirect methods use existing databases, large datasets from consecutive years including numerous hospitals or comprehensive national data can be included for incidence calculations.

Three different indirect methods are commonly used to estimate the proportion of all GE coded hospitalizations attributable to RV. The winter residual excess method measures the excess fraction of GE hospitalizations during winter months compared to summer months.[17;18] The estimated number of RV hospitalizations is calculated from the difference between the

seasonally higher numbers of GE coded hospitalizations during winter compared to summer months, assuming seasonal variation in GE hospitalizations is completely attributable to RV. The second method (Brandt method) applies the monthly proportion of RV detected among children hospitalized for GE during a longitudinal prospective surveillance study conducted in the US by Brandt et al. between 1974 and 1982,[19] to the monthly number of GE coded hospitalizations.[18] The same method has also been used by applying data from other prospective surveillance studies.[9;20] The third method uses weekly counts of RV positive isolates from laboratory data to estimate a regression based proportion of all GE coded discharges attributable to RV according to a model developed by Harris et al.[21] This method has however not been used on Canadian data.

The eligible ICD codes and the number of positions in discharge code lists to identify GE hospitalizations included in these indirect estimation methods have varied over time.[22] Furthermore, these methods rely on accurate and comprehensive coding practices. A recent study compared the total number of indirectly estimated RV hospitalizations over a two-year period in three hospitals with results from prospective surveillance for the same period and locations.[22] Only 52% of children hospitalized with GE received a qualifying diagnosis code at discharge. Relative to active surveillance, the sensitivity in identifying rotavirus-attributable hospitalizations was 45% for the residual method and 34% for the Brandt method. Specificities for both methods were 89% and 92%, respectively. These observations underline the limitations of these estimation methods and validity has therefore been criticized.[22-24]

In Canada, RV hospitalization rates have been assessed in one prospective and three retrospective studies. A prospective surveillance study by Ford-Jones et al. covering all 18 hospitals providing care to the population of the Toronto metropolitan region identified 1638 admissions for diarrhea over 8 months of study among children under five. Sixty-one percent of GE patients were tested for RV. The admission rate for RVGE was 200/100,000 child-years after adjustment for untested GE patients and the estimated 5-year cumulative risk 1 in 106.[8] Two retrospective studies used selected hospital discharges from the same administrative database Med-Echo for the province of Quebec in the period between 1985 and 1998.[9;20] Different indirect methods were used including the residual method, the Brandt method and a modified Brandt method with monthly RV prevalence estimates from two Canadian prospective surveillance studies performed in different geographic regions and time-periods.[8;9] The estimated RV hospitalization incidence ranged from 320 to 450/100,000 child-years, resulting in a cumulative five-year risk of 1 in 45 to 63. Variation in estimates results from differences in findings from prospective surveillance studies on the monthly proportion of GE hospitalizations attributable to RV. In a third study performed in a single hospital in a rural area of Quebec, both indirect estimation methods to calculate RV hospitalization rates were used.[25] Cumulative 5-year risks of 1 in 57 or 1 in 84 were found for either method. This study also analyzed short-stay hospitalizations (observations for 24 hours or less) in addition to standard hospitalizations. Short-stay hospitalizations represented 55% of all GE coded discharges. Including short-stay hospitalizations, the cumulative 5-year risk increased to 1 in 25 to 41, depending on the method used.

US-based studies with comparable methodology have reported cumulative risks varying between 1 in 60 to 85 for the first 5 years and 1 in 150 for the first 3 years of life.[10;12;26]

Applying the Canadian rates to an average national birth cohort of 340,000 per year, the estimated annual number of RV hospitalizations is 3380 to 7560 or 13,600 if short-stay hospitalizations are included.

Risk factors associated with RV hospitalization

Surveillance results on RV hospital admissions, performed as part of the Canadian Immunization Monitoring Program (IMPAct), a network of pediatric tertiary-care hospitals throughout Canada, recently demonstrated that a high proportion of children hospitalized for RV suffered from underlying medical conditions.[27] Of 1359 admissions, 427 (39%) patients had underlying medical conditions. Among ICU admissions 28 out of 48 patients (60%) had underlying medical conditions present. The prospective study by Ford-Jones et al. reported underlying medical conditions in 22% of children hospitalized for RVGE.[8] In addition, patients who were regularly seeing a physician, used as a proxy for underlying health problems, had an increased length of hospital stay (p<0.001). Other risk factors such as socio-economic status, breastfeeding, and daycare attendance were not associated with RV hospitalization.

Risk factors have also been studied in several international studies. A large case-control study in the US including 349 RV hospitalizations and 1242 age-matched population-based controls found several significant risk factors:[28] Low birth weight (OR: 2.8; 95%CI: 1.6-5.0), daycare attendance (OR: 3.0; 95%CI: 1.8-5.3), being on Medicaid (OR: 2.1; 95%CI: 1.4-3.2) and having young siblings in the same household (OR: 1.6; 95%CI: 1.1-2.3) were all associated with an increased risk of RV hospitalization. Increased risk among LBW infants for hospitalization due to viral GE including RV was also identified by Newman et al.[29] A history of prematurity was present in 18% of RV hospitalizations in children < 1 year of age and existence of congenital pathology in 10% in the district of New York.[30] In Switzerland, 70 of 539 patients hospitalized for RVGE (13%) had underlying chronic diseases.[31] In a Swedish retrospective study, 123 (17%) of 723 children hospitalized for community-acquired RVGE had underlying medical conditions.[32] Although RV is generally considered a universal disease of childhood, these findings suggest that certain patients are more at risk for RV hospitalization and may require more time to recover.

Nosocomial RV gastroenteritis

RV is also an important nosocomial pathogen.[33-37] In the developed world, on average 27% (14-51%) of all RV hospitalizations are nosocomial in nature.[38] More recent studies also report that 11-32% of all RV infections are hospital-acquired,[31;32;39;40] suggesting that nosocomial RV in pediatric hospitals has not decreased in recent years, despite increased awareness and stricter infection control policies. Little is known on the incidence of nosocomial RV in Canada. Langley et al. studied the incidence of different nosocomial infections in a hospital in Halifax by intermittent prospective surveillance between 1991 and 1999. Nosocomial diarrhea was the third most common hospital-acquired infection after bloodstream and respiratory infections. A causative pathogen was identified in 56% of 217 cases of nosocomial diarrhea. RV was the second most common pathogen (31%) after C. difficile (32%). Ford-Jones et al. performed prospective surveillance for nosocomial RVGE on 3 different pediatric hospital wards in Toronto during the first 6 months of 1985.[37] The nosocomial RV incidence rate was 9 per 1000 patient-days for all three wards combined. Nosocomial RVGE occurred in 3.5%, 1.0% and 3.0% of hospitalizations on general pediatrics, cardiology and neurosurgery wards, respectively. Nosocomial RV incidence for other ward-types or different time periods has not been determined in Canada.

Risk factors associated with nosocomial RV gastroenteritis

Typically, nosocomial RVGE occurs more frequently in children less than 6 months of age, whereas hospitalizations for community-acquired RV infections occur most frequently among children 6-24 months of age.[36;41-47]

The Canadian IMPAct surveillance program observed a high prevalence of chronic medical conditions among 497 identified nosocomial RV patients: Gastrointestinal or hepatic conditions were present in 56 patients (11%), cardiovascular in 55 (11%), multisystem diseases in 55 (11%), and neurological/developmental disorders in 51 (10%).[40] Results from other international studies support these observations. Underlying medical conditions were reported in 61% and 51% of nosocomial RV patients in two studies from Sweden and Israel.[32;48]

RV Mortality

Mortality due to RVGE is considered to be very low in countries with adequate access to healthcare.[49] The largest series of RV hospitalizations studied in Canada to date including 1359 admissions for RV reported no deaths. Similarly, no RV related deaths were described in two other Canadian surveillance studies including 372 and 405 RV hospitalizations.[8;9;27]

In the US, RV mortality and diarrheal related mortality in general has been assessed on the basis of RV or diarrheal specific ICD codes listed on death records or from hospital discharge data.[12;50-54] Approximately 300-370 cases of diarrheal mortality occur annually in the US among young children or infants.[52-54] Estimated RV prevalence among diarrhea related deaths ranged from 10-18%.[12;53] Among RV hospitalizations, the estimated case-fatality rate was 1 in 600 to 1600.[12;30] Four studies demonstrated an increased risk of RV or diarrhea related deaths in children with underlying medical conditions such as prematurity or low birth weight, congenital conditions and failure to thrive.[51-54]

Table 1. Summary of study results on RV epidemiology in Canada

	RV incidence per child year	RV Prevalence among all-cause GE	Method	Study population	Study-period	Source
General population	0.09 for children 0-24 months*	18%	Prospective cohort study	Child-care attendees 0-4 yrs	November 1997-June 1998	Ford-Jones[2]
	0.56, 0.37 and 0.31 for children 6-11, 12-17 and 18-23 months, respectively	23%	Prospective cohort study	Children 0-24 months	1976 -1979	Gurwith[14]
GP-visits		28%	Prospective cohort study	Child-care attendees 0-4 yrs	November 1997-June 1998	Ford-Jones[2]
		55%	Prospective cohort study	children < 3 yrs presenting to GP	January - June 2005	Senecal[6]
Hospitalizations	0.005	41% of GE hospitalizations among 0-35 months old	Prospective cohort study	children < 5 yrs hospitalized for GE	November 1997-June 1998	Ford-Jones[8]
	0.0045	52-78%	Prospective cohort study	children < 5 yrs hospitalized for GE	December 1999 - May 2000	Rivest[9]
	0.0032		Indirect method	children < 5 yrs hospitalized for GE	1985-1998	Buigues[20]
	0/0052-0.0082		Indirect method	children < 5 yrs hospitalized for GE	2002-2008	Bernard[25]
Nosocomial infections		31%	Intermittent nosocomial infection surveillance	Nosocomial GE patients	1991-1999	Langley[33]
	9/1000 patient-days		nosocomial infection surveillance	hospitalized children 0-15 years	January-June 1985	Ford-Jones[37]
Mortality	No death observed among 1359, 372 and 405 RV hospitalizations		Observational studies			Le Saux,[27] Ford-Jones,[8] Rivest[9]

* Calculated from available study-data

Part 2: Rotavirus Epidemiology in The Netherlands

RV prevalence and incidence

A one-year population-based study to determine the incidence of acute GE episodes in the general Dutch population (SENSOR-study) was performed between December 1998 and 1999.[55] Although the study was not specifically designed to estimate RV incidence in children, the available data allowed for incidence calculations. Participants were recruited from one of the 31 primary healthcare practices and asked to weekly report presence of GE symptoms. In addition, stool samples were collected when symptoms of GE developed. The participation rate among children under 10 years old was 54%. A total of 609 episodes of acute GE were observed in children < 5 years. The IR of all-cause GE standardized by age and demographic variables was 0.74 per child-year for children < 1 year (95%CI: 0.61-0.88) and 0.90 per child-year for children 1-4 years old (95%CI: 0.77-1.03). Out of 408 samples from children under five tested (67% of all GE episodes), RV was identified in 45 (11%), resulting in a calculated RV incidence rate of 0.08/child-year for children < 1 year of age and 0.1/child-year for children 1-4 years of age and an overall RV incidence of 0.10/child-year for children < 5 year of age.

Slightly higher all-cause GE incidence rates of 0.95 (95%CI: 0.68-1.29) for children under five were reported in an earlier Dutch population-based study, but RV testing was not performed.[56] A population-based study on infectious intestinal diseases performed in the UK between 1993 and 1996 and similar in design to the Dutch SENSOR study identified all-cause GE incidence rates close to the SENSOR-study estimates of 0.88 episodes per child-year for children under one and 0.71 for children 1-4 years old. RV was identified in 10% (17 of 177 tested).[57] Population-based studies in other surrounding countries have generally detected higher RV prevalence rates. Two studies from Denmark among child-care attendees 0-3 and 0-7 years old found RV prevalence rates of 40% over a six months and 24% over a 12 months period, repectively.[58;59] A Finnish cohort study of 336 infants followed during the first 2½ years of life identified RV in 26% of GE episodes.[4]

RV related General Practitioner (GP)-visits were calculated among 44 primary healthcare practices between 1996 and 1999 in a Dutch study that assessed the incidence and etiology of GE related physician visits among different age groups.[60] The incidence of all cause GE related physician visits was 0.036 per child-year for children less than 1 year and 0.022 for children 1-4 years old. In a nested case-control study including 168 patients < 5 years of age stool testing was performed and RV identified in 28 patients. GE episodes were attributed to RV in 21% and 16% for children < 1 year and 1-4 years of age, respectively. This would result in 0.008 and 0.003 RV related GP visits per child-year for children <1 year old and 1-4 year old, respectively.

Two large European studies have assessed the incidence and prevalence of RV related primary care visits across different countries. In general, a wide variation was observed between countries with highest rates in Germany (0.042 primary care visits per child-year for children < 5, and 0.066/child-year for children < 2 years old).[42;61] Lower rates of RV related primary care visit were observed in the UK and Belgium (0.016/child-year < 5), France (0.015/child-year < 5) and Austria (0.014/child-year < 2). RV prevalence in primary care ranged from 20-41%.[42;61] In all European countries studied, both RV incidence and prevalence were higher than those calculated for RV related GP visits in the Netherlands. It is unclear if this difference can be completely attributed to differences in local RV circulation and healthcare seeking behavior across European countries. In many European countries,

including Germany and Belgium, a medical certificate is required within the first 1-3 days if taking time off work to take care of a sick child, whereas no proof of illness is required in the Netherlands and the UK.

Incidence and prevalence of RV related hospitalizations

In 1998, the Surveillance Unit of the Dutch Pediatric Society implemented a RV surveillance program to obtain comprehensive national data on RV hospitalizations. The surveillance unit monitors incidence of several pediatric diseases by sending monthly questionnaires to all pediatricians practicing in Dutch hospitals. Response rates measured in 2001 were 92% and 83% for pediatricians practicing in general and tertiary care hospitals, respectively.[62] For the year 1998, pediatricians were requested to report all cases of RV hospitalization. A total of 1103 RV hospitalizations were reported corresponding to an incidence rate of 90/100,000 child-years for children under five.[63] Recently a study on pediatric GE hospitalizations was conducted among six hospitals with study periods varying between 8 and 19 months for different hospitals [64] A total of 144 patients with GE symptoms on admission were included, representing approximately 19% of GE hospitalizations identified in the Dutch Diagnostic Codes (DBC) System for the different observation periods. The DBC System contains patient diagnoses and treatment information and has been developed in recent years as a payment system for healthcare services delivered by hospitals. Little is known on completeness and accuracy of DBC charges for the purpose of disease burden estimation. Of 144 GE patients, 97 stool samples were obtained and tested positive for RV in 54 (56%). The estimated incidence of all-cause GE related hospitalizations calculated from DBC-based numbers was 940/100,000 child-years for children less than 5 years of age. Assuming 56% RV prevalence, RV hospitalizations incidence would be 530/100,000, generating 5000-5500 RV hospitalizations per year.

Other indirect estimates of RV hospitalization incidence in the Netherlands have been based on ICD discharge codes obtained from the national disease registry (Landelijke Medische Registratie) and weekly RV laboratory reports according to the method developed by Harris et al.[21;63;65;66] For the years 1996-1998 estimates of RV hospitalization incidence varied between 190 and 410/100,000 child-years under five, substantially higher than the estimate based on 1998 surveillance results, suggesting incomplete reporting.[63] The estimated RV prevalence among GE hospitalizations varied between 32% and 58% for the same years. Incidence estimates for the years 1999-2008 have also been calculated and varied between 302/100,000 child years in 2004 and 570/100,000 in 2008, generating between 3000 and 5400 RV hospitalizations each year (average 3500).[65;66]

Incidence and prevalence of nosocomial RV gastroenteritis

Of 1103 RV hospitalizations identified during the 1998 surveillance a nosocomial origin was reported in 16%.[63] In another study routine laboratory data from a Dutch pediatric tertiary care hospital were used to determine incidence and prevalence of nosocomial RVGE between June 2002 and 2007. Of 108 identified hospitalized RV patients, 42 (39%) had a nosocomial infection corresponding to a nosocomial RVGE incidence of 0.4 per 100 hospital admissions.[67] No further data are available from Dutch hospitals. Other recent reports from European tertiary care centers documented that 30% and 32% of RV infections were nosocomial in origin.[32;39] An international study including hospitals in Germany, France, Italy, Spain and the UK reported an overall incidence on nosocomial RVGE of 0.46 per 1000 patient-days, varying between 0 and 1.87 for different sites.[68] The incidence reported from a children's hospital in the UK was 0.9 per 1000 inpatient-days and 0.40 per 100 hospital admissions.[69] Whether hospital-based surveillance was used in these studies was not stated.

RV Mortality

Data on RV related mortality in the Netherlands are not available. We therefore evaluated deaths that occurred among RV hospitalizations in studies conducted in other European countries.

A study analyzing 1886 RV hospitalizations which occurred over a 10-year observation period in a German hospital identified 2 RV related deaths, generating an case-fatality rate of 1 in 943 RV hospitalizations.[70] A similar case-fatality rate was observed in Sweden where 1 RV death occurred among 986 RV hospitalizations analyzed.[32] In another German study one fatal case was observed among 686 RV hospitalizations.[31] Both studies reported presence of underlying disease in patients who died. Of note, no deaths were reported among 1271 and 594 RV hospitalizations identified in two international multicentre hospital-based studies with sites in Belgium, France, Germany, Italy, Spain, Sweden and the UK.[42;68]

Indirect estimates of RV mortality were calculated for the UK based on diagnoses listed on death records for children under five.[71] An estimated 3.3 (95% CI 1.6–4.9) RV related deaths occurred annually in the UK between 1995 and 2002, RV being responsible for 43% of GE related deaths. In the majority of GE related deaths identified, underlying diseases were present. In addition, the case-fatality rate was estimated indirectly from Hospital Episode Statistics (HES) records, which cover all National Health Service hospital admissions in the UK, at 0.2 per 1,000 RV hospitalizations.

Conclusion

Epidemiological data from both Canada and the Netherlands invariably demonstrate that RV is responsible for significant national disease burden among children, despite the self-limiting and generally benign character of RV disease. Studies from neighboring countries, used for comparison, demonstrate similar high RV disease burden, although some differences exist due to inconsistent health seeking behavior and healthcare practices across countries. Methodological shortcomings and incompleteness of data derived are major limitations of performed epidemiological studies affecting precision in some cases and potentially the validity of results. Uncertainty on national RV disease burden remains to some extent that needs to be appropriately addressed in the assessment of potential RV vaccination effects. More specifically, data on RV mortality show contradictory results with no to several deaths observed in large series of hospitalized RV patients and highly variable mortality estimates from indirect methods.

Several studies have demonstrated that patients with underlying medical conditions are overrepresented among the more severely affected patients and in those with fatal RV infections although no study to date has systematically assessed differences in RV disease burden between children with underlying medical conditions and otherwise healthy children.

Table 2. Summary of study results on RV epidemiology in the Netherlands

	RV incidence per child year	RV Prevalence among all-cause GE	Method	Study population	Study-period	Source
General population	0.08 and 0.1 in children < 1 yr and 1-4yr, respectively*		Prospective cohort study	General Dutch population	December 1998-December 1999	De Wit[55]
GP-visits	0.008 and 0.003 in children < 1 yr and 1-4yr, respectively*	21% an 16% for children < 1 yr and 1-4yr, respectively	Prospective cohort study	Patients presenting to GP for GE	1996-1999	De Wit[60]
Hospitalizations	0.0009 and 0.0019-0.0042 for children < 5 yrs for either method, respectively		Passive surveillance (1998) and indirect method (1996-1998)	Hospitalized children 0-15yrs with confirmed RV, Children 0-15yrs hospitalized for GE	1996-1998	De Wit[63]
	0.0053 for children < 5 yrs	56%	Indirect method	Children 0-15yrs hospitalized for GE	May2008-November 2009	Friesema[64]
	0.0019-0.0057 for children < 5 yrs	32%-58%	Indirect method	Children 0-15yrs hospitalized for GE	1996-2008	Van Pelt[65;66]
Nosocomial infections		16% of confirmed RV hospitalizations	Passive surveillance	Hospitalized children 0-15yrs with confirmed RV	1998	De Wit[60]
	0.4/100 hospital admissions	39% of confirmed RV hospitalizations	Routine laboratory reports	Confirmed RV infections in tertiary care centre	June 2002-June 2007	Beersma[67]
Mortality	-					

* Calculated from available study-data

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Chapter 3

Nosocomial Rotavirus Infections: A Meta-Analysis

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Abstract

Background: Nosocomial rotavirus infections (nRV) represent an important part of rotavirus-associated morbidity. The incidence of nRV influences the estimated total RV disease burden, an important determinant of cost-effectiveness of RV vaccination programs. Our aim is to summarize the existing evidence and produce reliable estimates of nRV incidence, before RV immunization programs, in pediatric settings in Europe and North America that can be used in assessments of RV disease burden.
Methods: We searched electronic databases for studies on nRV incidence among pediatric in-patients. To ascertain complete case reporting, only studies describing active nRV surveillance in their methodology were included. Random effects meta-analysis was performed. Metaregression was used to obtain results adjusted for important study characteristics.
Findings: Twenty surveillance studies met the quality criteria for inclusion. The pooled unadjusted nRV incidence was 2.9 per 100 hospitalizations (95%Confidence Interval [CI]: 1.6-4.4). Incidence was significantly influenced by the study months (RV epidemic season only or year-round) and the age range of included patients. Highest nRV incidence was found for children under two years of age, hospitalized during the epidemic months (8.1/100 hospitalizations; 95%CI: 6.4-9.9). The adjusted year-round nRV incidence estimate without age restriction was 0.4/100 hospitalizations (95%CI: 0.1-2.1) and 0.7 (95%CI: 0.0-1.8) for children under five.
Interpretation: This is the first meta-analysis summarizing results of surveillance studies on nRV incidence. nRV seems an important problem among hospitalized infants during winter months. The lower season and age adjusted nRV incidence estimate seems more appropriate for application in population-based burden of disease analysis.

Introduction

Rotavirus (RV) is the leading cause of dehydrating gastroenteritis (GE) in young children throughout the world. It causes significant morbidity and mortality in both developed and developing countries. Peak incidence occurs in children less than two years of age with an estimated 0.3 RVGE episodes per child-year (95%CI: 0.2; 0.5).[1]
Rotavirus is a highly contagious pathogen. The virus has the ability to survive on surfaces, hands and fomites for prolonged periods and is resistant to several antiseptic solutions.[2,3] Very few viral particles are needed to establish infection in the host.[4] The virus is therefore difficult to control in pediatric care settings where RV is repeatedly introduced from the community. RV is the most prevalent cause of hospital-acquired viral GE.[5-7] Vaccines now offer opportunities to control RV infection both in the community and in hospital settings. Universal infant vaccination programs have been implemented in several countries. Lack of cost-effectiveness of RV vaccination programs is however a concern that limits further implementation in parts of Europe and North America.
The estimated contribution of nRV infections to overall RV disease burden prior to introduction of RV vaccines varies considerably in the literature. A review on nosocomial RV infections published in 2004 reported that, in the developed world, on average 27% (14-51%) of all RV hospitalizations were nosocomial in nature.[8] More recent data report 11-32% of RV infections as hospital-acquired, suggesting that nosocomial infections represent a substantial disease burden.[9-14]
Studies investigating the incidence of nRV GE have used inconsistent methodology limiting their applicability. Moreover, in the absence of hospital-based active surveillance for RV, the completeness of reported cases is difficult to assess and underreporting forms a major threat to validity of results.

The purpose of our review was to provide a comprehensive overview of nRV incidence prior to the implementation of universal RV immunization programs among hospitalized patients as reported in the literature, taking into account differences in methodology and quality of study design, to produce summary estimates of nRV incidence. The results will provide meaningful information to policy-makers and healthcare professionals and will guide decision-making processes on immunization strategies for RV. In addition, summary estimates could be applied in cost-effectiveness analysis of RV immunization programs and prove useful in post-implementation surveillance to monitor vaccination impacts on nRV incidence.
Instead of a global summary of nRV, we chose to restrict the review to developed countries in North America and Western Europe which have comparable seasonal RV epidemiology and are more homogeneous in their healthcare systems.[15,16] This reduces heterogeneity due to external factors and facilitates pooling of results.

Methods

Search strategy

We performed a systematic review of available literature on nRV. The electronic databases PubMed and Embase were searched from 1950 and 1974 respectively, to March 17, 2011 using the following search terms: Rotavir* OR viral gastroenteritis AND (Hospital OR Nosocomial OR Hospital-acquired OR Hospital-associated OR Cross infection OR Healthcare-associated OR Healthcare-acquired). Studies published in languages other than English, Spanish, French, German or Dutch were excluded. The search was supplemented by reviewing reference lists of all selected studies.

Inclusion criteria

Nosocomial infection rates are generally reported as number of infections per 1000 or 10,000 hospital-days. In the nRV literature it is however more common to report incidence as infections per 100 pediatric hospital admissions, which can be interpreted as an incidence proportion. Observational studies reporting nRV incidence proportion or studies that provided data required to calculate this outcome measure were selected for inclusion. Authors were contacted in case of incomplete or inconsistent data. We excluded case reports or case series and reports on outbreaks of nRV. Additionally, studies that were performed on specialty wards exclusively, such as intensive care units (ICU) or hematology/oncology wards were excluded being not representative of pediatric hospitalizations in general. Data on nRV incidence after implementation of a RV vaccination program in the region where the study was conducted were also excluded from analysis.

Validity of results is a major concern in observational studies. Additional quality-criteria were used for inclusion based on the Newcastle–Ottawa scale for assessment of the quality of observational studies:[17] Selection of the study population had to be well described in terms of age-range, since age is an important risk factor for RV infection. Similarly, the study months had to be reported because of the well-known seasonal pattern of RV epidemiology. Additional quality criteria were used for the outcome assessment: Inclusion was limited to studies using prospective systematic surveillance for nRV GE. Retrospective studies using laboratory data and/or discharge codes to identify nRV cases were excluded, because complete case ascertainment cannot be guaranteed by these methods and high risk of biased incidence estimates exists.

Data extraction

Data extraction was performed in a standardized way. A data extraction sheet was developed and tested by two reviewers (PV and CQ) independently on a random sample of 7 included studies. Agreement between the two reviewers was determined adequate with consistent incidence estimates extracted from the seven studies and 94% agreement on other items of data extraction (kappa: 88%). One reviewer (PV) subsequently extracted data from the remaining included studies. Any difficulties encountered during data extraction were discussed by the two reviewers.

Data extracted from eligible studies included: Country and region; study year(s) and months; hospital setting (tertiary care or non-tertiary care); hospital units under surveillance; surveillance methods; definition for nRV GE; RV diagnostic methods; patient demographics; number of patients enrolled, excluded and assessed and final number at risk; number of nRV cases and RV related treatment interventions.

The following definitions were used:
Nosocomial Rotavirus Gastroenteritis: The occurrence of GE, defined as acute onset of watery stools or looser than normal stools and/or forceful vomiting in a period of 24 hours, with onset at least 48 hours after admission, where RV was identified in stool or rectal swab. Detection of RV by immuno-assays, RT-PCR or electron microscopy was considered a positive RV test result.
Population at risk: All patients in the studied population without RV on admission.

Quality assessment

A recently developed tool to assess risk of bias in reported outcomes for non-comparative observational studies was used to evaluate all included studies. This tool was developed and used for a meta-analysis on RV GE incidence in the general pediatric population.[1] The tool addresses key sources of bias (selection bias, confounding variables, losses to follow-up, and detection bias). Studies are classified as having 'low' or 'high' risk of bias in the reported outcomes. In the meta-analysis on RV incidence in the community, inter-rater agreement of this validity tool was good: All four assessors agreed upon the assessed risk of bias in each study.

Statistical analysis

The nRV incidence was calculated for each study as follows:
Number of nRV cases divided by the number of hospitalizations at risk. Some studies performed follow-up after discharge. To increase comparability of study estimates, cases of nRV GE identified during post-discharge follow-up were not included for incidence calculation, but reported separately.

Pooled estimates of nRV incidence with corresponding 95% confidence intervals were calculated using the inverse of the Freeman-Tuckey double arcsine transformation within a random effect model framework.[18,19] A random effects model was chosen because the distribution of RV incidence is assumed to vary due to year-to-year and regional variation in RV epidemic intensity and therefore the assumptions underlying fixed effects meta-analysis are not valid. Heterogeneity between studies was evaluated using DerSimonian and Laird Q-statistic and I^2 statistic. To determine sources of heterogeneity between studies, we performed random effects meta-regression. For this purpose, the pre-specified variables age and season, which could potentially explain incomparability between studies, were considered in the model. Covariates were retained in the multivariate model at a significance level for the parameter estimate of $p>0.05$ based on results of a permutation test rather than the standard T-statistic. Permutation tests in meta-regression lead to test statistics with better control of the Type 1 error rate.[20] In sensitivity analysis, we assessed the influence of bias and study setting on the overall incidence estimate. Additionally, we performed a subgroup analysis restricted to study populations < 5 years of age. Publication bias was assessed visually by inspecting funnel plots from both standard random effects and meta-regression models. Further details of the statistical analysis are discussed in the supplementary material.
All analyses were performed using R version 2.12.1 and the meta-analysis package 'Metafor'.[21]

Results

Our search yielded 2,848 hits. Of these, 84 publications were selected for full text review. Authors of seven studies were contacted for further information of which two authors could provide the requested information. Twenty studies met the criteria for inclusion (Figure 1). The nRV incidence proportion could be retrieved directly from 19 studies and six studies additionally reported incidence rate per patient-day. In one study, average length of stay and total patient-days at risk were used to estimate the number of hospitalizations at risk.[22] From this international study with sites in three different countries, complete data could only be retrieved for Germany.

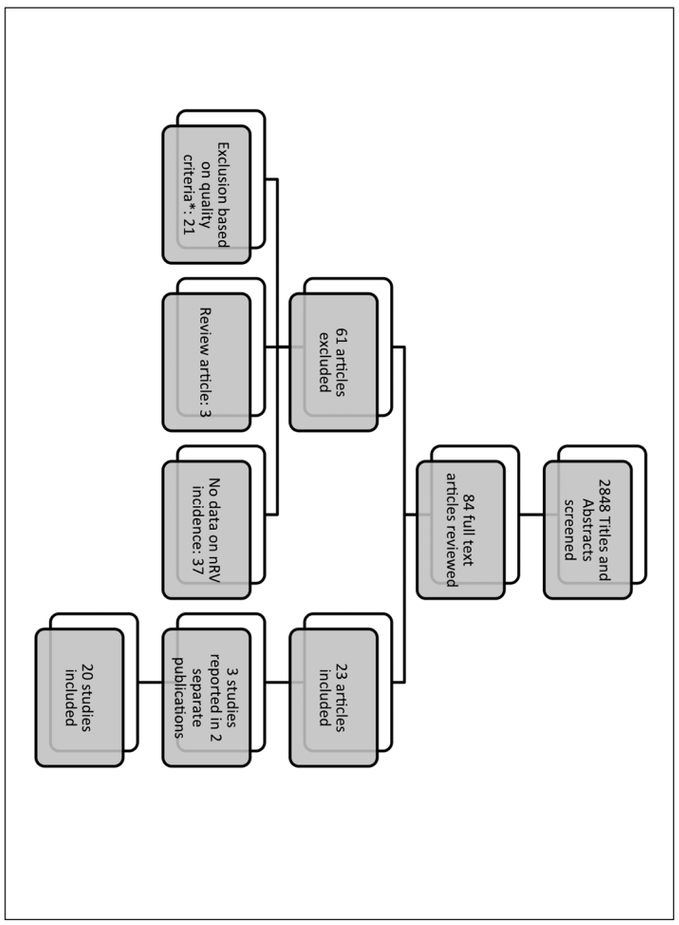


Figure 1. Results of systematic search

The majority of studies conducted surveillance during RV season between November and May, whereas both non-seasonal and seasonal months were included in nine. In seven studies, the age range was restricted to children < 24 months of age, which is considered the high-risk age group for RV. All but six studies were restricted to patients <5 years of age. For two studies without age restriction, additional data were available to calculate the incidence for the subset of patients <5 years of age.[23,24] In seven studies the study site under surveillance included both general pediatric and specialty wards such as neonatal and pediatric ICU and hematology/oncology units, spanning the entire range of pediatric hospitalizations. The remaining 13 studies focused on general pediatric wards only. Details of included studies are summarized in Table 1.

Table 1. Study characteristics of included studies

Author	Country (Location)	Year[1)]	RV season[2)]	Hospital setting	Specialty wards[3)]	Age[4)]	Onset[5)]	RV testing	N[6)]	PD[7)]	N nRV[8)]	Bias[9)]	Reference
Brady/Pacini	US (Columbus)	1986	N	tertiary	Y	all	72	EIA	18518		89	L	51,36
Roman Riechmann	Spain (Madrid)	1999	N	non-tert.	N	1-24 mo	72	EIA	709		34	L	32
Raymond	Europe, multicountry [a]	1997	N	both	Y	all	96	EIA	7468		51	H	52
Fruhwirth/Foppa	Germany (multicity)	1998	N	both	Y	< 5 yo	48	EIA	25553[b,c]	109878	165	L	22,41
Rodriguez-Baez	US (Stanford)	2000	N	tertiary	Y	< 5 yo	72	EIA	298		3	H	53
Kinnula	Finland (Oulu)	2003	N	tertiary	N	all	72	EIA	1927		7	L	26
Beuttcher	Switzerland (Basel)	2006-2008	N	tertiary	Y	all	72	EIA	6144	34608	21	H	24
Dennehy	US (Providence)	1983	Y	non-tert.	N	0-24 mo	72	EIA	663		36	L	54
Cone	US (Seattle)	1984	Y	tertiary	N	0-12 mo	72	EIA	291		22	L	40
Ford-Jones	Canada (Toronto)	1985	Y	tertiary	N	< 9 yo	72	EM	1501		33	L	23
Dennehy	US (Providence)	1984, 1986	Y	non-tert.	N	0-24 mo	72	EIA	209	1127	22[d]	L	55
Pina	France (Versailles)	1997	Y	non-tert.	N	0-36 mo	48	LA	276		9	L	56
Marc	France (Paris)	1998-2001	Y	non-tert.	N	0-24 mo	48	EIA +EM	389	2338	51	L	25
Sermet-Gaudelus	France (Paris)	2000	Y	non-tert.	N	3-36 mo	48	LA	108		5	L	31
Piednoir	France (Reims)	2002	Y	tertiary	N	1-24 mo	48	EIA	410	1709[b]	23	L	30
Festini	Italy (multicity)	2006-2008	Y	both	N	0-30 mo	72	EIA	520		28	L	28
Grassano Morin	France (CI-Ferrand)	1998	Y	tertiary	N	0-36 mo	72	EIA	817		40[d]	H	33
Thuret/Jusot	France (South-East)	1999	Y	both	Y	< 5 yo	48	LA or EIA	5470		108[b]	H	29, 37
Anderson	US (Chicago)	2006	N	tertiary	Y	all	72	LA	20861	141975[b]	82	H	57
Guttierez-Gimeno	Spain (Valencia)	2007	N	both	Y	1-24 mo	48	PCR	1233		23	H	27

RV: Rotavirus
PD: Patient-days
EIA: Enzyme-Immuno Assay
LA: Latex Agglutination
EM: Electron Microscopy
PCR: Polymerase-chain reaction

1) Year in which the studied RV season ended.
2) Study period included only rotavirus epidemic months between November and May.
3) Study site(s) includes specialty wards (i.e. ICU, hematology-oncology).
4) Age-range of patients included in the study.
5) Minimal time interval in hours between admission and onset of as nosocomial defined GE
6) Number of patients under surveillance at risk for nRV.
7) Total patient-days under surveillance at risk for nRV.
8) Number of confirmed nRV cases occurring during hospitalization.
9) Assessed risk of bias in study results; Low(L) or High(H).

[a] France, Greece, Italy, Sweden, Netherlands, Slovenia, Switzerland, UK.
[b] Number calculated by the authors from available data.
[c] Average LOS derived from national hospitalization-statistics for study years (retrieved from: http://www.gbe-bund.de/; Accessed: April 14th, 2011).
[d] Number may include some cases that occurred after discharge, could not be distinguished from available data.

Incidence of nRV GE

A total of 93,365 patients experiencing 852 nRV episodes were included. Pooling the results of the 20 included studies by standard random effects meta-analysis yielded an nRV incidence estimate of 2.9 per 100 hospitalizations (95% Confidence Interval [CI]: 1.6-4.4; I^2= 94%). Univariate and multivariate meta-regression showed significant influence of both age and season on nRV incidence (p< 0.0001). Comparing the residual heterogeneity of the standard random effect and meta-regression model, 89% of the total amount of heterogeneity was accounted for by including these covariates in the model. Residual heterogeneity was however still significant (Q_E[df = 17] = 99.15, p< .0001) suggesting that other covariates not included in the model accounted for heterogeneity between studies. The results of the meta-analysis and meta-regression are shown in figure 2, which demonstrates large differences in incidence estimates depending on the study characteristics for both the observed and predicted values. Highest nRV incidence is seen for children < 2 years of age hospitalized during the RV epidemic months (predicted: 8.1/100 hospitalizations [95%CI: 6.4-9.9]). By contrast, the yearly average estimate for children of all ages was 0.4/100 hospitalizations (95%CI: 0.2-0.9).

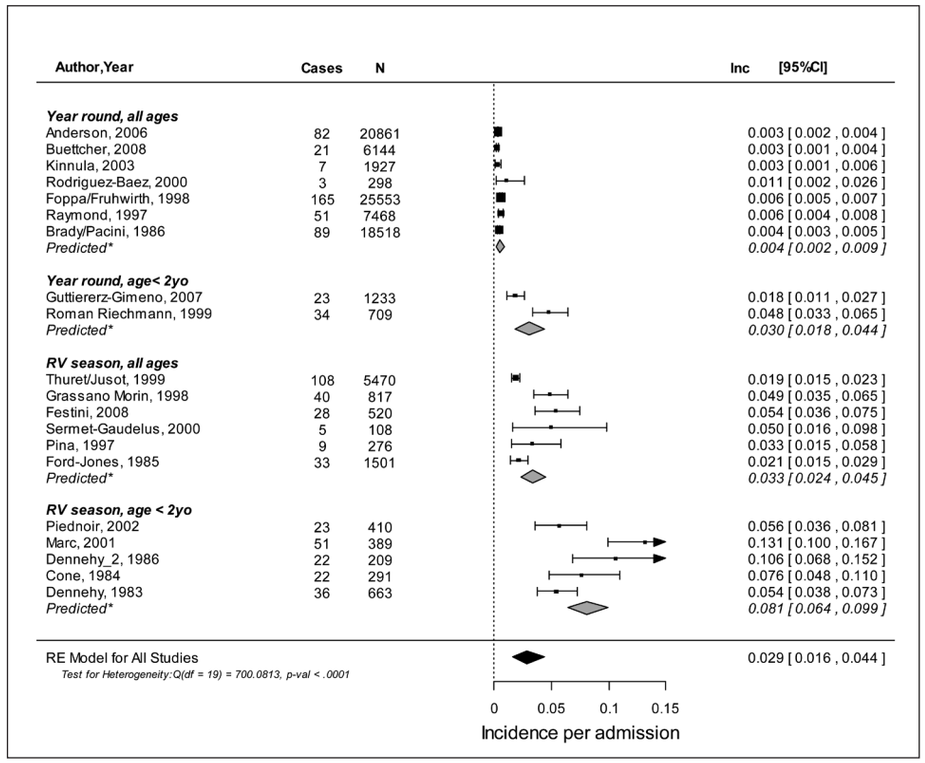
Several subgroup analyses were performed: Restricting the analysis to studies with low risk of bias, studies performed on general pediatric wards (N=13) without inclusion of any specialty wards and to children < 5 years of age all resulted in higher incidence estimates. Results for subgroups are summarized in table 2. The covariates age and season remained significant in all three subgroup analyses. The yearly average incidence for children < 5 years was estimated at 0.7 (95%CI: 0.0-1.8).

The influence of each study on the overall results and model fit was assessed by influential case diagnostics. An important effect on both residual heterogeneity and model fit came from the study by Marc et al.,[25] which can be explained by the extremely high incidence found in this study. Excluding the study from analysis reduced the overall incidence to 2.5/100 hospitalizations (95%CI: 1.4-3.8). Examination of funnel plots showed some asymmetry with a relative lack of smaller studies with low nRV incidence.

Follow-up after discharge

Follow-up of patients after discharge to identify additional cases of nosocomial infection was conducted in nine studies.[24, 26-33] Most studies assessed only the occurrence of gastrointestinal symptoms by telephone call or questionnaire. Supplemental stool testing for RV occurred in only two studies. Both studies were conducted during RV season in patients aged <24 months. Ten of 33 nRV cases (30%) occurred after discharge in a Spanish study with 60% of discharged patients having complete follow-up.[27] In a French study, four of 27 cases (15%) were detected after discharge with complete follow-up in 86%.[30] This would result in an additional 0.8-1.0 cases/100 patients <24 months of age and hospitalized during RV season (1.3 and 1.2/100 hospitalizations, respectively after correction for the untested fraction).

Figure 2. Forest plot of nosocomial RV incidence



* Predicted from multivariate meta-regression model

Table 2. Results of sensitivity analysis: nRV incidence per 100 hospitalizations

	Standard RA meta-analysis	Meta-regression analysis			
		Year round, all ages	Year round, age < 2	RV season, all ages	RV season, age < 2
Subset					
Low bias	4.0 (2.2-6.4)	0.5 (0.1-1.3)	3.5 (1.7-5.9)	3.3 (1.9-4.9)	8.4 (6.4-10.7)
General pediatric wards	4.6 (2.9-6.8)	0.8 (0.1-2.1)	3.7 (1.6-6.4)	3.6 (2.3-5.3)	8.4 (6.3-10.8)
Age < 5 years	4.3 (2.8-6.1)	0.7 (0.0-1.8)	3.2 (1.6-5.1)	3.6 (2.4-5.1)	8.0 (6.0-10.2)

RA: Random Effects

Discussion

This review summarizes and structures the existing evidence on nRV incidence among hospitalized patients, taking into account the most important methodological differences between studies. Across all included studies, approximately one in 35 pediatric hospital-patients experienced an episode of nRV GE. Considerable influence on the reported nRV incidence is exerted by the study population's age and the season in which the study took place. The incidence is highest during the RV epidemic months with up to one in 13 hospitalized patients infected among those aged < 2 years. By contrast, when including children of all ages and taking a yearly average, only one in 250 hospitalized children would acquire nRV. Studies that performed year-round surveillance are limited. Additionally, studies restricted to children in the age group most at risk for RV GE are overrepresented. Policy makers and healthcare professionals need to be aware of the influence of age and season on the measured nRV incidence in order to interpret the existing evidence in the appropriate context.

Sensitivity analysis

Bias analysis suggests nRV incidence may be slightly underestimated. Excluding specialty care wards from the analysis results in higher nRV infection rates, because general pediatrics wards tend to admit the bulk of community-acquired RV cases and therefore risk of transmission is highest on these wards. Funnel plot asymmetry suggests smaller studies with lower incidence estimates are relatively underrepresented. This could be the result of publication bias. It is however suggested that in observational studies, collecting more detailed data on a smaller number of patients is in many cases a better strategy for obtaining accurate results than collecting cruder data on a larger number of participants.[33] Smaller studies may have less detection bias and therefore produce higher incidence estimates, but this hypothesis is difficult to verify.

Additional nRV cases occur after discharge and the results from our analysis should be increased by 15-30% when taking these cases into account. The relevance of these additional cases in terms of additional healthcare usage is however minimal, since they are not associated with excess hospital-days or readmissions. By contrast, several included studies showed nRV occurring while still hospitalized increase length of stay by 2-5 days.[22,30,31,40,54,56]

Limitations

Our analysis is based on studies selected on quality criteria, which should minimize the risk of biased results. Nevertheless, it is possible that nRV incidence remains slightly underestimated. We included only confirmed nRV cases for incidence calculations although some studies reported incomplete RV testing (varying between 79-94%) among patients with nosocomial GE.[22,32,33]

We anticipated that there would be additional heterogeneity between studies due to unmeasured covariates. Factors known to influence nRV incidence are: admission rate for community-acquired RV cases,[35,36] local infection control policies and adherence,[37-39] and duration of hospitalization.[28,40] Additionally, differences in sensitivity and specificity of RV diagnostic tests may have influenced our results.

Moreover, we observed within-study variability in nRV incidence over time and by location. The study by Frühwirth with 13 study sites dispersed over three countries found different nRV incidence between and within countries.[22,41] Similar differences between hospital sites were observed in a French multicenter study.[29] Two longitudinal studies observed substantial differences in nRV incidence between consecutive years.[25,28]

The presence of residual heterogeneity between studies and true variability in nRV incidence is reflected in the measured heterogeneity in our analysis that yielded an I^2 well above 75%. Nevertheless, we chose to pool the results to produce an incidence estimate that is more reliable and stable than any estimate taken from an individual study. Additionally, meta-regression allowed us to investigate the expected nRV incidence under several different study conditions.

Until now, published cost-effectiveness studies have used indirect methods to calculate nRV incidence among pediatric populations, generally based on a proportion of GE coded hospital discharges. The results from this meta-analysis allow for a direct calculation of nRV incidence, by applying the numbers to aggregate statistics on hospital discharges, which are readily available (online) in most countries. As an illustration, we performed this simple calculation for several European regions for which cost-effectiveness analyses were available and compared our results to the applied estimates.[42-47] In most cases, the nRV incidence used in the analysis was higher than results from our calculations. Our incidence estimates varied between 0.95 and 1.3 per 1000 children less than five years of age, which is 20-70% lower than the estimates used in cost-effectiveness analyses, suggesting overestimating number of nRV cases is common. For one country however (the Netherlands), our estimate resulted in a two-fold higher incidence than those reported.[48-50] It was recently shown that RV incidence is one of the main drivers of cost-effectiveness analysis results in developed countries.[42,47] Thus, the influence of over- or underestimating nRV incidence can be substantial, especially since the cost burden of nRV infections is estimated to be almost comparable to that of hospitalization due to community-acquired infection.[42,47]

Conclusion

This is the first meta-analysis summarizing results of surveillance studies on nRV incidence among hospitalized pediatric patients prior to implementation of RV vaccination programs. The overall incidence in Europe and North America is 0.4 case per 100 hospitalizations and 0.7 for children under 5 years of age after adjustment for important study characteristics. Although nRV infections seem an important problem among hospitalized infants during winter months, adjusted nRV incidence estimates are representative of yearly population averages and therefore more appropriate for application in the analysis of regional or country-wide nRV disease burden.

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Supplementary Material: Statistical Methods

Analyses were performed using R version 2.12.1 and the meta-analysis package 'Metafor'.

Model development

For each study the number of nRV infections was divided by the number of hospitalizations at risk to calculate the incidence proportion. To achieve closer to normal distribution of the outcome measure, proportions were transformed before combining the data. We used the variance stabilizing Freeman-Tuckey double arcine transformation for data obtained from binomial distributions.

Model fitting was performed using the function 'rma' from the metafor package by restricted maximum-likelihood estimation.

We first fitted a linear random effects model without covariates and determined the I_2, which measures the proportion of between-studies variability that cannot be explained by chance.[1] In the presence of significant heterogeneity (I^2=94%), we examined prespecified possible sources of heterogeneity between studies.

Three models with incidence proportion as the dependent variable were subsequently fitted: a model with age as a binary independent covariate (high-risk age group yes/no), a model with season as binary independent covariate (RV season yes/no) and a model with the two covariates combined. The omnibus test was used to determine significance of the model coefficients. Each model was further examined by comparing I^2, the DerSimonian and Laird Q-statistic and AIC's.

To determine the final model we used a permutation test for model coefficients, rather than the standard T-statistic. Permutation tests in meta-regression lead to test statistics with better control of the Type 1 error rate.[2] Because of the large number of possible permutations, we used an approximate permutation test based on 1000 iterations. Covariates were retained in the multivariate model at a significance level for the parameter estimate of $p>0.05$. Residual-quantile plots were visually inspected to check the assumption of normality of errors.

Predicted proportions from the final model were calculated using the inverse of the Freeman-Tuckey double arcine transformation as suggested by Miller et al.[3]

In sensitivity analysis the above procedure was repeated for different subgroups of studies with specific study characteristics.

Assessment of publication bias

Both funnel plots from standard random effects meta-analysis and meta-regression were examined (Figure 3). Important asymmetry is observed in the funnel plot based on standard random effects meta-analysis suggesting that published large studies report lower-than-average incidence and smaller studies report higher-than-average incidence. However, after adjusting for the covariates of age and season, the funnel plot becomes more symmetric. This can be explained by the fact that smaller studies were more often performed among high risk age groups and during RV season in comparison with larger studies, resulting in higher incidence estimates. Small studies with negative residual values (i.e. lower-than-expected incidence for a given covariate pattern) are, however, still underrepresented, suggesting some publication bias of small studies with low incidence.

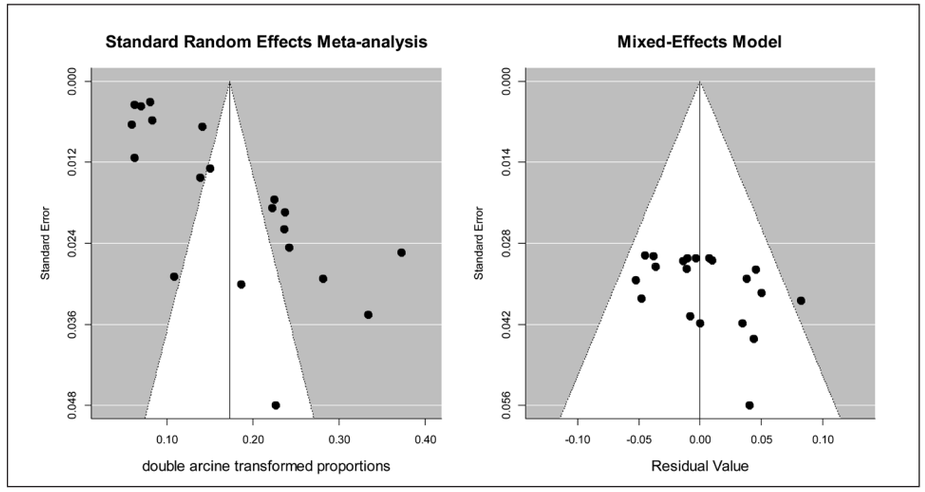

Figure 3. Funnel plots from standard random effects meta-analysis and metaregression

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Chapter 4

Nosocomial rotavirus gastroenteritis in a Canadian pediatric hospital: incidence, disease burden and patients affected

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Abstract

Background: The prominent role of rotavirus (RV) as a nosocomial pathogen in pediatric settings has been well recognized. Although RV is a vaccine preventable disease, there is currently no publicly funded program in Canada.
The objective was to determine incidence of nosocomial RV (nRV) gastroenteritis, disease burden and characteristics of patients to support decision-making on potential vaccination strategies.
Methods: We performed a retrospective cohort study of all nRV cases over a 10-year period in a Canadian tertiary care pediatric hospital. Cases were identified through the hospital's active prospective surveillance program for nosocomial infections. Patient characteristics, medical history, nRV symptoms and therapy were recorded.
Findings: A total of 214 cases occurred. The nRV incidence rate was 0.5/1000 patient-days (95%CI: 0.43, 0.57) with no significant decline in rates over the years. Infection rate was highest among patients with a hospital stay of >5 days. A chronic underlying medical condition was present in 126 patients (59%), frequently associated with previous hospitalization(s) and identifiable early in life for 95 patients (44%). Rehydration was required for 132 (62%) patients and was intravenous in 98 (46%). For patients treated intravenously, there was an additional 3.3 IV-days per patient. Readmission for nRVGE that occurred after discharge was necessary in 26 patients (12%) for a median hospital stay of 4 days.
Interpretation: nRV gastroenteritis continues to be an important problem in pediatric hospitals, predominantly for children with underlying medical conditions requiring recurrent and prolonged hospitalizations. Targeted immunization, providing RV vaccine for vulnerable patients, such as infants with congenital pathology and low birth weight, could be an interesting strategy.

Introduction

Rotavirus (RV) is the leading cause of dehydrating gastroenteritis (GE) in young children. Although mortality is low in developed countries, morbidity and associated healthcare utilization are significant. In the USA, RV caused an estimated 48,700 - 89,700 hospitalizations each year before implementation of RV vaccination.[1] In Canada, RV is the most common pathogen identified in children who seek healthcare for acute GE.[2] It is detected in 30-55% of all patients hospitalized for GE with a peak in the proportion of RV as high as 78% during winter months.[2-4] In addition, in developed countries 11-27% of all hospitalized cases of RVGE are nosocomially acquired (nRV).[5-7] The impact of a nRV episode on the individual patient can be substantial. Reported excess length of stay due to nRV is 1.5-4.9 days with 75% of patients requiring rehydration therapy, 64% of which is intravenous (IV).[8-11]
Several studies of nRV report that infection tends to occur in patients with longer hospital stays.[12-14] Nowadays, a substantial proportion of hospitalized children in developed countries have complex chronic medical conditions. Recurrent hospitalizations and lengthier hospital stays are common among these patients,[15-17] which places them at increased risk of acquiring nRV. Thus far, patients underlying health status in cases of nRV has not been systematically evaluated.
Currently, there are 2 licensed live attenuated RV vaccines available for purchase in Canada: a human-bovine reassortant vaccine (RotaTeq; Merck and Co, Inc) licensed in August 2006 and a G1P8-human RV vaccine (Rotarix; GlaxoSmithKline Biologicals) licensed in July 2007. For both vaccines immunization has to start before 15 weeks of age due to a potential link between risk of intussusception and RV vaccination when given at an older age, as was observed with the now withdrawn rhesus-human reassortant RV vaccine (RotaShield®). RV vaccine has been recommended for all infants by the National Advisory Committee on Immunization in Canada, but there is currently no publicly funded national RV immunization program.[18] More epidemiological data for Canada are needed to accurately predict the impact of universal RV vaccination.[18] Nosocomial infections represent a non-negligible part of total RV disease burden and knowing nRV incidence is important for reliable cost-effectiveness analysis of vaccination programs. Additionally, identifying characteristics of patients who acquire nRV, especially for those with more severe disease, may help to establish patient groups that would benefit most from vaccination.

The purpose of our study was therefore two-fold:
- To determine nRV disease burden at the hospital and the individual patient levels
- To describe characteristics of patients who experience nRV GE and possible risk factors for severe disease thereby defining a potential target group for vaccination

Methods

Study Setting and Design

The Montreal Children's Hospital (MCH) is a 180-bed Pediatric Hospital in a major urban area in eastern Canada, providing predominantly secondary and tertiary care. An active prospective surveillance program for nosocomial infections has been in place at MCH since 1987. As part of this surveillance program, checklists for new onset diarrhea or vomiting among in-patients are filled daily by the nursing staff and reviewed by infection control practitioners. In case of nosocomial GE, a stool specimen is tested for the presence of RV using a commercially available ELISA (Pathfinder Rotavirus EIA Kit, Bio-Rad Laboratories Inc.) within 48 hours of onset. Additional stool testing for other pathogens is performed if clinically indicated (i.e. *C.difficile*, bacterial stool culture) or in case of a suspected outbreak (norovirus). In addition, all cases with RV identified by laboratory tests are reviewed. We performed a retrospective cohort study of all cases of nRV in children aged 0–18 years that were prospectively identified by the surveillance program and occurring between April 1st, 1998 and March 31st, 2008. Medical records of all nRV patients were reviewed. The study focuses on nosocomial infections and thus any community-acquired RVGE was excluded.

Variables

The following data were collected: patient demographics, admission diagnosis, previous hospitalizations and existing chronic medical conditions. Chronic conditions were classified into one of 5 main categories: Respiratory, Cardiovascular, Malignant/Immunodeficient, Neuro-Developmental, Gastrointestinal and Other/Non-classifiable. Additionally, conditions present during the first two months of life and associated with hospitalization were classified as perinatal morbidity. These included conditions related to prematurity and/or low birth weight (LBW), birth defects, perinatal events and congenital syndromes. Defining perinatal morbidity as such allowed us to identify patients early enough for a possible intervention through RV vaccination. Symptoms of nRV, date of onset and associated fluid therapy were recorded. Catheter-days, defined as days on which a patient had an IV catheter exclusively for fluid therapy related to nRV GE were counted. Data on total number of hospital admissions and total number of patient-days per year were obtained from the hospital administrative database.

Definitions

Gastroenteritis was defined as an acute onset of diarrhea with or without vomiting or fever (≥38.5°C rectal), and no likely non-infectious cause. Diarrhea was defined as the occurrence of three or more watery stools in a period of 24 hours or loose or watery bowel movements that exceeded by two or more the usual daily number of bowel movements. Infection was defined as nosocomial if GE symptoms developed after 72hrs of hospitalization or within 72hrs of discharge. RV was considered the causative organism when detected in stool sample by ELISA. A case was defined as nRV GE when all of the above criteria were met.

Statistical analysis

Summary statistics were used to describe patient and nRV disease characteristics. Yearly nRV incidence rates per patient-day were calculated and their corresponding 95% exact Poisson confidence intervals (CI). Poisson regression was used to test for the trend in nRV incidence over time. Possible patient-risk factors for requiring fluid therapy due to nRV were examined by computing Risk Ratios (RR). For continuous variables Student's t-test and non-parametric testing were used where appropriate.
Multivariate logistic regression was performed to assess the impact of risk factors on the need for therapy while adjusting for other covariates. Where appropriate, continuous variables were grouped or dichotomized to increase power.

Results

Nosocomial Gastrointestinal Infections

During the study period from April 1st, 1998 until March 31st, 2008, 470 cases of nosocomial GE were identified. In 426 cases (91%), stool was tested for pathogens. RV was detected in 242 cases (51% of total number of nosocomial GE, 57% of stool tested). In 13 cases *C.difficile* was concomitantly identified in the stool. Twenty-eight cases were excluded from further analysis because the case definition of nRV GE was not met. Thus, 214 cases remained for the analysis (Figure 1).

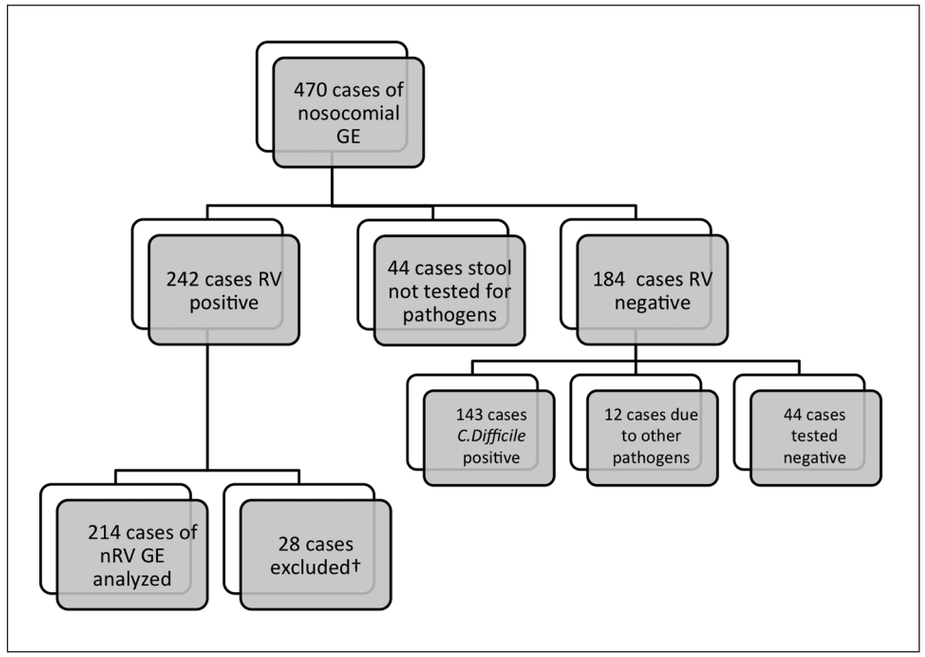

Figure 1.
Numbers of cases of nosocomial gastroenteritis over 10-year period. GE: Gastroenteritis; RV: Rotavirus
nRV: nosocomial rotavirus; † Reasons for exclusion: i) Criteria for acute GE not met (no diarrhea or other likely non-infectious cause of diarrhea), 12 cases; ii) Criteria for nosocomial infection not met (onset of symptoms <72 hours after admission or > 72 hours after discharge), 13 cases; iii) Patient's age >18 years at the time of disease onset, 3 cases

nRV incidence

Yearly nRV incidence rates varied between 0.26 and 0.81 per 1000 patient-days (average: 0.50/1000 patient-days; 95%CI: 0.43, 0.57). Poisson regression did not show a significant decline in rates during the 10-year period (Rate Ratio: 0.96; 95%CI: 0.91, 1.01).

Rates for RV season only, for children < 5 years or < 3 years of age and according to length of hospital-stay were also calculated as was incidence per 100 admissions (Table 1).

Incidence rate was significantly higher among those who stayed > 5 days than for those who stayed 3-5 days (0.65 and 0.09 per 1000 patient-days, respectively; Rate Ratio: 6.84; 95%CI: 3.24, 17.05).

Table 1. Incidence rate estimates for nRV using different denominators

Denominator	IR†	95%CI
Total patient-days	0.50/1000	0.43, 0.57
Patient-days during RV season (December-May)	0.88/1000	0.76, 1.01
Patient-days, < 5 years old	0.79/1000	0.68; 0.91
Patient-days, < 3 years old	0.84/1000	0.72; 0.97
Patient-days, excluding admissions < 72hrs*	0.57/1000	0.49, 0.64
Patient-days, admissions 3-5 days duration	0.09/1000	0.03, 0.20
Patient-days, admissions ≥ 6 days duration	0.65/1000	0.56, 0.74
Total admissions	0.30/100	0.26, 0.35

†IR: Incidence Rate
***** Admissions of <72hrs duration are by definition not considered at risk for nRVGE.

Patient Characteristics

Patient characteristics are summarized in Table 2. Patients from all age groups were affected by nRV GE, including those > 5 years old (24 cases, 11%). Of 214 patients, 174 (81%) were less than 2 years of age with a peak among those 2-6 months old (76 cases, 36%).

More than half of patients had chronic underlying conditions (59%). Perinatal morbidity existed in 95 patients (44%). Prematurity or LBW (61 cases), cardiovascular (21 cases), neuro-developmental (21 cases) and gastrointestinal (20 cases) conditions contributed most frequently to perinatal morbidity. None of the patients with perinatal morbidity had malignancy or immunodeficiency. In 60 cases, gestational age and weight at birth could not be retrieved. Among patients who experienced nRV during the first year of life, gestational age was available for all.

The duration of hospitalization was relatively long (median: 23 days). In 63 patients (30%) hospital-stay lasted more than 6 weeks. Thirty-two patients (15%) had been hospitalized since birth. Of the remaining patients, more than half had a history of previous hospitalization (101 patients, 56%). These proportions were even higher among those with chronic underlying conditions and perinatal morbidity (76% and 75%, respectively).

Half of the patients developed nRV GE between day 3 and day 10 of their hospital-stay. Patients with onset during the first 10 days of hospitalizations were less likely to have chronic underlying conditions (RR: 0.40; 95%CI: 0.31, 0.53). One patient experienced two nRV episodes.

Clinical manifestations

Diarrhea lasted 1-21 days, with a median duration of 4 days. Fever was present in 57% of patients, vomiting in 43%. Diarrhea, fever and vomiting occurred together in 37%. Gender, age, or presence of chronic conditions did not significantly influence duration of diarrhea or

Table 2. Patient characteristics for cases of nRV GE

	N=214	
Male (%)	118	(55%)
Age median (range)	8 months	(7 days - 17 years)
Prematurity or Dysmaturity (%)	61	(29%)
Chronic condition present (%)	126	(59%)
Respiratory (%)	19	(9%)
Cardiovascular (%)	21	(10%)
Malignant/Immunodeficient (%)	11	(5%)
Neuro-developmental (%)	27	(13%)
Gastro-intestinal (%)	25	(12%)
Other/Non-classifiable (%)	23	(11%)
Perinatal Morbidity present (%)	95	(44%)
Hospitalized since birth (%)	32	(15 %)
History of previous hospitalization(s)	101	(47%)
excluding those hospitalized since birth (n=182)		(56%)
History > 21 previous hospital-days	60	(28%)
excluding those hospitalized since birth (n=182)		(33%)
Median duration of present hospitalization (range)	23 days	(4-2251 days)
until onset of GE (range)	10 days	(3-1326 days)

RV: Rotavirus
GE: Gastroenteritis

total number of symptoms. Vomiting however was seen more frequently among otherwise healthy patients than in those with chronic underlying medical conditions (RR 0.78; 95%CI: 0.62, 0.99).

Therapy

Overall, 132 patients (62%) received rehydration therapy. Exclusive oral rehydration therapy was given to 33 patients (15%). The remaining 98 patients (46%) received IV-therapy, sometimes combined with oral hydration (26 patients, 12%). nRV was responsible for 3.3 catheter-days per patient treated IV. Two immunodeficient patients received oral immunoglobulins for prolonged RV diarrhea. Children with gastrointestinal pathology most frequently received therapy (18 of 25 patients, 72%). The proportion treated IV was also highest among these patients (16 of 25 patients, 64%) and they experienced highest number of catheter-days (5.5 days/patient treated IV). Twenty-six patients were readmitted for treatment of nRV GE that started within 72 hours after discharge. Readmission length of stay ranged from 2-17 days (median 4 days). A total of 135 additional patient-days were experienced due to nRV by these 26 patients. These readmitted patients were more likely to be >6 months old (p=0.01) and to present with vomiting (p<0.0001). To decrease bias, we restricted the analysis of risk factors for therapy requirements in multivariate logistic regression to those who developed RVGE while still hospitalized. Adjusting for age and presence of vomiting, there was a non-significant trend for chronic medical conditions (OR: 1.77; 95%CI: 0.91, 3.47) to be associated with therapy requirements. A similar trend was seen with the presence of perinatal morbidity (OR: 1.68, 95%CI: 0.85, 2.39). The separate effect of prematurity and/or LBW on therapy was less evident (OR: 1.24; 95%CI: 0.59, 2.64).

Discussion

Rotavirus was the most prevalent cause of nosocomial GE in our study, confirming the importance of RV as a cause of nosocomial diarrhea in Canadian pediatric hospitals, as described in earlier studies.[19;20] The data also show that nRV continues to be a problem in recent years with no significant decline in rates.

Our nRV incidence rate provides an estimate of the average burden due to nRV GE on a year-round basis in a pediatric hospital. For comparability, we have produced incidence rates based on different commonly used denominators. Table 3 summarizes published studies from North America and Europe reporting nRV incidence rates, denominators used and method of surveillance. This summary shows the differences in methodology across studies and the corresponding variability in incidence estimates. Reported estimates vary between 0.42 and 22.7 per 1000 patient-days, depending on study setting, denominator and surveillance technique used.[10-14;19-26] Whenever nRV incidence rates are used for the purpose of assessing overall burden of disease in a specific region or country, it is important to know how the rates were produced and the denominator used.

This study describes for the first time details on health status and hospitalization history of patients who acquire nRV. Our population was characterized by frequent presence of underlying medical conditions accompanied by recurrent and lengthy hospitalizations. Risk of infection seems to increase with increase in exposure time to potential sources of RV within the hospital. In addition, incidence rate per patient-day in our study was substantially higher among patients with a hospital-stay ≥ 6 days. This observation was also recently reported by Festini et al.[27] This possibly represents higher susceptibility among patients who suffer from underlying medical conditions. Additionally, it could be related to more intensive medical care and increased contact with medical care staff (and thus risk of RV transmission) among these patients. The individual contribution of length of hospital-stay and chronic conditions on risk of infection cannot be distinguished from our data because these were highly correlated. Our data suggest that patients with chronic underlying conditions require fluid therapy for nRV GE more often, but no firm conclusion can be drawn since significance was not reached. Larger numbers of patients would be needed to further analyze this. Readmission length of stay was significantly longer in those with chronic conditions.

Our study has some limitations. First, our study was undertaken in a tertiary care pediatric hospital, which could affect the potential generalizability of our results to non-tertiary care facilities. However, The Montreal Children's Hospital also fulfills an important role in first- and second-line healthcare for the Greater Montreal Area. Based on International Classification of Diseases 10th revision (ICD10) discharge codes, we estimated that on average 8% of total admissions per year are due to acute GE. RV testing, performed in approximately ¼ of GE admissions, is positive in 37% on average. Repeated introduction of RV from the community occurs at a high rate at our institution, like in many non-tertiary care facilities. Since this is one of the most important determinants of nRV infection rates, we believe our infection rates will apply to other pediatric hospital settings. The proportion of patients with complex chronic conditions at our institution is likely higher compared to non-tertiary care facilities. Second, we did not undertake active surveillance of nRV after discharge, but included only those cases severe enough to cause readmission. Previous research with systematic follow-up after discharge, showed that between 15% and 34% of nRV occur while patients are no longer hospitalized.[10;23;26] Therefore, the true number of nRV cases will be higher than we have reported.

Table 3. Summary of studies on nRV incidence rates by surveillance type

Location	Dates (year/month)	Onset*	nRV incidence /1000 PD	Denominators used (Additional surveillance)	Source
	Retrospective review of administrative, patient ward and/or laboratory data				
Pediatric hospital, Philadelphia, US	1999/12 – 2004/5	>48hrs	0.42	PD during each RV season (December – June) minus PD for CARV	1
General Pediatric ward, Toronto, Canada	1997/12 – 1999/3	>72hrs	0.73†	Total PD	2
	Prospective surveillance for cases of GE with onset after admission				
3 hospitals, Spain	2006/10 – 2007/3	>48hrs	4.8	PD of children 1 – 23 months old, minus PD for CARV (FU)	3
12 hospitals in France, Germany, Italy, Spain, United Kingdom	2005/2 – 2006/8	>4hrs	0.5 (range: 0–1.9)	PD of children < 5 years old	4
9 hospitals in Austria, Germany and Switzerland	1997/12 – 1998/5	>48hrs	2.3;2.3; 1.0	PD for children < 4 years old, stratified by country	5
Pediatric hospital, Halifax, Canada	1991/1 – 2000/1	>48hrs	0.2†	Total PD	6
3 pediatric wards, Toronto, Canada	1985/1 – 1985/7	>72hrs	0.9†	PD for children < 10 years old (AS)	7
Pediatric hospital, Columbus, US	1985/1 – 1985/5	>72hrs	1.1	Total PD, minus PD for CARV (AS)	8
	Systematic screening for RV in stool upon admission and active surveillance for symptoms of GE with onset after admission				
General pediatric ward, France	/11 – /2 , 1997 – 2000	>48hrs	22.7	PD for children < 2 years old	9
Infant ward, Seattle, US	1983/12 – 1984/5	>72hrs	2.2†	PD for children < 1 year old	10
Infant ward, France	2001/12 – 2002/3	>48hrs	15.8	PD for children < 2 years old, unclear exclusion of PD for CA RV (FU)	11
Infant ward, Italy	1999/12 – 2000/5	>24hrs	20.9†	PD for children < 18 months old, minus PD for CARV and admissions <48hrs (FU)	12;13
Infant ward, Spain	1998/6 – 1999/5	>72hrs	10	PD for children < 2 years of age, minus PD for CARV (FU)	14;15

D: Patient-Days
CARV: Community–acquired Rotavirus
***** time after admission defined as nosocomial
† calculated from data available in the published article
FU: Follow up for GE after discharge
AS: Active surveillance for symptoms of GE

The impact of these undetected, likely milder cases, on the overall burden of nRV disease is probably low.
Third, from our study we cannot conclude if suffering from chronic medical conditions is associated with an increased risk of acquiring nRV, since we do not know what proportions of hospitalized patients without nRV would qualify as having chronic medical conditions.
Although the study was retrospective in nature, identification of cases occurred prospectively during the 10-year study period by active prospective surveillance of all in-patients. Therefore, the risk of detection bias in this study is limited. The retrospective chart review limited us to the data collected at the time of case identification, which was quite uniform given our use of a standardized case report form for surveillance purposes.

Our study has shown that nRV is predominantly a disease of children with chronic medical conditions who require recurrent and prolonged hospitalizations. RV vaccine has not been specifically evaluated for children with compromised health but it is generally accepted that the benefits of vaccination outweigh the possible risks. Data for premature infants on safety, efficacy and immunogenicity show results comparable to those for term infants.[28;29] Current recommendations support RV vaccination in preterm infants and also in those with preexisting gastrointestinal disease.[18;30] RV vaccination is contraindicated in patients with severe combined immunodeficiency.[31]

A universal RV vaccination program would greatly benefit these vulnerable children through direct and indirect protection. However, limited financial resources have raised concerns about universal RV vaccination and have thus limited the introduction of these programs in Canada and many other countries. In the absence of a national, publicly funded immunization program for RV, prevention for specific target groups is a strategy worth considering. Many of the patients with chronic medical conditions in our study could be identified early in life, before the first dose of RV vaccine would have to be administered. Recent post-licensure data have shown that RV vaccination is already effective in decreasing RV hospitalizations from two weeks post-dose one.[32;33] We believe that patients with perinatal morbidity, as identified in our study, form an interesting potential target-group for immunization. While keeping costs low compared to universal RV vaccination, additional disease burden due to RV infection, which was shown to be substantial, can be prevented for those already suffering from chronic medical conditions due to other causes. Additionally, decreasing the spread and transmission of RV by these patients within the hospital may further diminish infection rates. Further research will have to assess the possible impact of such a targeted vaccination policy.

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Chapter 5

Rotavirus related hospitalizations are responsible for high seasonal peaks in all-cause pediatric hospitalizations

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Abstract

Background: Seasonal rotavirus (RV) epidemics partly overlap with those of other common childhood infections thereby generating enormous – but poorly quantified - pressure on hospital resources during winter and spring. We assessed RV contribution to seasonal excess in all-cause pediatric hospitalizations and RV hospitalizations incidence rate in an observational study.

Methods: The study was conducted among pediatric wards in 3 general hospitals and one pediatric tertiary care centre. Numbers of RV hospitalizations were determined from 5 year data on confirmed RV hospitalizations and adjusted for RV underreporting, assessed through active surveillance for acute gastroenteritis during the 2011 RV season. Incidence rate and RV contribution to all-cause hospitalizations was determined upon hospital administrative data and population statistics.

Findings: RV accounted for 6.2% (95%CI: 5.3 – 7.1) of all-cause pediatric hospitalizations among general hospitals and 3.1% (95%CI: 2.9 – 3.3) at the tertiary care centre, adjusted for the proportion RV underreporting among gastroenteritis patients (33%) as observed during active surveillance. Among general hospitals, there was a 30% increase in all-cause hospitalizations during the active season of common childhood infections compared to summer months. RV contributed 31% to seasonal excess in all-cause pediatric hospitalizations, representing 12.9% of hospitalizations between January and May. RV hospitalizations incidence rate in the population was 510/100,000 child-years under five (95%CI: 420-600).

Interpretation: RV is one of the main causes of seasonal peaks in pediatric hospitalizations, and as such contributes significantly to periodic high bed-capacity pressures and associated adverse effects. RV vaccination benefits in this respect should be considered in decision-making processes.

Introduction

There are clear seasonal trends in pediatric hospitalizations in temperate climates with increased admission rates during fall, winter and early spring compared with summer months. This trend results from seasonality of many common childhood infections that represent >40% of infant hospitalizations, creating a high seasonal pressure on pediatric resources.[1-3] Rotavirus (RV) is the most frequent cause of hospitalization due to viral gastroenteritis in young children; RV epidemics peak in winter and early spring overlapping with those of other seasonal infections. Acute gastroenteritis (AGE) related hospitalizations during winter seasons are almost completely attributed to RV.[4-6] RV vaccination is associated with 75-90% reductions in RV related hospitalizations and could significantly alleviate periodic pressures on pediatric bed-capacity.[7-9] Therefore, accurate quantification of RV contribution to seasonal excess in pediatric hospitalizations – before vaccine implementation – is important for efficient future resource allocation and planning in pediatric secondary care. Accounting for vaccination benefits in this respect in cost-effectiveness analyses could improve results, but reliable estimates in this field are lacking in most (if not all) countries.

Our study was set up to determine the relative contribution of RV to all-cause pediatric hospitalizations and bed-days in the Netherlands, where RV vaccination has not yet been implemented thus far.

Two previous reports on RV hospitalizations in the Netherlands revealed estimates of 3500 and 5000 hospitalizations per year among young children.[10;11] Both studies used indirect estimation methods based on either International Classification of Diseases (ICD) discharge codes or the Dutch diagnostic coding system. Many Dutch hospitals however do not apply ICD coding or only partially, limiting their validity and accuracy. The Dutch diagnostic coding system, developed specifically for the Netherlands for reimbursement purposes, has not been validated for estimating disease burden.[12] We therefore, applied a method independent of coding, based on active, prospective surveillance supplemented with 5-year data on confirmed RV hospitalizations, to quantify RV hospitalization rates and related healthcare resource utilization in the Dutch pediatric population.

Methods

The first part of the study consisted of prospective active surveillance, in which all patients with AGE, defined as an acute onset of diarrhea with or without vomiting or fever, and no likely non-infectious cause, were prospectively identified on pediatric wards between December 2010 and May 2011. An investigator checked physician and nursing admission logs, performed daily ward rounds and screened patient's medical files to record all admissions for AGE (ie. community-acquired) or nosocomial AGE defined as symptom onset after 72hrs of hospitalization. For each new AGE episode patient's age, gender and date of symptom onset was recorded and whether RV stool tests had been ordered by the physician in charge. If not routinely performed, RV stool tests were requested by the investigator on the third day if the patient was still hospitalized. In all participating hospitals, standard medical care for patients with AGE of presumed infectious origin includes RV stool tests and further microbiologic testing as clinically indicated. We estimated RV underreporting by determining the proportion of AGE patients not routinely tested for RV and by comparing characteristics of tested and untested patients. To minimize the risk of disturbing the diagnostic routine among the medical staff, active surveillance was conducted only every third week during seven-day periods.

The second part of the study consisted of a retrospective observational study to determine number, seasonal pattern and characteristics of laboratory confirmed, hospitalized RV patients over a 5 year study-period. Four study hospitals participated: The Wilhelmina Children's Hospital (University Medical Centre Utrecht), a 220-bed pediatric tertiary care facility, and three general hospitals with pediatric and infant wards providing mainly secondary care (Diakonessen Hospital, Utrecht; Spaarne Hospital, Hoofddorp; Kennemer Hospital, Haarlem). The four hospitals together represent approximately 6% of all pediatric hospitalizations in the Netherlands. Stool testing for RV occurred by commercially available enzyme-immunoassays in all participating hospitals during both study-periods.
Medical records of all confirmed RV patients identified in clinical laboratory reports between December 2005 and November 2010 were reviewed by trained pediatricians and pediatric residents to extract data on patient characteristics, RV disease course and origin (community-acquired or nosocomial) and admission and discharge dates. Length of stay (LOS) was counted in days, including the day of discharge and the admission day if hospitalization started before 8 pm. Excess LOS in case of nosocomial RV infection was assessed by counting additional hospitalizations days attributable to RV infection beyond a scheduled or expected discharge date on record. If no discharge was scheduled or expected shortly, we conservatively set additional hospitalization days to zero. Hospital administrative data were used to determine total number of all-cause pediatric hospitalizations and bed-days throughout the study-period. Admissions on the short-stay unit (8 hours maximum), ER-visits without subsequent admission to the ward and admissions for obstetric or neonatal care and surgical specialties were excluded. To calculate incidence rate of RV hospitalizations in the general pediatric population we collected data from the national healthcare registry (Landelijke Medische Registratie) on catchment population and proportionate market shares in total pediatric hospitalizations in the Netherlands for each of the participating hospitals. Numbers from laboratory confirmed RV cases were adjusted for underreporting based on results of our active surveillance study, because incidence is likely underestimated when based on confirmed RV cases only.[13;14]
This study was approved by the hospital institutional review boards with a waiver of informed consent.

Statistical analysis
Active surveillance and adjustment for RV underreporting
We compared patient characteristics between routinely and additionally tested, and between all tested and untested AGE patients identified during active surveillance by Pearson's Chi-squared and Fisher's exact test. Characteristics that were significantly associated with presence of RV among tested AGE patients ($p<0.10$) were added to a predictive regression model to estimate the additional number RV positive among untested patients. This model was validated using 150 bootstrap samples and adjusted by linear shrinkage.[15] From the predicted results we determined the degree of RV underreporting. Numbers from laboratory confirmed RV cases –identified in our retrospective study– were adjusted for underreporting accordingly.
Numbers of routine RV tests performed in each surveillance week were compared to numbers of tests in the week prior to each surveillance period by paired t-test to assess possible influence of our program on the routine testing practices.

RV contribution to all-cause pediatric hospitalizations and incidence rate
The proportion of RV among pediatric hospitalizations was calculated by dividing the number of RV, adjusted for underreporting, by the number of all-cause pediatric hospitalizations.
We assessed the relative contribution of RV epidemics to the seasonal excess in pediatric

hospitalizations. Seasonal excess in all-cause pediatric hospitalizations was determined by subtracting numbers of pediatric hospitalizations during baseline summer months (June - September) –when activity of most seasonal childhood infections including RV is low– from the numbers during the remaining months.[2;16] Seasonal excess in RV hospitalizations was determined in a similar way by subtracting numbers of RV hospitalizations during baseline months from numbers during RV epidemic season. RV epidemic months were defined as those in which the number of RV hospitalizations exceeded 5% of the annual total. Subsequently, we assessed the proportion of all-cause seasonal excess hospitalizations attributable to RV.
RV hospitalization rates were calculated by dividing the number per year by the population at risk, defined as the catchment's population of each hospital.
To account for the clustered design, weighted mean rates and proportions and corresponding 95% Confidence Intervals (CI's) were determined using survey design-based variance estimation by Taylor series linearization.[17] Total RV hospitalizations and bed-days were subsequently estimated by applying weighted incidence rates and LOS to national population data (Centraal Bureau voor de Statistiek).[18]

RV resource use
Outcomes of resource use including duration of (excess) hospital stay and ICU admissions for community-acquired and nosocomial infections were analyzed using multilevel linear and logistic regression to account for cluster effects within hospitals. We used the arithmetic mean for continuous outcomes such as duration of treatment and hospitalization, despite the usually skewed distribution. The arithmetic mean is considered most informative in evaluations designed to have an impact on medical policy, because it is the total disease burden that is important.[19]
All analyses were performed using R statistical software version 2.12.1.

Results

Active surveillance
During nine surveillance weeks 182 episodes of AGE were identified in four hospitals. Of these, 121 (66%) underwent routine testing for RV (requested by the physician in charge). The proportion of AGE patients tested routinely per hospital varied between 60-75% ($p=0.34$). Additional stool samples could be obtained in 8-14% of AGE patients. Thirty-eight children (21%) left the hospital without being tested for RV. Comparison of numbers of routine RV tests performed during surveillance weeks and prior weeks revealed a non-significant difference of 0.8 test per week ($p=0.18$), suggesting minimal influence of our program on routine RV testing practices.
RV was identified in 38% of routinely tested patients (Table 1) and 26% of additionally tested patients ($p=0.29$). No differences in patient characteristics were observed between routinely and additionally tested patients (data not shown). These groups were therefore combined in further analysis. Differences in patient demographics were observed between RV positive and negative patients (Table 1). Nosocomial infection ($p=0.001$) and hospitalization at the tertiary care centre ($p<0.001$) occurred less frequent among RV positive AGE patients. Furthermore, differences in age distribution ($p<0.001$) and LOS ($p=0.004$) were observed between RV positive and negative patients. Untested patients were similar to tested patients with respect to demographics and clinical characteristics. Our final prediction model included variables gender, age, LOS, and infection source (community or nosocomial). The model predicted that 37% of untested patients were RV positive, comparable to the 38%

RV positive among routinely tested patients. Confirmed cases together with predicted unconfirmed cases determined the estimated total number of RV positive patients, from which an underreporting correction factor was calculated (estimated total RV/confirmed cases). This was used to adjust numbers of confirmed RV patients from the retrospective study for underreporting.

Table 1. Characteristics of acute gastroenteritis patients identified by active surveillance

	No. (%) AGE cases tested for RV									No. AGE untested		
	RV positive		**RV negative**			**Total**						
Characteristic	(N=52)		(N=92)		P[a]	(N=144)				(N=38)		P[b]
Routinely tested	46	(38%,)	75	(62%,)		121	(84%)			0		
Study site					<0.001							0.466[c]
WKZ	7	(13%)	42	(46%)		49	(34%)			14	(37%)	
Diak	14	(27%)	24	(26%)		38	(26%)			14	(37%)	
Kennemer	15	(29%)	12	(13%)		27	(19%)			4	(10%)	
Spaarne	16	(31%)	14	(15%)		30	(21%)			6	(16%)	
Infection source					0.001[c]							0.770
Community	47	(90%)	61	(66%)		108	(75%)			30	(79%)	
Nosocomial	5	(10%)	31	(34%)		36	(25%)			8	(21%)	
Sex					0.054							0.236
Male	37	(71%)	49	(53%)		86	(60%)			18	(47%)	
Female	15	(29%)	43	(47%)		58	(40%)			20	(53%)	
Age, months					<0.001[c]							0.328
< 3	3	(6%)	20	(22%)		23	(16%)			3	(8%)	
3-11	17	(33%)	25	(27%)		42	(29%)			9	(24%)	
12-35	24	(46%)	18	(20%)		42	(29%)			11	(29%)	
≥ 36	8	(15%)	29	(31%)		37	(26%)			15	(39%)	
LOS, days					0.004[d]							0.080[d]
median (range)	4	(2-14)	5	(2-28)		4	(2-28)			4	(3-13)	

AGE: Acute Gastroenteritis
a P value for rotavirus positive cases versus rotavirus negative cases by Pearson's chi-squared test
b P value for AGE cases tested for rotavirus versus AGE cases not tested for rotavirus by Pearson's chi-squared test
c Fisher's exact test
d Wilcoxon rank sum test

RV contribution to pediatric hospitalizations and incidence rates

Laboratory reports identified 936 symptomatic RV infections between December 2005 and November 2010 of which 770 (81%) were community-acquired and 176 (19%) nosocomial (Table 2). The proportion of nosocomial infections was much higher at the tertiary care hospital compared to general hospitals (39% versus 5-16%; p<0.0001). Of all RV episodes, 677 occurred at one of the three general hospitals (Hospital B, C, D) and the remaining 259 episodes occurred at the tertiary care hospital (A). Adjustment for underreporting resulted in an estimated 1223 total cases that occurred during the five year study-period among the four hospitals.

Table 2. Characteristics of pediatric rotavirus hospitalizations among four hospital

	Community-acquired		**Nosocomial**		**Total**	
	N=770		N=176		N=936	
Hospital						
A*	157	(21%)	102	(58%)	259	(28%)
B	157	(21%)	30	(17%)	187	(20%)
C	283	(37%)	35	(20%)	318	(34%)
D	163	(21%)	9	(5%)	172	(18%)
Year†						
2006	151	(20%)	24	(14%)	175	(19%)
2007	132	(17%)	31	(18%)	163	(17%)
2008	166	(22%)	28	(16%)	194	(21%)
2009	178	(23%)	56	(32%)	234	(25%)
2010	133	(18%)	37	(21%)	170	(18%)
Male	413	(54%)	93	(53%)	506	(54%)
Median Age (range)	13 mo	(3 days-18 yrs)	6 mo	(4 days-11 yrs)	12 mo	(0-18 yrs)
< 3 months	56	(7%)	63	(36%)	119	(13%)
< 2 years	585	(77%)	152	(86%)	737	(79%)
< 5 years	723	(94%)	167	(95%)	890	(95%

***** Tertiary Care Hospital
† December 1st of the previous year until November 30st of the year stated

Figure 1a shows the proportion of all-cause pediatric hospitalizations in which RV was involved by year and hospital. Hospital B had an outbreak of nosocomial RV gastroenteritis in 2009 as reflected by a significantly higher number of cases in this year (p=0.0005). A significant difference was observed in RV hospitalizations and patient-days between general and tertiary care hospitals. On average 6.2% (95%CI: 5.3 – 7.1) of pediatric hospitalizations were RV related in general hospitals compared to 3.1% (95%CI: 2.9 – 3.3) at the tertiary care centre (p<0.001). Eighty-eight percent of RV hospitalizations occurred between January and May when RV accounted for 12.9% of all-cause pediatric hospitalizations in general hospitals. Figure 1b displays the temporal distribution of mean numbers of all-cause pediatric hospitalizations in 3 general study hospitals and the relative contribution of RV.

All-cause pediatric hospitalizations were 30% higher between October-May compared to summer-months. RV accounted for 31% of excess seasonal pediatric hospitalizations and predominated between January and May when this proportion increased to 61%. Similar proportions of excess seasonal patient-days were attributable to RV (29% and 61%, respectively). During early winter season (October-December), excess all-cause pediatric hospitalizations were likely caused by RSV and other respiratory infections with RV being responsible for 1% of admissions.[20]

The estimated incidence of RV hospitalizations in the population was 170 per 100 000 child-years < 15 (95%CI: 140 - 200) and 510 per 100 000 for those less than 5 years (95%CI: 420-600). At the national level, the estimated mean number of RV hospitalizations per year was 4870 (95%CI: 4060 – 5680) –of which 510 (95%CI: 340 – 680, 10%) nosocomial infections– leading to 18.700 patient-days (95%CI: 16.380 – 21.030).

RV resource use

Among community-acquired infections, 15 patients were primarily admitted for reasons unrelated to RV (scheduled medical or surgical intervention, unrelated infection or injury). These children were excluded from the analysis of LOS (Table 3). The overall mean LOS for community-acquired RV gastroenteritis was 4.2 days (95%CI: 3.4; 5.1), but differed significantly between general hospitals and the tertiary care centre (3.7 vs 5.6 days, p<0.0001).
In 100 out of 176 patients (57%) with nosocomial infection, hospitalization was prolonged due to the infection. Mean excess LOS for nosocomial infection was 3 days (95%CI: 2.4; 3.6).
Nineteen patients with nosocomial RV (11%) were readmitted for rehydration.
RV related ICU admission was required in 1.4% of patients (13 cases) for a mean duration of 5.4 days.
There were two patients in whom RV contributed to death: One severily dehydrated patient died of hypovolemic shock and one cardiac patient deteriorated profoundly due to intractable diarrhea and subsequently died in cardiac surgery. In addition, several severe complications were associated with RV: Four cases of necrotizing enterocolitis were observed among premature infants, one patient developed a paralytic ileus, one case of hypovolemia associated acute renal failure occurred and one case of hypernatremic encephalopathy with convulsions. One premature newborn developed severe encephalopathy after RV infection with RV presence confirmed in cerebrospinal fluid and other causes of encephalopathy being excluded.[21]

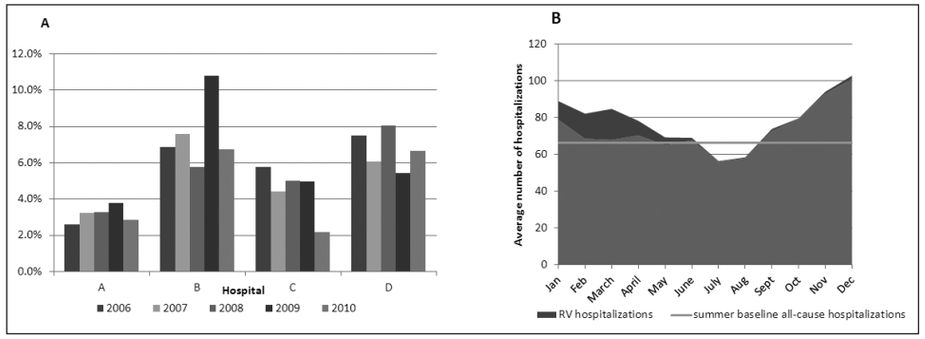

Figure 1.
Proportion of all-cause pediatric hospitalizations related to rotavirus (community-acquired and nosocomial) per hospital and year after adjustment for RV underreporting (A) and rotavirus contribution to seasonal excess in all-cause pediatric hospitalizations among general hospitals (B)

Table 3. Rotavirus related treatment and healthcare utilization

	Community-acquired		Nosocomial		Total	
	N=770		N=176		N=936	
Unknown	5	(0.6%)	2	(1.1%)	7	(0.7%)
RV reason for admission or prolonged stay	755	(98%)	100	(57%)	855	(91%)
Mean (excess) LOS (95%CI)	4.2	(3.4; 5.1)	3.0	(2.4; 3.6)		
General hospital (95%CI)	3.7	(3.5; 3.8)	2.6	(1.9; 3.4)		
Tertiary Care hospital (95%CI)	5.6	(5.3; 5.9)	3.3	(2.3; 4.2)		
ICU admission	9	(1.2%)	4	(2.3%)	13	(1.4%)
Mean LOS in ICU (range)	4.0	(2-8)	8.5	(5-12)	5.4	(2-12)
Severe complications	2	(0.3%)	5	(2.8%)	7	(0.7%)
Death	1	(0.1%)	1	(0.6%)	2	(0.2%)

LOS: Length of hospital-stay
CI: Confidence Interval
ICU: Intensive Care Unit
***** Oral or by nasogastric tube

Discussion

This study demonstrated that – in Dutch hospitals – up to 13% of all-cause pediatric hospitalizations and 60% of excess of all-cause hospitalizations during winter and early spring are caused by RV. This high seasonal RV related burden on general pediatric wards can contribute to periodic overcrowding resulting in understaffing (low healthcare worker to patient ratio) and shortness of isolation facilities due to limited capacities, which increases adverse event rates and associated costs.[2;22;23] Although difficult to quantify in economic terms, RV prevailing opportunity costs – defined as those resources that can no longer be used for alternative purposes - resulting from bed-capacity pressures and possible admission blocks could be reduced by RV vaccination, a phenomenon not routinely taken into account in decision making on RV vaccination policies.

Our study confirmed the high burden caused by RV hospitalizations among young children. Approximately one in 40 children in the Netherlands is admitted for RV gastroenteritis and approximately 1 in 400 will experience symptomatic nosocomial infection. Incidence of RV hospitalizations, when estimated from retrospective data, is usually determined using one of several indirect estimation methods based on ICD discharge codes for diarrhea related hospitalizations.[24-26] Accuracy and completeness of coding practices can however significantly influence results.[27;28] Our study used a unique method, independent of coding practices, estimating incidence from laboratory confirmed RV infections supplemented with an estimated number of additional undetected cases based on the findings from active prospective surveillance within the same hospitals. Our results are comparable to the estimated incidence rate of RV hospitalizations in Germany, Finland and the UK.[6;29;30] Furthermore, our estimate of approximately 5000 RV hospitalizations per year in the Netherlands is comparable to recently reported 5,000-5,500 hospitalizations by Friesema and coworkers,[31] based on Dutch AGE diagnostic codes. We conclude the methodology used in our study to estimate RV incidence offers a practical alternative approach that avoids the problems of coding validity. Of note, cost-effectiveness models of RV vaccination for the Netherlands have used a base-case scenario of 3,100-3,600 RV hospitalizations per year, suggesting cost-effectiveness may be more favorable in reality than estimated from

these models, where the majority of scenarios were determined not to be cost-effective.[32-35] We observed important differences in RV hospitalizations between general and tertiary care centres. LOS for RV gastroenteritis was significantly prolonged at the tertiary care centre probably reflecting an increased vulnerability of patients served here. Furthermore, the proportion of nosocomial infections was much higher, which can be explained by an increased RV acquisition risk associated with prolonged hospital stay.[36;37] Similar observations were obtained from another Dutch tertiary care centre of approximately similar bed-size, performing a retrospective audit of laboratory confirmed RV infections between 2000 and 2005. They identified 91 nosocomial RV infections out of 210 (43%, personal communication N. Hartwig, Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, November 11th, 2011). In other European tertiary care centers 30% and 32% of RV infections were nosocomial in origin.[38;39] Differences in RV hospitalizations, related healthcare utilization and costs between general and tertiary care hospitals should be taken into account when data from observational studies are used for estimating national RV related healthcare costs. For instance, based on our findings, the mean direct healthcare costs (using 2011 standard cost-prices/patient-day) associated with RV hospitalization were €1,646 and €3,294 for a general and tertiary care hospital, respectively.

The proportion of patients treated by enteral rehydration in our study was high (73%) compared to observations in other European countries.[40] The Dutch and European practice guideline for AGE promote enteral rehydration as the first-line therapy.[41;42] Adherence to these guidelines has been very high among Dutch pediatricians. As a result, IV fluids are only used when enteral rehydration fails.

Our estimates of RV related healthcare utilization are exclusively based on data from laboratory confirmed RV cases. It is possible that unconfirmed RV cases differ in health-care utilization, although our results from active surveillance do not support this hypothesis; no significant differences in patient characteristics and LOS between RV tested and untested patients were observed.

Conclusion

RV is one of the main causes of seasonal increases in number of pediatric hospitalizations, and as such contributes significantly to periodic high bed-occupancy. This in turn has been associated with increased costs and other adverse events. Our study provides important epidemiological data on RV related disease burden in a high-income country. RV vaccination could significantly alleviate periodic bed-pressures in pediatric secondary care, a factor that should be considered in the decision-making process on vaccination strategies.

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Chapter 6

Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination

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Submitted

Abstract

Background: Cost- effectiveness of universal rotavirus (RV) vaccination is controversial in developed countries. As a result, RV vaccination programs do not currently exist in most European countries. Hospitalization is the main driver of RV disease costs and prematurity, low birth weight (LBW) and underlying medical conditions have been associated with RV hospitalization and complications. We investigated cost-effectiveness of targeted vaccination of high-risk infants and universal vaccination.
Methods: Disease burden, mortality and healthcare costs of RV hospitalization for children with and without prematurity, LBW and congenital pathology were quantified in two hospital-based observational studies in the Netherlands. Cost-effectiveness analysis was based on an age-structured stochastic multi-cohort model of the Dutch population comparing universal RV vaccination and targeted vaccination of high-risk infants to no vaccination. The primary endpoint was the incremental cost-effectiveness ratio (ICER), with a threshold of €35,000/QALY from the healthcare perspective. Sensitivity analyses included vaccine price and coverage, herd-immunity and QALY losses.
Findings: 936 children with RV infection were included. Prematurity, LBW and congenital pathology were associated with increased risks of RV hospitalization (relative risks (RR) ranging from 1.6 to 4.4), ICU admission (RR ranging from 4.2 to 7.9), prolonged hospital stay (1.5 to 3.0 excess days) and higher healthcare costs (€648 to €1533 excess costs). Seven children succumbed due to RV complications, all belonging to the high-risk population. Targeted RV vaccination was highly cost-effective and potentially cost-saving from the healthcare perspective with ICERs below €20,000/QALY in all scenarios with total (undiscounted) healthcare costs between -€0.1 and €0.5 million/year. Results were most sensitive to mortality rates, but targeted vaccination remained highly cost-effective up to reductions of 90% compared to observed mortality. Universal vaccination was not considered cost-effective (mean ICER: €60,200/QALY), unless herd-immunity and caretaker QALY losses were included and vaccine prices were €60 at most (mean ICER: €21,309/QALY).
Interpretation: We recommend targeted RV vaccination for high-risk infants in developed countries.

Introduction

Rotavirus (RV) vaccination reduces severe RV gastroenteritis (GE), associated healthcare utilization and mortality among young children.[1,2] Universal infant vaccination with either the monovalent life-attenuated vaccine (RV1) or the pentavalent human-bovine reassortant vaccine (RV5) has therefore been recommended by professional healthcare organizations worldwide, [3-7] but results of cost-effectiveness analyses of RV vaccination in developed countries yielded conflicting results.[8-11] Consequently, RV vaccination programs have been introduced in only a very limited number of European countries.[12]
Although RV is widely considered a universal pediatric infection with young age as the only important risk factor, in the developed world hospitalization due to RV, the main driver of RV associated healthcare costs, seems to be associated with underlying chronic disease, congenital disorders, prematurity and low-birth weight (LBW).[13-24] Moreover, these children are more prone to complicated RV disease courses with more frequent ICU admission.[18] Prematurity or LBW has been associated with necrotizing enterocolitis, encephalopathy[25-29] and increased diarrheal mortality.[30-32]
A targeted vaccination strategy for RV, in which vaccination is offered to high-risk infants only, has not been economically evaluated thus far. We, therefore, set out to determine the cost-effectiveness of such an approach in the Netherlands, where universal RV vaccination has not been implemented yet, similar to the situation in most European countries. We first quantified RV related hospitalizations in the Netherlands and identified patient groups at increased risk of RV hospitalization or with increased healthcare needs when hospitalized. Subsequently these data were supplemented with relevant available epidemiological data to determine the cost-effectiveness of different RV vaccination strategies, including targeted vaccination.

Methods

Rotavirus Hospitalizations; Observational Study

The methodology of this study has been described elsewhere.[33] In brief, laboratory confirmed rotavirus related pediatric hospitalizations occurring in one of 4 participating hospitals (3 general hospitals, 1 tertiary care centre) during a 5 year period (December 2005-November 2010) were retrospectively studied. RV underreporting was subsequently assessed by hospital-based active surveillance during the 2011 RV season.[33]
A comprehensive chart review was performed for each case extracting data on RV disease course, healthcare resource utilization and patient's medical history to identify conditions potentially associated with increased clinical vulnerability such as prematurity of < 36 weeks gestational age and/or low birth weight (LBW, <2500 grams) and complex chronic conditions. Complex chronic conditions were those that (1) are expected to last longer than 12 months and (2) involve either several different organ systems or 1 organ system severely enough to require specialty pediatric care and hospitalization. This classification characterizes a group of patients with increased healthcare needs and mortality.[34-36] We further classified complex chronic conditions into those with congenital origin (i.e. severe congenital pathology) and those with onset later in life.
Prevalence rates for prematurity/LBW and severe congenital pathology were also derived for the Dutch infant population from national disease and birth registries, covering 96% of the Dutch infant population.[37,38] In addition, a nested case-control study was performed to investigate if the same conditions increased the risk of nosocomial RVGE compared to otherwise healthy age-matched hospital controls (details in supplement).

Healthcare resource utilization, assessed at the individual patient level, was used for cost calculations, adapting standard cost prices and charges (supplement Table S1).[39,40] Costs included hospitalization days, preceding emergency department visits, contact isolation precautions[41] and ambulance transportation. For nosocomial RVGE costs for RV related excess hospitalization days were used,[33] or - when hospitalization was not prolonged - isolation costs and RVGE related diagnostic and therapeutic costs.
This study was approved by institutional review boards of participating hospitals.

Statistical analysis
Prevalence of prematurity/LBW and severe congenital pathology among RV hospitalizations compared to the general infant population were used to compute Risk Ratios (RR). To account for the clustered study design and for oversampling of tertiary-care hospitalizations compared to their national share in pediatric hospitalizations (20%), weighted prevalence estimates were calculated with variance estimated using Taylor series linearization.[42]

Rates of ICU admission and RV related deaths were compared between RV patients with and without potential high-risk conditions by computing RR. (Excess) length of stay and healthcare costs were compared by t-test, using the arithmetic mean despite the usually skewed distribution. The arithmetic mean is considered most informative in evaluations designed to have an impact on medical policy, because it is the total disease burden that is important.[43]

Any of the assessed risk factors (prematurity/LBW or congenital pathology) that were associated with increased risk of RV hospitalization, nosocomial RVGE, RV related death and/or increased length of stay were included to determine eligibility for targeted vaccination, excluding those who suffered from severe immunodeficiencies, in whom RV vaccination is contra-indicated.[44]
Differential RV hospitalization rates were calculated for eligible and ineligible children from RVGE numbers adjusted for underreporting using weighted estimation.[42]
Analyses were performed using R software, version 1.14.1.

Model Design
We used an age-structured stochastic multi-cohort model of the Dutch population, as previously described by Mangen et al.[45] to investigate three RV vaccination strategies: (1) no vaccination, (2) universal vaccination of all infants, (3) targeted vaccination of high-risk infants.
Strategies were compared assuming an annual birth cohort of 180,000 infants, equivalent to the 2010 Dutch birth cohort. Effect of vaccination was modeled as a reduction in RVGE and associated health outcomes in vaccinated compared to non-vaccinated children between 0 and 15 years with RV disease risk stratified by age and time since vaccination (Figure S1). Time steps of one month were used for ages 0-11 months and of one year thereafter. Effects were modeled over a time-horizon of 20 years with year one being the start of either vaccination program. The model was adapted to simulate targeted vaccination by splitting the population into a vaccination eligible and an ineligible fraction. We assumed no effect on adult RV infections from any of the infant vaccination strategies.

Model Parameters
Estimates of RV infection rates, outpatient healthcare visits and related direct and indirect healthcare costs for different age-groups were derived from existing epidemiological sources as previously described by Mangen et al (Table 1).[45] Hospitalization rates and costs

for children eligible and ineligible for targeted vaccination and for combined groups were derived from our multi-centre observational study.

Mortality due to RV was determined by combining data from the multi-centre observational study and from another tertiary-care hospital. In this hospital RV related mortality was determined for all children who had died within 3 weeks of confirmed RV infection between 2000 and 2006. Conservative estimates were used for national mortality figures, assuming that fatal cases exclusively occurred among RV hospitalizations at tertiary care centers without underreporting.

An expert panel of four pediatricians was consulted to determine years of life lost (YLL) due to RV infection among observed fatal cases (Table 1).
We used Quality Adjusted Life Years (QALYs), the product of the health-state utility and the length of time in that state, to weigh losses as a result of RV episodes requiring different levels of healthcare, similar to those used in previous cost-effectiveness analyses.[9,10,45] QALY losses due to RV mortality were based on YLL estimates for observed fatal RV cases.
European vaccine efficacy data were used for age-specific vaccination effects (supplementary table S3).[46-50] Linear waning immunity was assumed for the 3rd, 4th and 5th year post-vaccination, and zero protection thereafter. We assumed 88% adherence to vaccination recommendations, the observed current vaccine coverage in neighboring Belgium where universal RV vaccination was implemented in 2007,[51] and used coverage rates from 65-97% in sensitivity analysis.
Vaccine costs for universal vaccination were based on Rozenbaum et al. who assumed tender processes lower vaccine prices by almost 50% (€75 per vaccinated child) compared to the current free market price.[10] Targeted vaccination was assumed to generate price reductions of 25% (€100 per vaccinated child). We also included scenarios with the free market price for both vaccination strategies. We assumed vaccine doses would be administered during routine immunization clinic visits at a standard application fee of €6.44 per vaccination.[45]
Indirect vaccination effects (herd-immunity) among unvaccinated children was considered as part of the sensitivity analysis (Table 1).[52-54] No herd-immunity was assumed in the case of targeted vaccination, as vaccine coverage was considered too low for herd-immunity to occur.

Cost-effectiveness analysis
Our primary perspective was that of the healthcare provider and a societal perspective was included in sensitivity analysis taking non-healthcare costs into account, updated from Mangen et al with additional data on parental work loss due to RV hospitalizations in children.[55] All costs were converted to 2011 Euros. A 3% discount rate for costs and benefits was used in base-case scenarios according to WHO guidelines.[56] Other discount rates, including those recommended for Dutch health economic evaluations, were used in sensitivity analysis.[39] Although there is no consensus on a cut-off point for good value for resources, we present our results in the context of commonly cited thresholds per QALY of $50,000 equivalent to €35,000.[57,58] This amount is approximately equal to the Dutch Gross Domestic Product per capita in 2011, the recommended threshold for highly cost-effective interventions by the WHO.[56] In addition, we use the unofficial threshold of €20,000/QALY commonly applied in the Netherlands for preventive healthcare interventions.

Total net healthcare costs for either vaccination strategy compared to no vaccination are reported (cost-analysis) as well as incremental cost-effectiveness ratios (ICERs), representing costs per QALY gained. Strategies were considered cost-effective if they generated ICER's

Table 1. Parameters for model input

Parameter	Value (95%CI) *Total Population*	*Ineligible Population*	*Eligible Population*	Distribution	Data source	Method
Birth cohort (%) RV Incidence	182,662	168,215 (92.1%)	14,448 (7.9%)	-	Statistics Netherlands[86], Dutch Perinatal Registry[38], Eurocat[37]	Published results on birth cohort size and prevalence of high risk conditions
RV Incidence						
<1 years	18,075 (11,768; 22,932)	Calculated	Calculated	Pert	Community-based cohort study[87]	Incidence based on simulations from original study data updated to 2011 population size, see Mangen et al for details[45] Distribution among eligible and ineligible based on relative size of each group in birth cohort
1-4 years	42,218 (24,711; 56,272)					
5-64 years	147,997 (41,573;282,866)					
5-9 years	6.2% of 5-64 years					Based on Age-distribution of cases 5-64 years in original study data
10-14 years	2.9% of 5-64 years					
GP visits 0-1 years	21.2% (12.8; 26.5)	Calculated	Calculated	Pert	GP based cohort study GP[88]	Percentage of all RV cases, based on simulations from original GP study data, see Mangen et al for details.[45] Distribution among eligible and ineligible based on relative size of each group in birth cohort
GP visits 1-4 years	18.7% (16-4; 19.9)					
GP visits 5-14 years	4.0% (1.8; 4.7)					
Hospitalization (95%CI)	Calculated	3884 (3244; 4524)	491 (357; 626)	Pert	RoHo-study	Weighted incidence estimation based on original study data, see Bruijning-Verhagen et al for details[33]
Nosocomial (95%CI)	Calculated	227 (162; 293)	269 (172; 365)	Pert	RoHo-study	Weighted incidence estimation based on original study data, see Bruijning-Verhagen et al for details[33]
Mortality rate (per 1000 RV hospitalizations)	Calculated	0.00 (0.00; 0.04)	0.81 (0.36; 1.46)	Triangular	RoHo study, External dataset Sophia Children's hospital	Observed mortality cases from both sources were combined for weighted mortality rate estimation
Age distribution of RV hospitalizations and fatal cases	Table S2				RoHo study	
Utilities RV gastroenteritis	QALY/QALY2‡					
Mild (RV episode without medical care)	0.0011/0.002				GP study in Canada[89], Previous CEA[9]	Published data
Moderate (GP visit)	0.0022/0.004					
Severe (Hospitalization)	0.0022/0.004					
Nosocomial	Calculated	Calculated	Calculated		RoHo Study	Based on severity distribution of nosocomial cases observed in RoHo-study
Mortality	Calculated	80.7 minus patient's age	Simulated, whereby assuming a life expectancy of 1; 20; 41.3 minus patient's age with probability of 1/3 each†	Uniform	Statistics Netherlands,[86] Expert opinion	For ineligible: Based on average life expectancy in the Netherlands. For eligible: Based on expert panel†

YLL: Years of Life Lost
† All observed fatal RV cases occurred among patients with severe congenital conditions associated with limited life-expectancy. To generate valid estimates of life years lost (YLL) due to RV, four pediatricians (PB, MF, MvH, NH) were individually asked to provide estimates of YLL for each case of RV mortality based on patient's medical records. Independent estimates for all 7 observed cases were pooled to generate a distribution of mean YLL per fatal RV case.
‡ QALY2 includes QALY's lost by caretakers

Table 1. Continued

Direct healthcare costs (Euro)	*Total Population*	*Ineligible Population*	*Eligible Population*			
Gastroenteritis episodes without medical care	0			Fixed		
Standard GP visits	29				Guidelines for health-economic evaluations[39]	Standard Cost Prices. See Mangen et al for details[45]
Home visit GP	45					
GP Consultation by phone	15					
Prescriptions	40				Community-based cohort study and GP based cohort study[87,88]	See Mangen et al.[45]
Laboratory costs	73					
Hospitalization	Calculated	2179 (2027;2330)	2550 (2508; 3606)	Pert	RoHo study	Weighted estimates from original study data, see web-supplement 1
Nosocomial	Calculated	1995 (1242; 2748)	2129 (1203; 3055)			
Direct non-healthcare costs						
RV episode without medical care	Additional diapers			Uniform	Assumption	See Mangen et al.[45]
GP visits	Additional diapers and travel costs				Guidelines for health-economic evaluations[39]	
Hospitalization Nosocomial	Travel costs			Pert		
Indirect non-healthcare costs#						
Costs per hour work loss (euro)	31.11			Fixed	Statistics Netherlands[86] Guidelines for health-economic evaluations[39]	See Mangen et al.[45]
Hours of work loss for RV episode without medical care	0.93; 1.36; 0.84 for ages 0-4; 5-9 and 10-14 years respectively			Uniform	Community-based cohort study and GP based cohort study[87,88]	Dependent of patient-age. See Mangen et al.
Hours of work loss GP visits	1.35; 1.98; 1.23 for ages 0-4; 5-9 and 10-14 years respectively			Uniform		
Hours of work loss Hospitalization	37.32				Hospital based observational study[67]	Based on the findings from Friesema et al. (2012) for children up to 18, Further details see Mangen et al.[45]
Hours of work loss Nosocomial	24.58					Based on the findings from Friesema et al. (2012) for children up to 18, adjusted for excess duration of hospitalization among nosocomial in RoHo study (2.7 vs 2.9 days)
Vaccine efficacy	Table S3				Vaccine trials[46-48,91]	
Herd-immunity	Universal vaccination		Targeted vaccination			
	30% (0-46%)		-	Triangular	Observational studies from US[53,54], Australia[52,92], Belgium[93]	Published data
Vaccination costs						
RV1	60; 75; 90		80; 100; 120		Previous CEA[10] For Eligible: Assumption	Assumed tender Price
RV5	60; 75; 90		80; 100; 120			
Startup costs first year	218,440		-			See Mangen et al.[45]
Application costs	6.44					
Administration costs	1.64					

YLL: Years of Life Lost
† All observed fatal RV cases occurred among patients with severe congenital conditions associated with limited life-expectancy. To generate valid estimates of life years lost (YLL) due to RV, four pediatricians (PB, MF, MvH, NH) were individually asked to provide estimates of YLL for each case of RV mortality based on patient's medical records. Independent estimates for all 7 observed cases were pooled to generate a distribution of mean YLL per fatal RV case.
‡ QALY2 includes QALY's lost by caretakers

less than a willingness-to-pay threshold of €35,000/QALY from the healthcare provider perspective. An ICER below €20,000/QALY was considered highly cost-effective.
The simulation model was built in Microsoft Excel using add-in software @Risk, version 5.5 (Palisade). Results are presented as means and 95% confidence interval (CI) of simulated results, based on 10,000 iterations. Parameters were varied simultaneously in probabilistic sensitivity analyses, performing random draws from distributions. Distributions were chosen based on parameter characteristics and level of certainty. Input parameters and their distributions with corresponding information source are presented in Table 1. In addition, we performed one-way sensitivity analysis to determine variables which were most influential on model results.

Results

Rotavirus Hospitalizations; Observational Study

Overall, 944 RV infections were identified. After excluding six patients with asymptomatic disease and two without medical records available, 936 patients were analyzed. RVGE was community-acquired and nosocomial in 770 (81%) and 176 (19%) episodes, respectively (Supplementary Table S4).

In 134 patients (14%) RVGE occurred before 15 weeks of age and would not be prevented by vaccination, unless by herd-immunity. Prevalence of prematurity <36 weeks was 9% (n=83), of low birth weight was 11% (n=104) and of complex chronic conditions at the time of RV infection was 23% (n=219). The latter was more frequent among nosocomial than among community-acquired infections (64% versus 14%, p<0.0001). Most of these patients (n=116, 53%) suffered from severe congenital pathology. Based on weighted prevalence of prematurity, LBW and congenital pathology among RV hospitalizations and the general infant population, all three conditions were significantly more common among children hospitalized for RVGE and were, therefore, classified as high-risk for RV hospitalization (mean RR: 1.7; 1.6; 4.4, respectively; Table 2). RVGE related ICU admission occurred more frequently among children with prematurity, LBW and congenital pathology than among otherwise healthy patients (mean RR ranging from 4.2 – 7.9). Mean length of stay was increased by 1.5 to 3.0 days and mean healthcare costs were €648 to €1533 per patient higher. Results from the nested matched case-control study demonstrated increased risks of acquiring nosocomial RVGE for prematurity (aOR: 3.3, 95%CI: 1.5 – 7.3), LBW (aOR: 3.2, 95%CI: 1.5 – 7.1) and congenital pathology (aOR: 3.6, 95%CI: 1.8–7.0) compared to healthy hospitalized controls (details in Supplement).

RV mortality

Two RV related fatalities were observed in the multi-centre study and an additional 5 among 214 confirmed RVGE episodes at the external tertiary care hospital during 6 years of observation. All seven had congenital pathology and 2 patients also had a history of LBW. One child died before 2 months of age, the remaining 6 children died between 2 and 14 months of age.

RV epidemiology and vaccination effects

Without vaccination, there were an estimated 75,000 (95%CI: 58,000 – 90,000) RVGE episodes annually, with 5000 (95%CI: 4300 – 5400) hospitalizations and 500 nosocomial infections among children 0-15 years old, generating €11.9 (95%CI: 10.5 – 13.3) million in total healthcare costs and €18.2 million (95%CI: 16.2 – 20.3) when societal costs are included

(Table 3). An estimated 6-7 children (95%CI: 3 – 11) die prematurely due to RV each year in the Netherlands. A total of 260 QALY's (95%CI: 140 –420) are lost due to RV, of which 170 (95%CI: 50 – 330) are due to fatal RV cases.
A universal RV vaccination program (at €75 per vaccine course per child) generates €15.2 million in healthcare costs annually when the two-dosage RV1 and €16.7 million when the

Table 2. Prevalence of high risk conditions among RV hospitalizations and their association with disease outcome and healthcare utilization

	Prevalence						P-value†	RR†
	RoHo		*Weighted estimates national RV hospitalizations (95%CI)*		*General Infant Population**			
High Risk Conditions	%	N	%	N	%	N		
GA < 36 weeks	8.9	83	6.8 (5.1; 8.5)	347 (243; 451)	4.3	7617	0.005	1.7 (1.2; 2.8)
LBW	11.1	104	8.8 (6.6; 11.1)	462 (309; 615)	6.0	10545	0.014	1.6 (1.1; 2.3)
Congenital pathology	12.4	116	6.2 (4.9; 7.4)	309 (244; 374)	1.5	2719	<0.0001	4.4 (3.4; 5.4)

	Healthy (N=657)	High Risk Conditions					
		GA < 36 weeks (N=83)		*LBW (N=104)*		*Congenital pathology (N=116)*	
Outcome and healthcare utilization			RR (95%CI)		RR		RR
ICU admission (number, %)	4 (0.6%)	4 (4.8%)	7.9 (2.0; 31.1)	3 (2.9%)	4.7 (1.1; 20.9)	3 (2.6%)	4.2 (1.0; 18.7)
RV related death (number, %)	0	0		0		2 (1.7%)	NA
			Mean difference (95%CI)		Mean difference (95%CI)		Mean difference (95%CI)
LOS (mean, SD)	3.6 (2.1)	5.2 (4.7)	+1.6 (0.1; 3.0)	5.1 (4.5)	+1.5 (0.3; 2.7)	6.6 (4.2)	+3.0 (1.9; 4.1)
Healthcare costs (mean, SD)	2203 (2113)	3001 (3407)	+798 (28; 1568)	2851 (3206)	+648 (-2; 1297)	3737 (3500)	+1533 (867; 2199)

GA: Gestational Age
LBW: Low Birth Weight
SD: Standard Deviation
† Comparing weighted RV hospitalizations prevalence to population prevalence
***** Dutch birth cohort alive after 1 month, 2005-200838

three-dosage RV5 is used. The difference is explained by the additional application costs of a third RV5 dose. A total of 3500 (95%CI: 3050 – 3960) and 3430 (95%CI: 2980 – 3880) RV hospitalizations are avoided by RV1 and RV5, respectively. QALY's gained mount to 194 (95%CI: 83 – 348) for RV1 and 188 (95%CI: 80 – 342) for RV5. On average, 6.1 (95%CI: 3.0 – 10.2) fatal cases are avoided.
Using targeted vaccination, approximately 8% of the infant population would be eligible for vaccination (i.e. children with one or more high-risk conditions). At €100 per vaccinated child, annual vaccination costs are €1.5 million or €1.6 million (RV1 or RV5). Five hundred (RV1, 95%CI: 420 – 590) or 490 (RV5, 95%CI: 410; 570) hospitalizations are avoided while the number of avoided fatal infections is similar to results for universal vaccination (5.8 cases, 95%CI: 3.0 – 9.5).
As outcome results for either vaccine were almost identical, further analyses presented are based on RV1 vaccination with results for RV5 available in the supplement, Table S7.

Table 3. Annual results of universal and targeted RV vaccination under base-case assumptions

	RV disease burden (95%CI)‡				RV disease costs‡		Vaccination costs (€ million)
	Disease episodes (x1000)	hospitalizations*	Fatal cases	QALY's lost (undiscounted)	Direct healthcare costs (€ million)	Societal costs (€ million)	
No vaccination	74.1(57.8; 90.0)	4870 (4310; 5430)	6.5 (3.2; 11.0)	257 (136; 422)	11.9 (10.5; 13.3)	18.2 (16.2; 20.3)	-
Universal vaccination							
RV1	40.6 (30.1; 51.2)	1370 (1150; 1650)	0.4 (0.2; 0.8)	60 (42; 81)	3·4 (2·8; 4·1)	5.9 (5.0; 6.9)	15.2
Percent reduction	45%	72%	94%	77%	71%	67%	
RV5	42.6 (31.7; 53.6)	1440 (1210; 1710)	0.5(0.2; 0.9)	66 (45; 91)	3·6 (3·1; 4·3)	6.3 (5.3; 7.3)	16.7
Percent reduction	43%	70%	92%	80%	70%	65%	
Targeted vaccination							
RV1	67.3 (51.3; 82.4)	4370 (3890; 4870)	0.7(0.2; 1.6)	119 (79; 177)	10.5 (9.3; 11.8)	16.4 (14.6; 18.2)	1.5
Percent reduction	8%	10%	89%	54%	12%	10%	
RV5	67.4 (51.5; 82.7)	4384 (3892; 4870)	1.1 (0.3; 2.4)	124 (81; 195)	10.6 (9.4; 11.8)	16.4 (14.6; 18.2)	1.6
Percent reduction	8%	10%	89%	64%	11%	10%	

***** including nosocomial infections
‡ Results reflect those 5 years and more after initial implementation of a vaccination strategy when steady state is reached.

Net healthcare costs (defined as vaccination costs minus healthcare savings) were compared for different scenarios (Figure 1). Undiscounted annual net healthcare costs of universal vaccination varied between €3.7 and €9.6 million, depending on assumptions about vaccine price, herd-immunity and vaccine coverage. Results of targeted vaccination varied between net savings of €0.1 million up to maximum costs of €0.4 million.
Comparing the free market vaccine price in both strategies resulted in a difference of €16

million annually (€16.9 vs. €0.6 million for universal and targeted vaccination, respectively). Universal RV vaccination is unlikely to be cost-effective from the healthcare perspective at a willingness-to-pay threshold of €35,000/QALY gained (Figure 2). Only when herd immunity and caretaker QALY losses are included universal vaccination is considered cost-effective if vaccine prices are at most €60/child (ICER: €21,309/QALY, 95%CI: 11,079 – 36,047). Targeted vaccination, as compared to no vaccination, is highly cost-effective in all scenarios with mean ICER's varying between €-300/QALY for the best case scenario up to €6300/QALY when using the free market price (Figure 2). Outcome results from the societal perspective and analyses based on different discount rates are provided in supplement table S6.

Cost-effectiveness was most sensitive to the estimated mortality rate. We therefore included a threshold analysis to identify the cut-off value of the parameter at which targeted vaccination would no longer be cost-effective. Targeted vaccination remained highly cost-effective up to a reduction of 90% in mortality rate, which translates to less than 1 RV death per year (Figure 3).

Choosing between competing strategies requires consideration of cost-effectiveness acceptability curves, which visualize the probability of cost-effectiveness dependent on the willingness-to-pay for health benefits. At a threshold of €35,000/QALY, we estimate the probability of cost-effectiveness of universal vaccination under basecase assumptions from the healthcare perspective to be 6%, and 71% from a societal perspective (Figure 4). The probability of cost-effectiveness of targeted vaccination both at the €35,000/QALY and €20,000/QALY thresholds is 100% for both healthcare and societal perspectives.

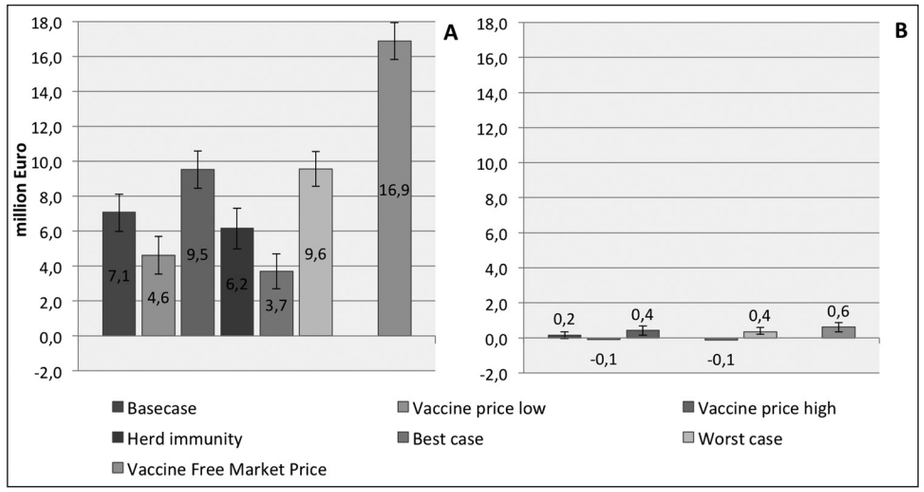

Figure 1: Net annual healthcare costs for universal (A) and targeted (B) vaccination under different assumptions and corresponding 95% CI. "Basecase" represents results when the vaccine price is €75 (universal) and €100 (targeted) per child, coverage is 88%, and no herd immunity is present. Vaccine price "low" and "high" represent results for €60 and €95 per vaccinated child, respectively for universal vaccination and €80 and €120 for targeted vaccination. "Herd immunity" includes protection of unvaccinated children. A scenario with herd immunity effects was not included for targeted vaccination. "Best case" represents results for low vaccine price, coverage of 97% and presence of herd immunity. "Worst case" represents a high vaccine price, coverage of 65% and no herd immunity. "Vaccine Free Market Price" shows results when the current listed vaccine price is used without any tender effects.

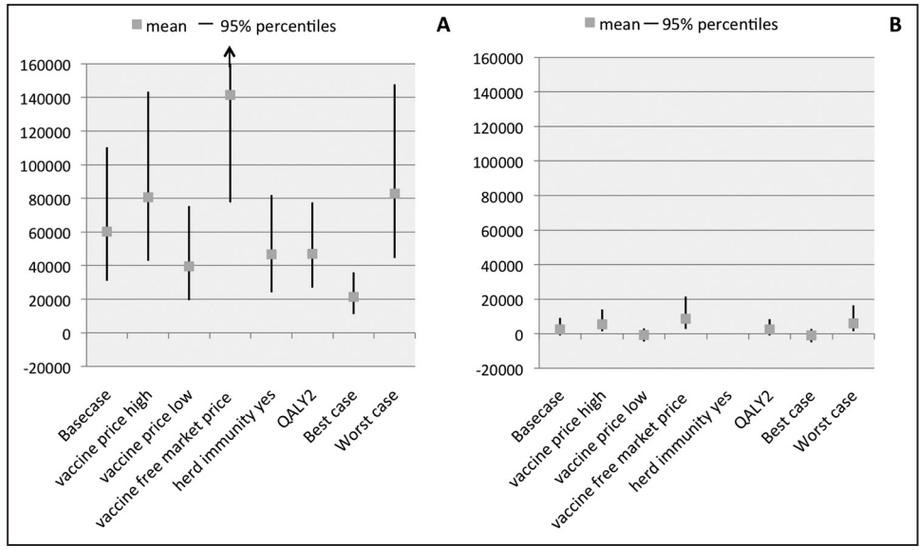

Figure 2: Cost per QALY gained (mean and 95%CI) for universal (A) and targeted vaccination (B) under different assumptions. "Basecase" represents results when the vaccine price is €75 (universal) and €100 (targeted) per child, coverage is 88%, and no herd immunity is present. "Vaccine price low" and "high" represent results for €60 and €95 per vaccinated child, respectively for universal vaccination and €80 and €120 for targeted vaccination. "Herd immunity" includes protection of unvaccinated children (only used in universal vaccination). "QALY2" represents results when QALY loss of caretakers is taken into account. "Best case" represents results for low vaccine price, coverage of 97%, including caretaker QALY's and presence of herd immunity. "Worst case" represents a high vaccine price, coverage of 65%, no caretaker QALY's included and no herd immunity. "Vaccine Free Market Price" shows results when the current listed vaccine price is used without any tender effects under base-case assumptions.

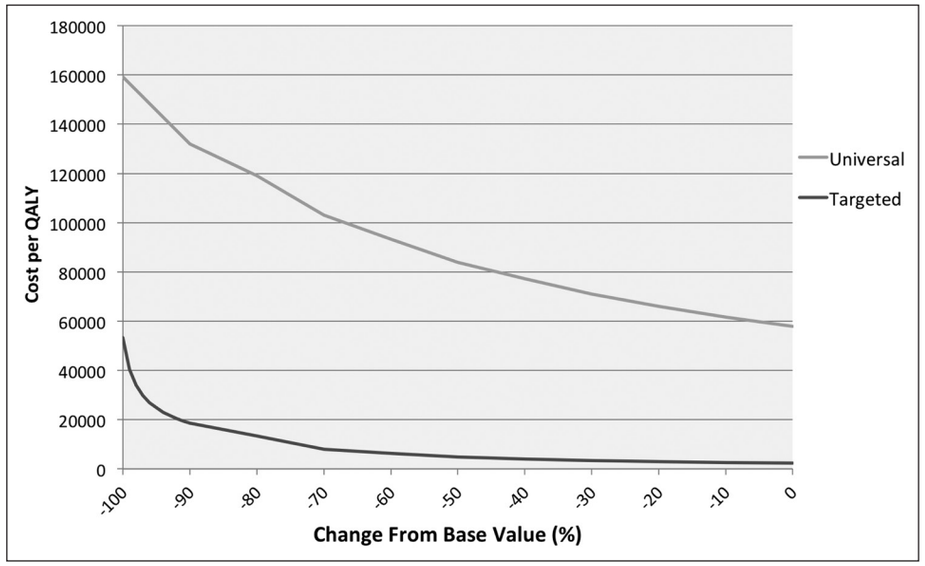

Figure 3: Mean Cost per QALY of universal and targeted vaccination as a function of change in mortality rate between 0% and -100% (i.e. no mortality at all) compared to baseline

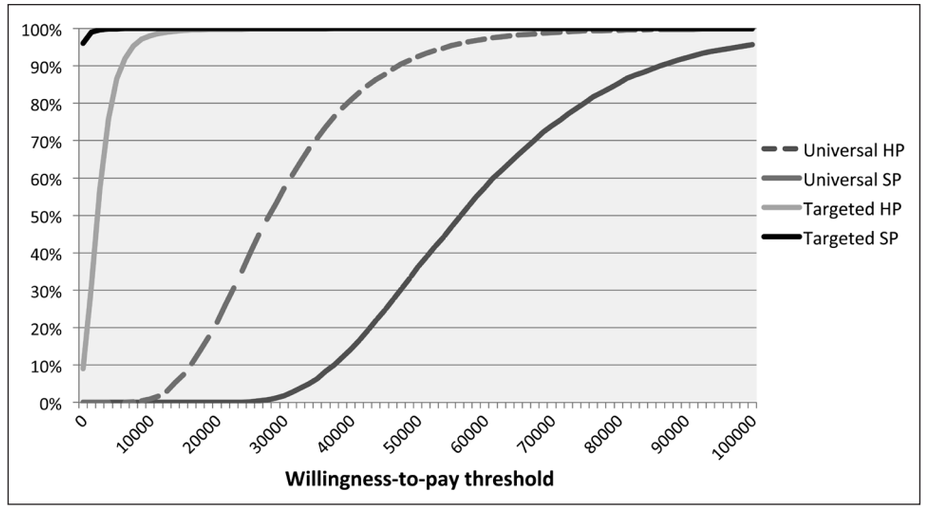

Figure 4: Probability of Willingness-to-pay at different thresholds for universal and targeted vaccination under base-case assumptions showing results for both healthcare (HP) and societal perspective (SP)

Discussion

Based on detailed epidemiological data analyzed in an age-structured stochastic multi-cohort model we conclude that (in the Netherlands) targeted RV vaccination of high-risk infants is highly cost-effective and potentially cost-saving. Cost-effectiveness estimates were most sensitive to RV mortality rates, but targeted vaccination remained cost-effective when mortality would be 90% lower than observed.

In our analysis, universal vaccination was not considered cost-effective from the healthcare perspective, and would only become cost-effective when herd-immunity and caretaker QALY losses were included and if vaccine prices would be at most €60/child. Universal RV vaccination could, however, be considered cost-effective from the societal perspective at the €35,000/QALY threshold. These findings differ somewhat from previous economic analyses of universal RV vaccination in the Netherlands,[9,10,45] which can be explained by the updated and more reliable parameter estimates used. Incidence and costs of RV hospitalizations in the Netherlands determined in our study are comparable to estimates from Germany, Finland and the UK and another recent Dutch observational study.[55,59-61] Previously, lower incidence and cost estimates were derived for the Netherlands by using indirect methods combining sentinel laboratory data and hospital discharge codes.[62,63] The accuracy and completeness of methods using discharge codes has been criticized and depends on local coding practices.[64,65,66] In addition, we could include recent estimates of parental work loss in children hospitalized for RV.[67]

Our analysis did not account for potential costs and QALY losses associated with vaccination induced intussusception. Based on observed intussusception risks attributable to RV vaccination in different populations, 0-9 additional cases would occur each year in the Netherlands when universal vaccination is implemented.[68-76] Clearly, this could have a negative impact on cost-effectiveness, although overall effects may be small. Furthermore, the recent reports on an increased risk of intussusception after the first dose of RV vaccine may raise concerns about exposing healthy children at low risk of RV related complications to vaccination risks.[77,78]

Our study confirms that prematurity, LBW and congenital pathology are important risk factors for RV hospitalization and increased healthcare needs. Furthermore, we observed RV mortality exclusively among patients with any of these high-risk conditions. Although absolute numbers were low, similar observations in other European and US studies and the association between diarrhea related mortality and birth weight confirm existence of differential mortality risks.[17,19,30-32] Of note, in five out of 7 patients that succumbed the underlying illness rather than RV was stated as the cause of death in death-records. Yet, in these patients RV caused a profound medical deterioration leading to premature death, as confirmed by expert review of case histories. These findings suggest that among children with severe underlying conditions fatal RV disease is underreported.

Although limited data are available on vaccine safety and efficacy among high risk patients, protection from RV vaccine was comparable in premature and non-premature infants without additional safety risk.[79-81] Current recommendations support RV vaccination in preterm infants and also in those with preexisting underlying disease, including gastrointestinal disease, in non-acute phases of illness.[3,5,82] Recently, it was shown that RV vaccination among short bowel patients was well tolerated.[83]

Targeted vaccination does not offer the potential benefits of herd-protection, which have been described after implementation of universal RV vaccination. Observed effects among unvaccinated individuals ranged from 0 and 72% with substantial differences between consecutive years and effects declining with increasing age.[53,54,84] As severe RVGE occurs mainly in those < 5 years, herd-immunity could be a transient effect post-implementation, which disappears when coverage rates among this age-group approach 100%. Therefore, herd-immunity effects on the population level are difficult to predict.[85] Continued surveillance may provide more insights in coming years.

Naturally, our findings and conclusions may not hold for countries with high RV mortality among the general infant population and with higher RVGE incidences. In such countries universal vaccination remains the recommended approach.

Conclusion

Universal vaccination is the preferred strategy to decrease the high disease burden among young children caused by RV in European countries and elsewhere, but is probably not cost-effective from the healthcare perspective. Targeted RV vaccination of high-risk infants is highly cost-effective and can nearly eliminate RV mortality in developed countries with very limited impact on healthcare budgets. We therefore encourage policy makers in countries without RV vaccination programs to prioritize RV vaccination for high-risk infants.

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Supplementary Material

Observational Study; Nested Case Control study

A nested case-control study was performed within the observational study to determine whether children with prematurity, LBW or severe congenital pathology are at increased risk of acquiring nosocomial RVGE. All children hospitalized at the tertiary care hospital and who acquired nosocomial RVGE during the 5 year study period were included as cases. Controls were randomly selected from the hospital population of the same hospital and were individually matched to the cases in a 1:2 ratio. Patients were eligible as controls when hospitalized for at least 72 hours and without a history of known previous RV infection. Matching on age and admission date (± 1 month) was performed to account for differences in age-dependent risk of RV disease and the seasonal circulation of RV. The eligible age-range for controls was ± 1 month difference for cases less than one year of age, ± 3 months difference for cases 1-2 year old and ± 6 months thereafter. Data extraction for cases and controls occurred in a similar way by review of medical records.

Statistical Analysis

Characteristics of cases and controls were compared using Chi-Square and Mann-Whitney U test. Case-control pairs were analyzed by using conditional logistic regression for binary outcomes to account for the matched design. We assessed the presence of potential risk factors prematurity, LBW and congenital pathology for nosocomial RVGE. Candidate covariates in the model were gender and admission ward. Results from conditional logistic regression analyses are reported as adjusted Odds Ratios (aOR) and 95% CIs.

Results

Nested case-control study

One hundred and two nosocomial cases occurred at the tertiary care centre and were included in the case-control study. An age and admission date matched hospital control was available for 100 cases. Two suitable controls were available for 96 cases (Table S1). Presence of congenital pathology was less common among controls than among cases and length of stay was significantly shorter in controls. Patients with congenital pathology were significantly more likely to acquire RV infection during an episode of hospitalization than otherwise healthy children (aOR: 3.6, 95%CI: 1.8 – 7.0). Similar results were seen for children born before 36 weeks (aOR): 3.3, 95%CI: 1.5 – 7.3) or those with LBW (aOR: 3.2, 95%CI: 1.5 – 7.1) The increased risk among patients with congenital pathology, prematurity and LBW is largely mediated through an increased length of stay as was shown by a sub-analysis in which only controls matched on exposure time were included (i.e. hospitalization of the control for at least the number of days until the case develops nosocomial RVGE). Although a smaller number of case-control pairs was included this analysis (N= 44 cases, 96 controls) the effect of all three risk factors was reduced and no longer significant (aOR congenital pathology: 1.4, 95%CI: 0.6 – 3.3; aOR GA<36weeks: 1.3, 95%CI: 0.4; 3.7; aOR LBW: 1.4, 95%CI: 0.5; 3.8). Irrespective of the underlying mechanism, due to the increased risk to acquire nosocomial RVGE during an episode of hospitalization, children with one of the risk factors are overrepresented among cases compared to controls.

Table S1. Standard Cost prices applied to units of care for RV hospitalizations*

Hospital care community-acquired and nosocomial RV hospitalizations‡		Source
Tertiary-care centre patient-day	€ 595.95	
General hospital patient-day	€ 450.85	39
Intensive Care patient-day	€ 2,262.55	
ER visit	€ 156.90	
Additional costs for contact isolation	€ 75.00	41
Ambulance	€ 522.14	40
Standard cost prices of most frequent diagnostic and therapeutic interventions related to nosocomial RVGE and those with highest budget impact†		40
Microbiology testing		
RV immuno-essay	€ 20.09	
Combined rota-, adenovirus immuno-essay	€ 40.18	
RV viral culture	€ 26.80	
Norovirus PCR	€ 202.21	
Bacterial stool culture	€ 40.19	
C. difficile toxin	€ 20.09	
Bacterial blood culture	€ 26.80	
Urinary culture	€ 21.43	
Blood chemistry/hematology		
C-reactive Protein	€ 4.69	
Serum electrolytes (natrium, kalium)	€ 3.40	
Blood glucose	€ 1.70	
Blood Gas Analysis (pH, base excess, HCO3)	€ 4.69	
Renal function studies	€ 3.40	
Urinalysis	€ 1.70	
Complete blood cell (CBC) count	€ 5.10	
Differential count	€ 3.35	
Imaging		
Abdominal ultrasound	€ 43.98	
Abdominal X-ray	€ 49.77	
Therapeutic interventions		
Oral rehydration solution	€ 1.92/ day	
Ringer's lactate	€ 2.48/ day	
Insertion of Central venous catheter	€ 348.60	
Parental nutrition (depending on amount)	€ 46-117/day	
Antimicrobial therapy (depending on agents and amount)	€ 0.80-73.7/ day	
Prescription fee	€ 9.49	
Packed cells	€ 208.24	
Trombocytes	€ 502.46	
Fresh Frozen Plasma	€ 179.23	

* prices adjusted to 2011 level according to Dutch Consumer Price Index
‡ Standard cost prices include staff, consumables, overheads, diagnostic tests and pharmaceuticals
† Costs were only included for nosocomial RV patients when no excess days of hospitalization were incurred

Table S2. Age Distribution of RV patients with different levels of healthcare and fatal cases

		0-2mo	2-4mo	4-6mo	6-12mo	0-1 yrs	1-2yrs	2-3yr	3-4yr	4-5yr	1-4yrs	5-9yr	10-14yr	Source
RV incidence		2%	3%	4%	15%	24%	37%	10%	7%	2%	57%	13%	6%	Distributions for age groups from cohort study, subdistributions for children < 1 yr and 1-4yr taken from RoHo study
Hospitalizations														
Ineligible	CA	5%	5%	8%	28%		34%	9%	6%	2%		3%	0%	RoHo study
	Noso	11%	17%	11%	31%		15%	6%	4%	0%		2%	3%	
Eligible	CA	0%	9%	3%	21%		40%	13%	2%	4%		4%	2%	
	Noso	30%	15%	7%	25%		17%	0%	5%	0%		2%	0%	
Mortality														
Ineligible		14%	28%	0%	42%		14%	0%	0%	0%		0%	0%	Assumed equal to distribution among eligible
Eligible		14%	28%	0%	42%		14%	0%	0%	0%		0%	0%	RoHo study

CA: Community-acquired
Noso: Nosocomial

Table S3. Vaccine Efficacy estimates against mild, moderate and severe RV gastroenteritis

	Vaccine Efficacy#				**Method**	**Source**
	Mild (RV episode without medical care)	Moderate (GP visit)	Severe (Hospitalization)*	Nosocomial†		
RV1						
After first dose	Calculated	Calculated	89.8% (8.9-99.8)	Calculated	(Calculated from) Published data	46
First season (after second dose)	71.7% (50.4-83.9)	91.8% (84.0–96.3)	100% (81.8–100)		Efficacy for mild and moderate cases after first season calculated from efficacy ratios for mild, moderate, severe during first season	
Second season	50.5% (24.3-67.7)	76.2% (63.0–85.0)	92.2% (65.6–99.1)			
Third-Fifth season	Calculated				Efficacy during third to fifth season calculated as linear decline equal to reduction between first and second season	
RV5						
After first dose	Calculated	Calculated	88% (65–97)	Calculated	(Calculated from) Published data	91
					Efficacy after first dose and between first and second dose for mild and moderate cases calculated from efficacy ratios for mild, moderate, severe during first season	
After second dose			88% (69–96)			
First season (after third dose)	65.1% (54.1-73.5)	72.0% 63.2-78.9)	94.8% (89.4-97.8)		(Calculated from) Published data	47,48
Second season	49.8% (27.0-65.4)	58.5% (40.1-71.7)	90.8% (76.9-97.1)			
Third season	Calculated	Calculated	100.0% (27.9-100)		Efficacy during third season for mild and moderate cases calculated from efficacy ratios for mild, moderate, severe during second season	48
Fourth-Fifth season	Calculated				Efficacy during third to fifth season calculated as linear decline equal to reduction between first and second season	

Vaccine Efficacy was assumed equal between Eligible and Ineligible, data were modeled as Pert distribution
***** Efficacy against fatal RVGE was assumed equal to efficacy for severe disease
† Efficacy against nosocomial infection based on severity distribution as observed in RoHo study

Table S4. Characteristics of RV hospitalizations identified in the multi-centre observational study

	Community-acquired N=760 (81%)		**Nosocomial** N=176 (19%)		**Total** N=936	
Hospital						
A*	157	(21%)	103	(59%)	260	(28%)
B	157	(21%)	29	(16%)	186	(20%)
C	283	(37%)	35	(20%)	318	(34%)
D	163	(21%)	9	(5%)	172	(18%)
Year†						
2006	151	(20%)	24	(14%)	175	(19%)
2007	132	(17%)	31	(18%)	163	(17%)
2008	166	(22%)	28	(16%)	194	(21%)
2009	178	(23%)	56	(32%)	234	(25%)
2010	133	(18%)	37	(21%)	170	(18%)
Male	413	(54%)	93	(53%)	506	(54%)
Median Age (range)	13 mo	(3 days-18yrs)	6 mo	(4 days-11yrs)	12 mo	(0-18yrs)
Age < 15 weeks	65	(8%)	67	(38%)	132	(14%)
GA < 36 weeks	43	(6%)	43	(24%)	83	(9%)
Low Birth Weight (< 2500gr)	57	(8%)	47	(27%)	104	(11%)
Presence of CCC	105	(14%)	114	(65%)	219	(23%)
Congenital pathology	56	(8%)	60	(48%)	116	(15%)

***** Tertiary Care Hospital
† December 1st of the previous year until November 30st of the year stated
GA: Gestational Age

Table S5. Characteristics of nosocomial cases and controls

	Cases N=100		**Controls** N=196		**P-value**
Age (median, range)	5.8	(0-139)	5.9	(0-139)	0.78
Male (%)	54	(54%)	107	(55%)	0.92
GA < 36 (%)	20	(23%)	33	(24%)	0.63
LBW (%)	20	(20%)	34	(17%)	0.70
Presence of CCC (%)	89	(89%)	119	(61%)	<0.0001
Congenital pathology (%)	51	(51%)	61	(31%)	0.001
Healthy†	10	(10%)	69	(35%)	<0.0001
Admission during RVseason* (%)	63	(63%)	124	(63%)	0.96
Ward type					
Pediatric medicine and surgery (%)	60	(60%)	124	(63%)	0.19
Hematology/ Oncology (%)	17	(17%)	17	(9%)	
Neonatology (%)	18	(18%)	43	(22%)	
Pediatric ICU (%)	5	(5%)	12	(6%)	
Length of stay (median, range)	24.5	(1-272)	7.5	(4-495)	<0.001

***** January through April
† Gestational age ≥ 36 weeks, normal birth weight and no CCC.

Table S6. Costs per different health outcome for universal and targeted vaccination under base-case assumptions (RV1) using healthcare payer perspective

	Universal vaccination (95%CI)	Targeted vaccination (95%CI)
Costs (€)		
per case avoided	174 (127; 239)	21 (-10; 53)
per life year saved	96,600 (38,600; 241,200)	2400 (-300; 8400)
per fatal case	1,026,500(501,200; 1,957,100)	28,900 (-10,500; 91,100)
per QALY gained	60,200(31,100; 110,300)	2600 (-900;9200)

Table S7. Results of cost-effectiveness analysis for universal and targeted vaccination in different scenarios (average)

		Annual undiscounted Vaccination Costs (€ million)	Net Direct Healthcare Costs (€ million)	Net Societal Costs (€ million)	ICER, Healthcare perpective	ICER, Societal perspective
Universal Vaccination						
RV1	Basecase	15.2	5.5	2.7	60182	30335
	Undiscounted	15.2	7.1	3.4	42072	20670
	Discounted 5%	15.2	4.7	2.4	71390	36655
	Discounted 4/1.5%†	15.2	5.1	2.6	41742	21182
	Low vaccine price	12.8	3.6	0.9	39613	9803
	High vaccine price	17.7	7.4	4.6	80470	50657
	Herd immunity	15.2	4.8	1.6	46819	15550
	Best case	12.8	2.9	-0.4	21309	-2251
	Worst case	17.4	7.4	4.7	82899	53304
	Free market Price	25.0	13.0	10.3	141445	111686
RV5	Basecase	16.7	6.8	4.2	77385	47458
	Undiscounted	16.7	8.8	5.3	53820	32515
	Discounted 5%	16.7	5.2	2.5	71341	35077
	Discounted 4/1.5%†	16.7	5.6	2.7	42628	20766
	Low vaccine price	14.2	4.9	2.3	56036	26187
	High vaccine price	19.1	8.7	6.0	98456	68595
	Herd immunity	16.7	6.1	2.9	60430	29120
	Best case	14.3	4.2	1.0	31447	7641
	Worst case	18.8	8.7	6.1	102084	72198
	Free market Price	26.5	14.3	11.7	162563	132631

Table S7. Continued

		Annual undiscounted Vaccination Costs (€ million)	Net Direct Healthcare Costs (€ million)	Net Societal Costs (€ million)	ICER, Healthcare perpective	ICER, Societal perspective
Targeted Vaccination						
RV1	Basecase	1.5	0.1	-0.2	2633	-3399
	Undiscounted	1.5	0.2	-0.3	1623	-2445
	Discounted 5%	1.5	0.1	-0.2	3510	-4012
	Discounted 4/1.5%†	1.5	0.1	-0.2	1839	-2204
	Low vaccine price	1.2	-0.1	-0.4	-811	-6857
	High vaccine price	1.7	0.3	0.0	6116	76
	Herd immunity	NA	NA	NA	NA	NA
	Best case	1.3	-0.1	-0.5	-1083	-7308
	Worst case	1.3	0.3	0.0	5437	724
	Free market Price	1.9	0.5	0.1	8728	2677
RV5	Basecase	1.6	0.3	0.0	3723	-276
	Undiscounted	1.6	0.4	-0.1	2349	-303
	Discounted 5%	1.6	0.2	-0.1	5812	-1604
	Discounted 4/1.5%†	1.6	0.2	-0.1	3058	-905
	Low vaccine price	1.3	0.1	-0.3	1458	-4472
	High vaccine price	1.8	0.4	0.1	8082	2083
	Herd immunity	NA	NA	NA	NA	NA
	Best case	1.6	0.2	-0.1	5812	-1604
	Worst case	2.0	0.5	0.1	8292	1846
	Free market Price	2.0	0.6	0.3	10915	4929

† According to Dutch guidelines for health economic evaluations: 4% discount rate for costs and 1.5% for benefits.

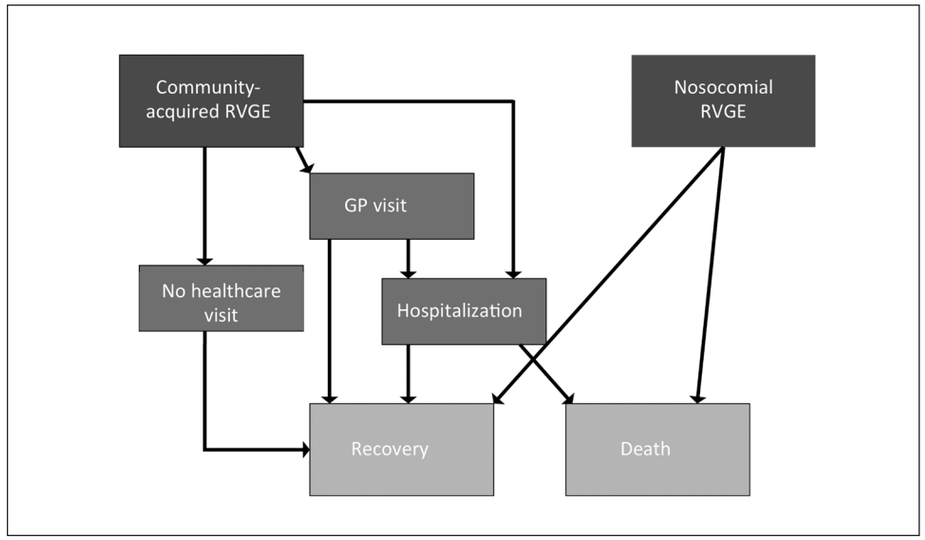

Figure S1: Outcome tree and different healthcare paths considered in cohort simulation.

Chapter 7

Rotavirus among immunocompromised patients; significant and underestimated disease burden among children and adults in a tertiary care medical centre

P Bruijning-Verhagen, H de Graaf, MJM Bonten

Submitted

Abstract

Background: Rotavirus (RV) is highly endemic inside and outside hospital settings and an important potential pathogen among immunocompromised patients. Severe RV gastroenteritis (GE) has been described in these patients, but little is known on general RV disease severity and manifestations among immunocompromised patients and relative importance of RV as gastrointestinal pathogen prior to RV vaccination.
Methods: We used 5-year laboratory records from a Dutch tertiary care hospital to identify adult and pediatric RV infections. Medical records were reviewed for immunocompromising conditions and, when present, RV disease manifestations and interventions were evaluated. In addition, 3-year hospital viral and bacterial stool-testing records were used as surrogate for GE episodes to determine rates of RV testing, prevalence and underreporting among adult and pediatric GE.
Results: Among 35 and 259 confirmed RV infections in hospitalized adults and children, respectively, 20 (57%) and 35 (12%) patients were immunocompromised. Apart from GE, complicating disease manifestations among immunocompromised patients included high transaminases (46%), hypokalemia (41%), feeding intolerance (31%) and, among children, prolonged illness (> 14 days, 28%).
Common interventions apart from rehydration (77%) included antibiotic treatment (24%), adjusting medication including chemotherapy (31%) and parental nutrition (18%).
Of 3653 and 2215 adult and pediatric GE episodes, 433 (12%) and 1493 (67%) were tested for RV, with RV confirmed in 27 (6%) and 182 (12%), respectively. We estimated that 87% and 30% of RV infections in adult and pediatric GE remain unreported.
Interpretation: RVGE has significant impact on immunocompromised patients and interferes with underlying disease management. RV contribution to GE among hospitalized adults seems significantly underestimated and affects mainly immunocompromised patients. Anticipating sustained herd-immunity of infant RV vaccination, indirect benefits could be substantial among these patients.

Introduction

Rotavirus (RV) causes symptoms of acute diarrhea, vomiting and fever in young children. Among adults and older children RV disease is usually the result of reinfection rather than primary infection and generally produces only mild diarrhea or asymptomatic infection because of pre-existing immunity.[1-4] RV is highly endemic inside and outside the hospital-setting, easily transmitted and resistant to many aseptic solutions.[5-8] Therefore, RV is a potentially important pathogen among patients with compromised immunity, such as those receiving anti-cancer treatment, transplant recipients and those with congenital immunodeficiency syndromes. Prolonged diarrhea and extra-intestinal manifestations have been described among immunocompromised patients and associations with other gastrointestinal pathology such as Graft versus Host Disease (GvHD), mucositis and colitis has been suggested.[9-14] These manifestations however have been described in case reports or small case-series and little is known on general RV disease severity and frequency of complications among immunocompromised patients. Furthermore, RV contribution relative to other causes of acute gastrointestinal symptoms among both pediatric and adult immunocompromised patients has not been well described, due to lack of routine diagnostic testing for RV, especially among adults.
From 2006 onwards, infant RV vaccination programs have been implemented in several countries. Recently indirect effects of infant RV vaccination programs reducing RV infections among unvaccinated children and adults have been suggested by observational and mathematical modeling studies.[15-18] Quantifying RV disease burden among immunocompromised patients may allow more accurate quantification of vaccination benefits due to indirect protection, i.e. herd-immunity.
The objective of the present study is to determine RV disease severity and frequency of complications among both adult and pediatric immunocompromised patients and to estimate RV underreporting among this patient group relative to other common gastrointestinal pathogens.

Methods

The University Medical Centre Utrecht (UMCU) is a 1042-bed tertiary healthcare centre in the Netherlands. The hospital hosts pediatric and adult hematology/oncology units covering different cancer diagnoses and treatment modalities and pediatric and adult stem cell transplantation units. In addition, the hospital offers different solid organ transplant programs such as renal, heart and lung transplantation.
RV stool testing by commercially available enzyme-immuno assay is performed on request by physicians in charge of patients with acute gastroenteritis (GE). Laboratory reports for the years 2006 to 2010 were used to identify all RV stool tests performed, the number of RV positive specimens and basic patient demographics. Subsequently, medical records of RV positive patients were screened for presence of immunocompromising conditions and other underlying pathology at the time of RV infection after the Institutional Review Board of the UMCU approved the study. Patients were classified as immunocompromised if they were on active anti-cancer treatment, had received stem-cell transplantation within the past year or a solid organ transplant, or suffered from immunodeficiency syndromes with hypogammaglobulinaemia. This classification distinguishes a group of immunocompromised, clinically vulnerable patients with frequent healthcare encounters including hospitalization which are known risk factors for RV disease.[19-21] RV disease course was evaluated for all immunocompromised patients by detailed review of medical records performed by two trained pediatricians (PBV and HdG) independently. Presenting symptoms had to include either acute onset of diarrhea (≥ 3 liquid stools per day) or vomiting or both to qualify as RVGE. RV disease symptoms and signs, treatment interventions and complications either directly or indirectly (i.e. secondary to fluid losses) related to RV infection were assessed. The reviewers then discussed and compared their findings for each case. When present, discrepancies were discussed between the two reviewers and solved.

RV testing is commonly performed for pediatric patients presenting with symptoms of acute GE,[22] but is probably infrequent among adult patients. To quantify RV underreporting, we used laboratory records to compare the number of RV tests among adults to those for Norovirus (NV), Campylobacter and *C. Difficile* toxin, the most common pathogens identified among adult GE hospitalizations and nosocomial infections.[23] Diagnostic testing of patient stool specimens for one or several of these pathogens is ordered on clinical grounds for suspected infectious diarrhea. As such, we used the number of microbiological tests for NV, RV, *C. Difficile* toxin assay and bacterial stool cultures for Campylobacter as a proxy for the number of acute GE episodes. To account for multiple testing during an episode of GE, several microbiological tests performed less than 3 weeks apart in the same patient were counted as one episode. At the UMCU, PCR-based NV testing has been routinely available for patient care since 2008, therefore comparisons were made for data from 2008 onwards.

Statistical analysis

Summary statistics were used to describe frequency and duration of symptoms and signs, treatment interventions and complications among immunocompromised patients with RVGE. We compared disease characteristics between those with RV as the exclusive identified cause of gastrointestinal symptoms and those with other concomitant causes and between adult and pediatric patients. We used Mann-Whitney U-test for continuous outcomes and Chi-square or Fisher's exact test for categorical variables, where appropriate. We assessed the total number and seasonal distribution of GE episodes, the number of tests for each of the four pathogens and number positive for both adult and pediatric patients. Seasonality of GE episodes, proportions tested for RV and RV positive episodes

was assessed using linear regression with an indicator variable for month of the year. To identify any differences in microbiological testing practices among immunocompromised compared to non-immunocompromised GE patients, a subgroup analysis was performed for GE episodes occurring on oncology and hematology/immunology (H/I) wards which predominantly admit immunocompromised patients.
Analyses were performed using R statistical software version 2.14.2

Results

Between 2006 and 2010, 4584 RV stool tests were performed of which 845 among adult patients and 3739 in children (Figure 1). RV was identified in 40 and 395 stool specimens from adult and pediatric patients, respectively, of which 35 (88%) and 259 were in-hospital patients. Nosocomial infections represented 23% (N=8) and 40% (N=103) of RV patients among adults and children, respectively.

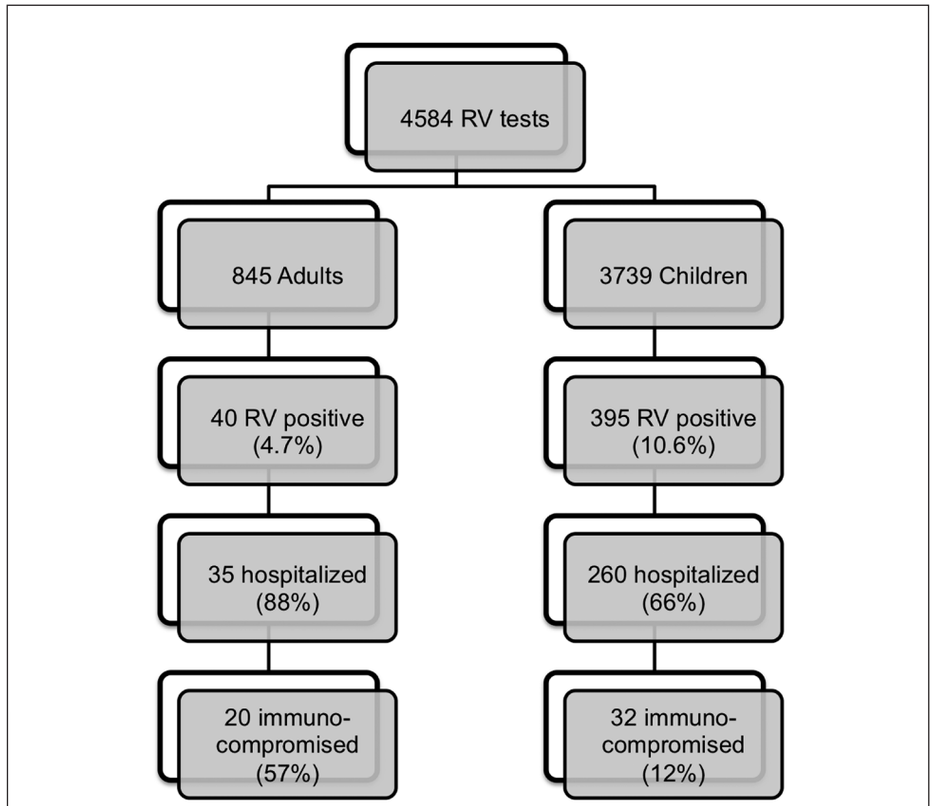

Figure 1.
Flow-chart of RV tests performed, number positive, number hospitalized and number of immunocompromised patients among adults and children during 2006-2010 at the UMC Utrecht.

Patient characteristics RV hospitalizations

Comorbidities were present in all but 3 adult RV patients (92%). Malignancies (N=17, 49%), cardiovascular or renal disease (N=9, 26%) and pulmonary or gastrointestinal disease (N=8, 23%) were most common. Among pediatric patients, underlying chronic diseases were present in 155 (60%) children, including gastrointestinal (N=34, 13%), neurodevelopmental (N=27, 10%) and cardiovascular (N=21, 8%) disease most frequently. Twenty adult (57%) and 32 pediatric patients (12%) were severely immunocompromised (Table 1). No significant differences were observed in patient demographics of immunocompromised versus non-immunocompromised adults, whereas among children those with immunocompromising conditions were significantly older (median age 2.6 years vs. 11 months, p>0.001), and had longer hospital-stays (median 7 vs. 4 days, p=0.007). The majority of immunocompromised patients were admitted to oncology or hematology/immunology wards, where they represented 70% of all RV positive patients. Recent stem cell transplantation (N=20, 38%) and intense anti-cancer treatment (N=20, 38%) were the most frequent immunocompromising conditions present. Eight patients (15%) had received a solid organ transplant and 6 patients (12%) suffered from a common variable immunodeficiency (CVID) with hypogammaglobulinaemia. Two patients with CVID and one renal transplant recipient also received anti-cancer treatment.

Table 1. Patient characteristics of immunocompromised and non-immunocompromised RV patients

	Adult			**Pediatric**		
	Imm.compromised	Non- imm. compromised	P-value	Imm.compromised	Non-imm. compromised	P-value
N	20 (57%)	15 (43%)		32 (12%)	227 (88%)	
Patient Demographics						
Male	8 (40%)	9 (60%)	0.407	23 (72%)	128 (56%)	0.141
Median Age (range)	58 yrs (23-83)	67 yrs (25-86)	0.160	2.6 yrs (2 mo- 17 yrs)	11 mo (1 mo-18yrs)	<0.0001
Length of hospital stay (for community-acquired RV)	7 days (4-30)	8 days (4-23)	0.322	7 days (4-23)	4 days (2-42)	0.007
Hospital Ward			0.153			<0.0001
Oncology or H/I	14 (70%)	6 (40%)		25 (78%)	11 (4%)	
Other	6 (30%)	9 (60%)		7 (22%)	216 (96%)	
Medical History						
Underlying chronic illness	20 (100%)	12 (80%)	0.070	32 (100%)	123 (54%)	<0.0001
Stoma present	5 (25%)	4 (27%)	>0.99	2 (6%)	6 (3%)	0.2583
HSCT	6 (%)	0		14	0	
Post-HSCT < 30 days	3			4		
Post HSCT 31-100 days	1			5		
Post HSCT 100-365 days	2			5		
Solid organ transplant	6 (%)	0		2	0	
Kidney	4			2		
Heart	1			0		
Lung and Heart	1			0		
Anti-cancer treatment	8 (%)	0		12	0	
Common variable immunodeficiency	3 (%)	0		3	0	

H/I: Haematology/Immunology
HSCT: Human stem cell transplantation performed < 1 year prior to RV infection

RV disease course

In 13 immunocompromised patients (25%), RV infections occurred together with infections caused by NV (N=7) and *C. Difficile* (N=1), reactivations of latent adenovirus (N=1) and CMV infection (N=1) or acute intestinal GvHD (N=3). In these patients the relative contribution of RV to symptoms of acute gastroenteritis could not be determined and these GE episodes were analyzed separately (Table 2).

RV was considered the exclusive cause of acute gastrointestinal symptoms in 39 patients (75%). Diarrhea was present in all patients, 22 patients (56%) vomited and 16 (41%) had fever. In two patients, RV was associated with and exacerbation of preexisting chronic diarrhea due to auto-immune enteritis and unexplained malabsorbtion, respectively. Dehydration was present in 18 patients (46%). A temporary rise in serum aminotranferases was observed in 13 of 28 patients tested (46%).

Hypokalemia was the most frequent complication (N=16, 41%), followed by feeding intolerance (N=12, 31%), acute kidney injury (N=7, 18%), acidosis (N=5, 13%) and hypotension (N=4, 10%). Four young children suffered from severe dermatitis of the buttocks requiring opioid-treatment. Two patients developed paralytic ileus. Furthermore, acute bleeding of pre-existing stomal varices and ulcer bleeding were observed in two patients occurring simultaneously with severe RV diarrhea. One adult patient developed neutropenic enterocolitis with pneumatosis, three patients (two adults, one child) developed intestinal mucositis following RV infection. In only 8 (21%) of 39 immunocompromised patients RV disease course was uneventful.

Most patients required intravenous rehydration (N=27, 69%). Other frequent interventions were adjustments in maintenance medication or chemotherapy schedules (N=12, 31%), antibiotic treatment despite absence of confirmed bacterial infection (N=9, 24%), parental nutrition (N=7, 18%) and feeding by nasogastric tube (N=4, 10%). One patient required ICU admission. In five patients (13%) no treatment was required.

Frequency and duration of different symptoms and treatment interventions did not significantly differ between patients with RV as exclusive and those with concomitant causes of acute gastroenteritis symptoms. Comparing adults and children (Table S1) we observed increased duration of diarrhea among immunocompromised children (range: 3-34, median: 9 days) compared to adults (range: 2-13, median 6 days, p=0.045). Prolonged RV illness lasting more than 14 days occurred exclusively among children (p=0.019). Acute kidney injury was more common among adult patients (p=0.032).

Table 2. RV disease course among immunocompromised patients

	acute GI symptoms		P-value
	RV exclusive	Other concomitant causes	
N	39 (75%)	13 (25%)	
Symptoms and signs			
Diarrhea	39 (100%)	13 (100%)	>0.99
Duration in days (median)	3-34 (9)	2-18 (9)	0.9545
Vomiting	22 (56%)	8 (62%)	0.74
Duration in days (median)	1-11 (3)	1-12 (3)	0.6491
Fever†	16 (41%)	4 (31%)	0.7432
Illness duration (median)	3-34 (9)	2-18 (9)	0.855
Illness duration >14 days	6 (15%)	3 (23%)	0.3767
Dehydration	18 (46%)	5 (38%)	0.8173
AST/ALT rise‡	13/28 (46%)	5/8 (63%)	0.858
Complications			
Feeding intolerance	12 (31%)	4 (31%)	0.7286
Hypokalemia	16 (41%)	2 (15%)	0.1765
Hypotension	4 (10%)	3 (23%)	0.3473
Acidosis	5 (13%)	2 (15%)	0.986
Acute kidney injury*	7 (18%)	3 (23%)	0.6967
Severe dermatitis	4 (10%)	1 (8%)	>0.99
Ileus	2 (5%)	0	>0.99
GI bleeding	2	1	>0.99
Neutropenic enterocolitis	1	0	>0.99
Mucositis	2	1	>0.99
Uneventful disease course	8 (21%)	2(15%)	>0.99
Treatment			
Fluid therapy			0.3813
Iv	27 (69%)	8 (62%)	
Oral	3 (8%)	3 (23%)	
None	9 (23%)	2 (15%)	
Antibiotics	9 (24%)	2 (15%)	0.7087
Adjustments in maintenance medication or chemotherapy	12 (31%)	5 (38%)	0.8645
Parental nutrition	7 (18%)	2 (15%)	0.8324
Feeding by nasogastric tube	4 (10%)	0	0.5612
Opioids	4 (10%)	1 (8%)	>0.99
ICU admission	1	1	0.9127
No treatment	5 (13%)	2 (15%)	>0.99

† ≥38.5 degrees Celsius
‡ ≥20% increase from baseline
* ≥0.3-mg/dl increase in serum creatinine

GE episodes and RV underreporting

Based on number of stool specimens tested for RV, NV, campylobacter and *C. Difficile* combined, we estimated that 3653 GE episodes occurred among adult patients and 2215 among children at the UMCU between 2008 and 2010 (Table 3). A RV stool test was requested for 433 adult GE episodes (11.8%) and positive in 27 (6.2% of tested patients). Campylobacter stool culture (2516 GE episodes, 68.9%) and *C. Difficile* toxin assay (2530 GE episodes, 69.3%) were most frequently performed among adults and were positive in 0.9% and 5.8%, respectively. NV PCR was performed in 372 GE episodes (10.2%) and positive in 12.9%.

Among pediatric patients, RV stool testing occurred in 1493 GE episodes (67.4%) and was positive in 182 (12.2%). Campylobacter stool culture was second in frequency after RV testing (1037 GE episodes, 46.8%), but was rarely positive (0.7%).

Table 3. Number of stool tests performed and number positive for each of the four pathogens included among adult and pediatric GE episodes

	Adult		Pediatric	
	No. stool tests performed (%)	No. positive % of tested)	No. stool tests performed (%)	No. positive (% of tested)
All GE episodes				
Total	3653	237 (6.5%)	2215	324 (14.6%)
Rotavirus	433 (11.8%)	27 (6.2%)	1493 (67.4%)	182 (12.2%)
Norovirus	372 (10.2%)	48 (12.9%)	850 (38.4%)	148 (17.4%)
Campylobacter	2516 (68.9%)	22 (0.9%)	1037 (46.8%)	7 (0/7%)
C. difficile toxin	2530 (69.3%)	147 (5.8%)	268 (12.1%)	13 (4.9%)
Oncology and H/I wards				
Total	968	60 (6.2%)	341	56 (16.4%)
Rotavirus	146 (15.1%)	14 (9.6%)	205 (60.1%)	30 (14.6%)
Norovirus	126 (13.0%)	10 (7.9%)	104 (41.1%)	29 (20.7%)
Campylobacter	794 (82.0%)	6 (0.8%)	250 (73.3%)	0 (0%)
C. difficile toxin	577 (59.6%)	32 (5.5%)	88 (25.8%)	6 (6.8%)

Testing for NV occurred in 850 GE episodes (38.4%) and had the highest positive rate (17.4%). *C. Difficile* toxin assay was performed in 268 GE episodes (12.1%) and was positive in 4.9%.
The seasonal distribution, the number tested for RV and RV prevalence among those tested is illustrated in Figure 2A and B for adult and pediatric GE episodes. Among children, the number of GE episodes was increased by 18% during winter (December-April) compared to the remaining months of the year (p=0.003). Seasonality was less pronounced among adult patients (6% increase in GE episodes during winter months, p=0.09). RV prevalence among those tested was highest in March (7.8% among adults and 28% among children). Overall, 89% of confirmed RV infections in adults and 77% in children occurred during winter months. RV testing was most common for GE episodes occurring in February or March (for adults: 17% vs. 10%. p=0.023; for children: 74% vs. 66%, p=0.010).
Assuming similar RV prevalence and seasonality among patients not tested for RV, it was estimated that an additional 169 RV episodes among adults and 79 among children occurred but remained unconfirmed. This suggests that confirmed RV infections represent only 13% of RV episodes occurring among adults and 70% among children. RV would represent 5.3% of adult and 11.8% of pediatric GE episodes.
In subgroup analysis we analyzed the GE episodes occurring on adult and pediatric oncology and H/I wards. A total of 968 (26%) and 341 (15%) GE occurred on these wards. RV detection rates were slightly higher compared to the overall averages (9.6% vs. 6.2% for adults, p=0.05; 14.6% vs. 12.2% for children, p=0.25). For both adults and children similar patterns were observed in seasonality of RV testing and RV prevalence (Figure S1). Assuming similar RV prevalence and seasonality among patients not tested for RV, an additional 57 unconfirmed RV episodes among adults and 17 among children occurred on oncology and H/I wards suggesting confirmed RV infections represent 20% and 64%, respectively of all RV episodes. RV would represent 7.3% of adult and 13.7% of pediatric GE episodes.

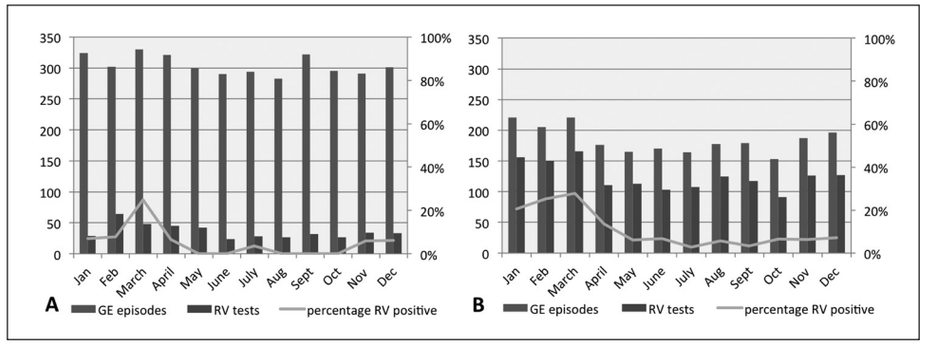

Figure2.
Seasonal distribution of all GE episodes, those tested for RV and RV prevalence among those tested for adult (A) and pediatric (B) patients for the years 2008-2010.

Discussion

Our observations demonstrated that RV causes significant disease burden among both immunocompromised adults and children. Eighty percent of RVGE episodes have complications requiring intense monitoring and additional medical interventions apart from rehydration. Typical manifestations besides diarrhea, vomiting and fever included high serum transaminases (46%) and hypokalemia (41%). High transaminases as a manifestation of RVGE have been observed in both immunocompromised and non-immunocompromised children with proportions varying between 20 and 72%,[24-27] but has not been previously described in adults. The frequent occurrence of RV associated elevations in transaminases and hypokalemia warrant close biochemical monitoring of immunocompromised RV patients prone to medication induced hepatotoxicity or electrolyte disturbances.

Prolonged diarrhea and illness duration, which is typically described among immunocompromised patients, was observed in 28% of immunocompromised children, but in none of the adult RV patients, suggesting it may be less frequent than previously estimated. [11;13] Other intestinal complications such as paralytic ileus, GI bleeding and mucositis have been previously described among immunocompromised RV patients.[12;27] Enterocolitis associated with RVGE has been observed among immunocompromised infants, but not in adults as identified in our study.[11;28;29] The causality of RV in the development of these GI complications remains, however, uncertain.

Frequent medical interventions among immunocompromised RV patients apart from rehydration included antibiotic treatment, adjusted medication schedules and dosage, parental nutrition, tube feeding and opioids which further underscore the high impact of RVGE on these patients.

The role of RV in GE symptoms among immunocompromised adults seems underestimated; only 12% of adult GE episodes and 15% of GE episodes occurring in oncology or H/I wards were tested for RV. Detection rates for RV (9.6%) on oncology or H/I wards were higher than those for NV, *C. Difficile* and Campylobacter, which suggests that RV is one of the most common GI pathogens in immunocompromised adults, especially during February and March when detection rates increased to 30%. We estimated that RV infections among

immunocompromised adults are underreported by 80%. Prospective studies on GE etiology among immunocompromised adult patients have identified RV infections in 0-12% of GE episodes.[10;30-34] Infectious and non-infectious causes often co-exist with RV presence, which was also observed in our study.[10;12;35] The exact etiologic role of RV in these patients could not be determined, but others have confirmed an additive effect of RV by matched-pairs analysis.[12]

The relative contribution of RV to GE episodes among hospitalized adults was estimated at 5.3% in our study. Previously Anderson et al. studied RV contribution to adult GE hospitalizations by using stool specimens sent for bacterial culture within 72hrs of admission as a surrogate for clinically significant diarrhea. Sixty percent of these samples were subsequently tested for RV and the virus was identified in 2.9%.[36] In our study, the additional inclusion of stool specimens sent for viral and *C. Difficile* toxin testing as well as the inclusion of nosocomial infections provides a more comprehensive estimate of GE episodes, which may explain the higher RV prevalence observed. Almost a quarter of observed RV infections in adults were acquired in hospital suggesting that nosocomial RV infections contribute substantially to overall RV disease burden in adults, similar to the situation in children.[37]

Our study further demonstrated that adult RVGE is predominantly a disease of immunocompromised patients, who represented > 50% of RV cases, which confirms the findings from Anderson et al. who reported that 41% of adult patients with RV were immunocompromised. If herd-immunity effects from infant RV vaccination programs appear to reduce RV disease among these high-risk groups, substantial additional vaccination benefits can be expected. However, at this point it is still uncertain if observed herd-immunity among unvaccinated individuals is a persistent phenomen of infant RV vaccination programs or a temporary post-implementation effect.[15-18]

Our study has several limitations. We cannot determine if our findings of RV disease burden among immunocompromised patients with confirmed infection are similar for those cases that remain undetected. The estimated contribution of RV to overall GE episodes is based on a limited number of RV stool tests and confirmed infections especially among adults and could be subject to random error. The total number of GE episodes could be underestimated because our method did not account for GE patients without any viral or bacterial microbiological investigations performed. Therefore, some uncertainty about the overall RV disease burden and in particular among immunocompromised patients remains. Furthermore, our analysis includes data from a single centre providing specialty care for oncology and transplant patients. The proportion of immunocompromised patients in this setting is high and our results may therefore not necessarily apply to hospitals without these specialty programs. In addition, local RV epidemiology may differ to some extent which could limit the generalizability of our results.
Despite these limitations, our study demonstrated RV infections have a significant impact on severely immunocompromised patients, generate additional medical interventions and interfere with management of the underlying disease. RV as a cause of GE episodes may be significantly underestimated among adults and seem to affect immunocompromised patients in a disproportionally high percentage. Since many episodes appear to be hospital-acquired we recommend to include RV testing in patients from these risk groups with GE symptoms.
Furthermore, the data from this study could be used to better quantify the magnitude of potential herd-immunity benefits from RV vaccination among immunocompromised patients.

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Supplementary material

Table S1. RV disease course among adult and pediatric immunocompromised patients

	Adult		Pediatric		P-value
N	20		32		
Symptoms and signs					
Diarrhea					
Duration in days (median)	2-13(6)		3-34 (9)		0.04527
Vomiting	10	(50%)	20	(63%)	0.5925
Duration in days (median)					
Fever†	5	(25%)	15	(47%)	0.199
Illness duration (median)	3-13 (7.5)		3-34 (9)		0.04482
Illness duration >14 days	0	(0%)	9	(28%)	0.019
Dehydration	10	(50%)	13	(41%)	0.5326
AST/ALT rise‡	3	(15%)	15	(47%)	0.2642
Complications					
Feeding intolerance	4	(20%)	12	(38%)	0.228
Hypokalaemia	8	(40%)	10	(31%)	0.5605
Hypotension	3	(15%)	4	(13%)	0.8724
Acidosis	1	(5%)	6	(19%)	0.228
Acute kidney injury*	7	(35%)	3	(9%)	0.03268
Severe dermatitis	0	(0%)	5	(16%)	0.1431
Ileus	0	(0%)	2	(6%)	
GI bleeding	2	(10%)	1	(3%)	
Neutropenic enterocolitis	1	(5%)	0	(0%)	
Mucositis	2	(10%)	1	(3%)	
Uneventful disease course	1	(5%)	9	(28%)	0.06814
Treatment					
Fluid therapy					0.08851
Iv	16	(80%)	19	(59%)	
Oral	0	(0%)	6	(19%)	
None	3	(15%)	7	(22%)	
Antibiotics	2	(10%)	9	(28%)	0.1697
Adjustments in maintenance medication	8	(40%)	9	(28%)	0.559
Parental nutrition	1	(5%)	8	(25%)	0.1287
Feeding by nasogastric tube	0		4	(13%)	0.1507
Opioids	0		5	(16%)	0.1431
ICU admission	0		2	(6%)	
No treatment	3	(15%)	4	(13%)	0.8724

† ≥38.5 degrees Celsius
‡ ≥20% increase from baseline
* ≥0.3-mg/dl increase in serum creatinine

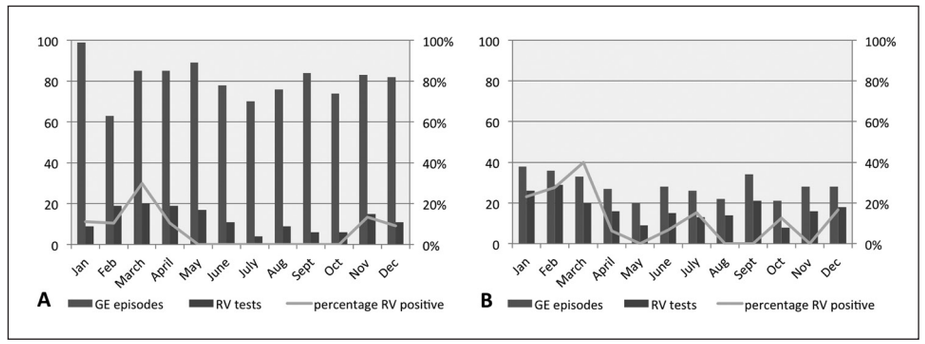

Figure S1.
Seasonal distribution of all GE episodes, those tested for RV and RV prevalence among those tested for adult (A) and pediatric (B) patients on oncology or Haematology/Immunology wards for the years 2008-2010.

Chapter 8

General Discussion

P Bruijning-Verhagen, MJM Bonten

Who should get vaccinated against rotavirus?

This thesis has described various aspects of rotavirus (RV) epidemiology and economics which are critical in the policy decision making on RV vaccination. After summarizing the main findings of this thesis we try to set out further considerations and future research priorities regarding RV vaccination programs.

Hospitalizations for community-acquired RVGE

Hospitalization of a previously healthy child because of failing oral rehydration in the home-setting is one of the most severe health events caused by RVGE in developed countries and has a significant impact on both the child and the parents. [1-3] Furthermore, hospitalizations are responsible for the bulk of RV related healthcare costs.[4-6] In a multi-centre observational study described in Chapter 5 and 6 we assessed the number of community-acquired RV hospitalizations among children in the Netherlands, associated healthcare utilization and costs. We found that approximately 4400 pediatric hospitalizations due to community-acquired RV infections occur annually at an average cost per episode between €2200 and €2600. Almost 90% of these hospitalizations occur between January and May posing a substantial seasonal pressure on pediatric hospital beds. This occurs predominantly in general hospitals where RV patients are typically admitted. It was demonstrated that RV accounts for 2/3 of seasonal increases in all-cause pediatric hospitalizations between January and May.

Although a similar study was not performed in Canada, the typical seasonal effects of RV on all-cause hospitalizations are inherent to the seasonal patterns of RV epidemics in regions with temperate climates, including North-America.[7] It will be interesting to see in coming years to what extent universal RV vaccination has reduced all-cause pediatric hospitalizations, especially during the winter months, in regions of Canada and whether this is accompanied by reductions in staffing and bed-capacity.

Among adults, RV disease is generally considered mild. However, our analysis of laboratory reports for common gastrointestinal pathogens in a Dutch tertiary care hospital described in Chapter 7, demonstrated that RVGE is estimated to cause almost 6% of GE episodes among adults hospitalized at this centre and that RV infections among adults and children share a similar seasonal distribution.

Nosocomial RVGE

Rotavirus is the most common nosocomial gastrointestinal infection occurring among hospitalized children.[8-10] This thesis aimed to further quantify nRV disease burden in several ways. The risk of acquiring symptomatic RV infection for a child hospitalized in one of the developed countries of North-America and Europe was assessed in a meta-analysis described in Chapter 3. We estimated an overall risk of 0.7 (95%CI: 0.0-1.8) per 100 hospitalizations for children under five but variability in nosocomial RV risk was observed for different age groups, seasons and locations. The summary estimate is a useful tool to determine the number of nosocomial RV infections by country or province from hospital administrative databases prior to RV vaccination. For more detailed analysis of nosocomial RV disease burden at the hospital and regional level, two observational studies were described in Chapter 4 and Chapters 5 and 6 measuring incidence, medical interventions, costs and the contribution of nosocomial infections to overall RV hospitalizations. In Chapter 4 an analysis of 10-years active surveillance data on nRV infections in a tertiary care hospital in Montreal, Canada demonstrated a nRV incidence of 0.30 per 100 hospitalizations (95%CI: 0.26, 0.35) for children of all ages, almost similar to the summary risk estimate determined by meta-analysis (incidence: 0.4, 95%CI: 0.2–0.9). In the Canadian and the multi-centre Dutch

study nRV infections lead to similar medical interventions such as rehydration in 62% and 63% of episodes and readmissions in 12% and 11% of episodes, respectively. Furthermore, nosocomial RV infections were associated with increased length of stay by 3 days on average in Dutch hospitals (95%CI: 2.4; 3.6). Among adults and children hospitalized at the Dutch tertiary care centre, nosocomial infections represented 23% and 39% of all RV episodes, suggesting high intra-hospital transmission in a very susceptible population.

These observations re-emphasize that nosocomial RV infections contribute substantially to overall RV disease burden and are an important problem from the hospital infection control perspective.[11-16] RV vaccination can significantly reduce the repeated introduction of RV from the community in the hospital.[17] This could have additional impact on nRV infections even among unvaccinated children by reducing in-hospital circulation of the virus.[18]

Risk factors for RV hospitalization

Although careful review of the literature demonstrates that for many years certain patient-groups have been recognized at increased risk for RV hospitalization and mortality,[19-29] this has never been addressed in detail or linked to targeted prevention strategies.

Both the Canadian and Dutch observational studies described in Chapter 4 to 7 demonstrated that children with underlying medical conditions are substantially overrepresented among RV hospitalizations, which was most pronounced among nosocomial infections (59% in the Canadian study, 64% in the Dutch study). Furthermore, prematurity or LBW was observed in 28% in de Canadian study and represented 24% and 28% of nosocomial RV patients, respectively in de Dutch study. In a nested case-control study described in Chapter 6 it was confirmed that the high prevalence of congenital pathology, prematurity and LBW among nosocomial RV patients is not simply a reflection of hospital population characteristics but indicates an increased risk of acquisition among these children (adjusted ORs: 3·6, 95%CI: 1·8–7·0; 3·3, 95%CI: 1·5 – 7·3; 3·2, 95%CI: 1·5 – 7·1, respectively). A comparison of observations from the Dutch study to national prevalence rates of prematurity, LBW and congenital pathology further revealed increased risks of RV hospitalization for all three patient groups (RR: 1.7 , 95%CI:1.2-2.8; 1.6, 95%CI: 1.1-2.3; 4.4, 95%CI: 3.4-5.4, respectively). In addition, healthcare utilization was increased among high-risk patients compared to otherwise healthy children in both the Canadian and Dutch study and, more importantly, we found RV mortality (7 cases) exclusively among children with congenital pathology.

Immunocompromised patients, both among adults and children, form a separate patient-group highly vulnerable to RV disease. Eighty percent of immunocompromised RV patients in a Dutch tertiary care hospital experienced complications requiring intense monitoring and additional medical interventions apart from rehydration, as described in Chapter 7. Due to the increasing use of immunosuppressive therapy, morbidity due to RVGE among immunocompromised patients will likely expand in coming years, unless these patients benefit from herd-immunity effects generated by universal infant vaccination programs.

Cost-effectiveness of RV vaccination programs

With ever increasing expenditures and limitations of the healthcare budget, identifying the optimal allocation of available resources to maximize health will be the key challenge to stakeholders over the next decades. Economic evaluations of health intervention programs are increasingly being used to guide these decision making processes.[30] Cost-effectiveness has become a key component in the evaluation of vaccination strategies and is considered a prerequisite for implementation of new vaccine programs.[31;32]

Despite the disappointing results of many cost-effectiveness analyses of RV vaccination programs in developed countries,[5;33-36] the concept of vaccinating only the most vulnerable infants against RV (targeted vaccination) as opposed to all infants or no vaccination was

never considered. Chapter 6 describes a cost-effectiveness analysis of universal vaccination, targeted vaccination and no vaccination for the Dutch infant population and demonstrated high cost-effectiveness of targeted RV vaccination under all scenarios tested (mean cost per QALY varying between -€1083 and €8728) with minimal or no net costs for the Dutch healthcare system (varying between mean net savings of €0.1 to €0.5 million in costs). The significant health gains that could be realized by targeted RV vaccination at low costs should motivate health policy makers in European countries to implement this intervention even if they don't consider RV vaccination for the general infant population at this point.
Even greater health benefits could be realized when universal RV vaccination is implemented, although it is unlikely that this intervention will be cost-effective in the Netherlands from the healthcare perspective (mean cost per QALY varying between €21,309 and €141,445) unless vaccine prices drop substantially. From the societal perspective, universal vaccination is likely to be cost-effective at vaccine prices less than €75 per child when applying the recommended Dutch discount rates for cost and effects and the €20,000 threshold for preventive health measures.[37]
It is difficult, if not impossible, to determine what is good value for money in the allocation of scarce resources to new health interventions. Diseases that are currently covered by the Dutch Infant Immunization Program all share a significant risk of serious long term sequelae or mortality. This is fundamentally different in the case of RVGE, at least for otherwise healthy children, and raises the question if accepted cost-effectiveness procedures for vaccine evaluation should be applied. The appropriate cost-effectiveness threshold and the perspective used in the evaluation (healthcare or societal) to guide decision-making on vaccination policies for self-limiting and non-fatal diseases may need some further consideration. The use of generic measures of health and health loss such as QALY's or the DALY's (Disability Adjusted Life-Years) provides a means of comparing health effects across different diseases and health outcomes, but has been criticized for use in self-limiting and non-fatal diseases.[38-40] Alternatives have been developed such as the healthy-years equivalent (HYE), a measure in which preferences over health status and the duration of health states are estimated jointly to yield a single measure of preference for health outcomes over time.[41] Recently, a method was developed to estimate HYE for RVGE among young children.[42] Thus far, HYE have not been applied to cost-effectiveness analysis of RV vaccination but could prove a suitable alternative to the use of QALY's or DALY's.

Future research priorities

One important additional benefit of universal infant RV vaccination could be the induction of herd-immunity thereby protecting adults and children ineligible for vaccination due to medical reasons from RV disease. Observational studies from several countries have shown herd-immunity effects among unvaccinated children in the first, and to a lesser extent in the second year in which nearly complete vaccine coverage among the infant population is reached. [43-45] In addition, an observational study among adults suggests that herd-immunity may have been present in the first year after fully implemented RV vaccination.[46] However, to date sustained herd-immunity effects in the third and following years after implementation have not been confirmed. Mathematical modeling studies on long-term RV herd-immunity demonstrate contradictory results with some predicting elimination of RV from the population at high vaccine coverage rates and others predicting that short-term indirect benefits may be offset by a partial shifting of the burden of RVGE to older unvaccinated individuals.[47] Further evidence on presence of sustained herd-immunity effects beyond the first 2 years after implementation of universal infant RV vaccination should come available in the near future and provide further insight. However, the analysis of herd-immunity effects is hampered by a lack of adequate surveillance data on RV disease

among adults prior to implementation of RV vaccination. Therefore, trends over time are difficult to analyze and could be subject to detection bias. A prospective observational study on RV disease among adults in the Netherlands could provide critical information for adequate post-implementation surveillance of RV herd-immunity effects.

An important potential drawback of universal RV vaccination is the interference with diversity in population immunity against different RV strains and consequently RV strain replacement. Strain replacement could lead to reduced vaccine efficacy and epidemics caused by new emerging RV strains for which few people in the population have adequate immunity.[48] Monitoring vaccine-induced strain-replacement is hampered by the naturally high year-to-year variability in circulating RV strains such that many years of post-implementation strain-surveillance are needed to distinguish vaccination effects from naturally occurring variation. It is therefore still uncertain how the shifts in circulating dominant strains observed after implementation of universal RV vaccination programs in some countries should be interpreted.[49-52] Further understanding of RV strain dynamics, evolution of new strains and mathematical modeling of RV vaccination effects on these processes can help understand and project long-term effects of universal infant RV vaccination programs.

The effectiveness of RV vaccination and in particular targeted vaccination could be diminished when vaccine efficacy appears to be lower among high-risk groups who suffer from increased RV morbidity and mortality. Although available data do not suggest lower vaccine efficacy or additional safety risks in children with prematurity and LBW compared to healthy children born at term,[53;54] there is a lack of adequate data on children with congenital pathology and further vaccine studies in this group of patients are needed.

Although self-limiting in nature, RVGE can have significant impact on children and their parents. RV related healthcare usage is high and generates important monetary costs. The different chapters of this thesis have provided further insight in the magnitude and characteristics of RV disease burden for the general and specific populations and analyzed cost-effectiveness of different RV vaccination strategies. Information which is intended to support informed decision-making on who should get vaccinated against RV in developed countries currently without RV vaccination programs.

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Chapter 9

To Conclude

Summary

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) in young children worldwide. Nearly every child gets infected with RV during the first 5 years of life. In the developed countries RV remains a common cause of physician consultations and hospital admissions, while in developing countries RV still accounts for nearly 500,000 deaths annually. Furthermore, hospital-acquired (nosocomial) RV infections cause significant additional disease burden in patients already hospitalized for other reasons. The availability of two licensed RV vaccines provides opportunities for prevention of rotavirus gastroenteritis (RVGE). In recent years RV vaccination has been implemented in the national immunization programs of several countries, but contradictory results on cost-effectiveness of RV vaccination limit widespread implementation, especially in Europe, where only few countries have adopted RV vaccination thus far.
Hospitalization is the main driver of RV disease costs and prematurity, low birth weight (LBW) and underlying medical conditions have been associated with RV hospitalization and complications. Detailed evaluations of high-risk groups are lacking however, as are evaluations of targeted prevention strategies.

This thesis aims to quantify RV disease burden caused by RV hospitalizations in developed countries and to identify risk factors for RV hospitalizations. This thesis further aims to identify an optimal vaccination strategy for RV in developed countries based on cost-effectiveness analysis of different vaccination strategies.
In addition, this thesis aims to provide better insight in specific features of severe RVGE among susceptible populations such as premature and LBW infants, children with complex chronic conditions and immunocompromised patients.

This thesis focuses on two countries: Canada and the Netherlands. In Canada, RV vaccination was still under consideration at the start of this thesis project, but has recently been implemented in several provinces. In the Netherlands, RV vaccination is currently considered for inclusion in the national immunization program but has not been implemented thus far.

After a general introduction about rotavirus and outline of this thesis in **Chapter 1**, **Chapter 2** summarizes what is known on rotavirus epidemiology in Canada and the Netherlands from literature. Available data indicate that in both countries RV is responsible for significant national disease burden among children, despite the self-limiting and generally benign character of RV disease. Methodological shortcomings and incompleteness of data derived are major limitations of performed epidemiological studies affecting precision in some cases and potentially the validity of results. Data on RV mortality show contradictory results with no to several deaths observed in large series of hospitalized RV patients and highly variable mortality estimates from indirect methods. Therefore, uncertainty on national RV disease burden remains to some extent.
Although several studies have demonstrated that patients with underlying medical conditions are overrepresented among the more severely affected patients and in those with fatal RV infections it is concluded that no study to date has systematically assessed differences in RV disease burden between children with underlying medical conditions and otherwise healthy children.

Chapter 3 describes a systematic review and meta-analysis on the incidence of nosocomial RV infections (nRV), which are known to represent an important part of rotavirus-associated morbidity in high-income countries. The objective of this study was to summarize the existing evidence and produce reliable estimates of nRV incidence, before RV immunization programs, in pediatric settings in Europe and North America that can be used in assessments of RV disease burden. Electronic databases were searched for studies on nRV incidence among pediatric in-patients. To ascertain complete case reporting, only studies describing active nRV surveillance in their methodology were included. Random effects meta-analysis was performed. Metaregression was used to obtain results adjusted for important study characteristics. Based on twenty surveillance studies that met the quality criteria for inclusion, the pooled unadjusted nRV incidence was 2.9 per 100 hospitalizations (95%Confidence Interval [CI]: 1.6-4.4). Incidence was significantly influenced by the study months (RV epidemic season only or year-round) and the age range of included patients. Highest nRV incidence was found for children under two years of age, hospitalized during the epidemic months (8.1/100 hospitalizations; 95%CI: 6.4-9.9). The adjusted year-round nRV incidence estimate without age restriction was 0.4/100 hospitalizations (95%CI: 0.1-2.1) and 0.7 (95%CI: 0.0-1.8) for children under five.
It is concluded that nRV seems an important problem among hospitalized infants during winter months. The summary estimate is a useful tool to determine the number of nosocomial RV infections by country or province from hospital administrative databases prior to RV vaccination. The lower season and age adjusted nRV incidence estimate seems most appropriate for this application.

Chapter 4 reports on an observational study of nRV infections in a large Canadian tertiary-care hospital. The objective of this study was to determine nRV incidence, disease burden and characteristics of patients to support decision-making on potential vaccination strategies. In a retrospective cohort study of all nRV cases identified through the hospital's active prospective surveillance program for nosocomial infections, patient characteristics, medical history, nRV symptoms and therapy were determined. A total of 214 cases occurred. The nRV incidence rate was 0.5/1000 patient-days (95%CI: 0.43, 0.57) with no significant decline in rates over the years. Infection rate was highest among patients with a hospital stay of >5 days. A chronic underlying medical condition was present in 126 patients (59%), frequently associated with previous hospitalization(s) and of congenital or perinatal origin in 95 patients (44%). Rehydration was required for 132 (62%) patients and was intravenous in 98 (46%). For patients treated intravenously, there was an additional 3.3 IV-days per patient. Readmission for nRV GE that occurred after discharge was necessary in 26 patients (12%) for a median hospital stay of 4 days. It is concluded that nRV GE continues to be an important problem in pediatric hospitals, predominantly for children with underlying medical conditions requiring recurrent and prolonged hospitalizations and that targeted immunization of these vulnerable patients could be an interesting strategy.

In **Chapter 5** an epidemiological study on RV hospitalizations in the Netherlands is described assessing national disease burden and impact on pediatric wards of seasonal RV epidemics.
Seasonal rotavirus (RV) epidemics partly overlap with those of other common childhood infections thereby generating enormous – but poorly quantified - pressure on hospital resources during winter and spring. We assessed RV contribution to seasonal excess in all-cause pediatric hospitalizations and RV hospitalizations incidence rate by studying pediatric wards in 3 general hospitals and one pediatric tertiary care centre. Numbers of RV hospitalizations were determined from 5 year data on confirmed RV hospitalizations and adjusted for RV underreporting, assessed through active surveillance for acute gastroenteritis during the 2011 RV season. Incidence rate and RV contribution to all-cause hospitalizations was determined upon hospital administrative data and population statistics.

RV accounted for 6.2% (95%CI: 5.3 – 7.1) of all-cause pediatric hospitalizations among general hospitals and 3.1% (95%CI: 2.9 – 3.3) at the tertiary care centre, adjusted for the proportion RV underreporting among GE patients (33%) as observed during active surveillance. Among general hospitals, there was a 30% increase in all-cause hospitalizations during the active season of common childhood infections compared to summer months. RV contributed 31% to seasonal excess in all-cause pediatric hospitalizations, representing 13% of hospitalizations between January and May. RV hospitalizations incidence rate in the population was 510/100,000 child-years under five (95%CI: 420-600) leading to almost 5000 hospitalizations annually. The study demonstrated that RV is one of the main causes of seasonal peaks in pediatric hospitalizations, and as such contributes significantly to periodic high bed-capacity pressures and associated adverse effects.

Chapter 6 reports additional findings from the epidemiological study on the implications of high-risk conditions for RV hospitalization, healthcare costs and mortality. Next, the cost-effectiveness of two different RV vaccination strategies is assessed.
Disease burden, mortality and healthcare costs of RV hospitalization for children with and without prematurity, LBW and congenital pathology were quantified based on the epidemiological study described in chapter 5 and an additional observational study at a second tertiary care hospital in the Netherlands. Prematurity, LBW and congenital pathology were associated with increased risks of RV hospitalization (RR ranging from 1.6 to 4.4), ICU admission (RR ranging from 4.2 to 7.9), prolonged hospital stay (1.5 to 3.0 excess days) and higher healthcare costs (€648 to €1533 excess costs). Seven children succumbed due to RV complications, all belonging to the high-risk population. We investigated cost-effectiveness of targeted vaccination of high-risk infants and universal vaccination, based on analysis using an age-structured stochastic multi-cohort model of the Dutch population. We compared universal RV vaccination and targeted vaccination of high-risk infants to no vaccination. The primary endpoint was the incremental cost-effectiveness ratio (ICER), with a threshold of €35,000/QALY from the healthcare perspective. Sensitivity analyses included vaccine price and coverage, herd-immunity and QALY losses. Targeted RV vaccination was highly cost-effective and potentially cost-saving from the healthcare perspective with ICERs below €20,000/QALY in all scenarios with total (undiscounted) healthcare costs between -€0.1 and €0.5 million/year. Results were most sensitive to mortality rates, but targeted vaccination remained highly cost-effective up to reductions of 90% compared to observed mortality. Universal vaccination was not considered cost-effective (mean ICER: €60,200/QALY), unless herd-immunity and caretaker QALY losses were included and vaccine prices were €60 at most (mean ICER: €21,309/QALY).

Chapter 7 focuses on RV infections among immunocompromised patients, both children and adults, describing RV disease course, complications and interventions. RV is highly endemic inside and outside hospital settings and an important potential pathogen among immunocompromised patients. Severe RVGE has been described in these patients, but little is known on general RV disease severity and manifestations among immunocompromised patients and relative importance of RV as gastrointestinal pathogen prior to RV vaccination. We used 5-year laboratory records from a Dutch tertiary care hospital to identify adult and pediatric RV infections. Medical records were reviewed for immunocompromising conditions and, when present, RV disease manifestations and interventions were evaluated. In addition, 3-year hospital viral and bacterial stool-testing records were used as surrogate for GE episodes to determine rates of RV testing, prevalence and underreporting among adult and pediatric GE. Among 35 and 259 confirmed RV infections in hospitalized adults and children, respectively, 20 (57%) and 35 (12%) patients were immunocompromised.

Apart from GE, complicating disease manifestations among immunocompromised patients included high transaminases (46%), hypokalemia (41%), feeding intolerance (31%) and, among children, prolonged illness (> 14 days, 28%). Common interventions apart from rehydration (77%) included antibiotic treatment (24%), adjusting medication including chemotherapy (31%) and parental nutrition (18%).
In addition, we estimated RV contribution to acute GE among adults and immunocompromised patients in particular, relative to other gastrointestinal pathogens.
Of 3653 and 2215 adult and pediatric GE episodes, 433 (12%) and 1493 (67%) were tested for RV, with RV confirmed in 27 (6%) and 182 (12%), respectively. We estimated that 87% and 30% of RV infections in adult and pediatric GE remain unreported.
The study demonstrated that RVGE has significant impact on immunocompromised patients and interferes with underlying disease management. RV contribution to GE among hospitalized adults seems significantly underestimated and affects mainly immunocompromised patients. Anticipating sustained herd-immunity of infant RV vaccination, indirect benefits could be substantial among these patients.

Chapter 8 is a general discussion of the findings and implications of this thesis:

Hospitalizations for community-acquired RVGE
We found that in the Netherlands approximately 1 in 40 children experiences an episode of hospitalization for RVGE. Almost 90% of RV hospitalizations occur between January and May posing a substantial seasonal pressure on pediatric hospital beds. We suggest that RV vaccination benefits in this respect should be considered in decision-making processes.
It will be interesting to see in coming years to what extent universal RV vaccination in other countries reduces the peak in all-cause pediatric hospitalizations during the winter months, and whether this is accompanied by additional economic savings through reductions in staffing and bed-capacity.

Among adults, RV disease is generally considered mild. We estimated however that RVGE causes almost 6% of GE episodes among adults hospitalized at a tertiary care centre.

Nosocomial RVGE
This thesis demonstrated that nosocomial RV infections contribute substantially to overall RV disease burden and are an important problem from the hospital infection control perspective. Disease burden due to nRV infections is significant and prolongs hospitalization. Intra-hospital transmission of rotavirus seems high, especially in settings with very vulnerable patients such as tertiary care centres, where a significant proportion of adult and pediatric RV episodes are nosocomially acquired. For infection control purposes, we suggest RV testing should be routinely performed for suspected nosocomial GE, even among adults.

Risk factors for RV hospitalization
Both the Canadian and Dutch observational studies demonstrated that children with underlying medical conditions are substantially overrepresented among RV hospitalizations, which was most pronounced among nosocomial infections. Furthermore, we demonstrated an increased risk of RV hospitalization among children with prematurity, LBW and congenital pathology, increased healthcare utilization and, more importantly, we found RV exclusively among children with congenital pathology. These patients are most in need of protection from RVGE, yet vaccine efficacy studies have not been performed in this specific population. It is generally assumed that protection against severe RVGE through vaccination is similar in

high-risk patients compared to results for healthy children, but additional vaccine efficacy studies among high-risk patients are needed to confirm this.
Immunocompromised patients, both among adults and children, form a separate patient-group highly vulnerable to RV disease. Most immunocompromised RV patients experience complications requiring intense monitoring and additional medical interventions apart from rehydration. Initial observations of herd-immunity effects through infant RV vaccination and its potential to reduce RV morbidity in these patients seem promising. Adequate RV surveillance, including adults, is essential to monitor these effects and will have to demonstrate in coming years if currently observed herd-immunity is substantial and sustained over time.

Cost-effectiveness of RV vaccination programs
Cost-effectiveness has become a key component in the evaluation of vaccination strategies and is considered a prerequisite for implementation of new vaccine programs. We demonstrated high cost-effectiveness of targeted RV vaccination. The significant health gains that could be realized by targeted RV vaccination at low costs should motivate health policy makers in European countries to implement this intervention even if they don't consider RV vaccination for the general infant population at this point.
Even greater health benefits could be realized when universal RV vaccination is implemented, although it is unlikely that this intervention will be cost-effective in the Netherlands from the healthcare perspective unless vaccine prices drop substantially.
Diseases that are currently covered by the Dutch Infant Immunization Program all share a significant risk of serious long term sequelae or mortality. This is fundamentally different in the case of RVGE, at least for otherwise healthy children, and raises the question if accepted cost-effectiveness procedures for vaccine evaluation should be applied. The appropriate cost-effectiveness threshold and the perspective used in the evaluation (healthcare or societal) to guide decision-making on vaccination policies for self-limiting and non-fatal diseases may need some further consideration.

Chapter 9

To Conclude

Samenvatting

Infecties die gepaard gaan met diarree, al dan niet in combinatie met misselijkheid, braken en koorts, (gastro-enteritis) komen veelvuldig voor op de kinderleeftijd. Met name bij zuigelingen en jonge kinderen kan gastro-enteritis al snel leiden tot uitdroging, hetgeen resulteert in veelvuldig bezoek aan huisarts, spoedeisende hulp of zelfs opname in het ziekenhuis. Ongeveer 10-20% van alle episoden van gastro-enteritis bij 0-5 jarigen wordt veroorzaakt door het rotavirus, waarmee het een van de belangrijkste oorzaken van diarree op de kinderleeftijd is. Rotavirus gastro-enteritis duurt doorgaans zo'n 4 tot 7 dagen. De behandeling bestaat uitsluitend uit het waarborgen van adequate vochttoediening.
Omdat rotavirus gastro-enteritis vaak heftiger verloopt dan andere vormen is zij verantwoordelijk voor een aanzienlijk deel van de ziekenhuisopnames wegens gastro-enteritis onder kinderen, zo'n 40-50%. Driekwart van hen is onder de twee jaar. In ontwikkelingslanden sterven jaarlijks een half miljoen jonge kinderen wegens uitdroging bij rotavirus gastro-enteritis.

Het rotavirus is zeer besmettelijk en overleeft langdurig buiten het menselijk lichaam. Door deze kenmerken kan het virus zich gemakkelijk verspreiden binnen ziekenhuis-afdelingen. Rotavirus is een belangrijke oorzaak van ziekenhuisinfecties (nosocomiale infecties), met name op kinder- en zuigelingen afdelingen, waar het virus frequent wordt geintroduceerd door opnames van patiënten met rotavirus gastro-enteritis.
Resultaten van verschillende studies suggereren dat bepaalde kinderen een verhoogd risico hebben op ziekenhuisopname wegens rotavirus-gastroenteritis. Het betreft kinderen die prematuur geboren zijn of met een te laag geboortegewicht (< 2500 gram) en kinderen met ernstige onderliggende ziektebeelden. Ook onder de kinderen die rotavirus oplopen in het ziekenhuis behoort een groot deel tot deze kwetsbare groep.

Sinds enkele jaren zijn er vaccins op de markt die beschermen tegen rotavirus gastro-enteritis. De vaccins zijn ontwikkeld voor orale toediening aan zuigelingen in 2 of 3 doses, afhankelijk van het vaccin type. De eerste dosis wordt rond de leeftijd van 2 maanden gegeven, volgende doses worden met tussenposen van 4-10 weken toegediend. Zowel in grote internationale gerandomiseerde vaccin-studies, als in observationele studies in landen met rotavirus vaccinatie programma's is de effectiviteit tegen de ernstige vormen van rotavirus gastro-enteritis en gerelateerde ziekenhuisopname aangetoond. In westerse landen reduceert vaccinatie het risico op rotavirus gerelateerde ziekenhuisopnames met 80-95%.

Momenteel wordt er in Nederland niet gevaccineerd tegen rotavirus. In enkele andere westerse landen zoals de VS, Australië, België, Luxemburg, Oostenrijk en recent ook Finland en Canada is rotavirus vaccinatie inmiddels onderdeel van het standaard vaccinatie programma voor zuigelingen.
Het implementeren van een nieuwe vaccinatie is kostbaar. Een grondige afweging van de gezondheidswinst en economische besparingen als gevolg van ziektereductie enerzijds, en de kosten van vaccinatie anderzijds is essentieel voor efficiënt gezondheidszorgbeleid. In het licht van groeiende zorgkosten en beperkte budgetten zijn de resultaten van kosten-effectiviteits analyses, een analyse waarin de kosten en effecten van verschillende vaccinatie strategiën met elkaar worden vergeleken, een belangrijke factor in de besluitvorming rondom nieuw vaccinatiebeleid. Voor betrouwbare analyses zijn gegevens over aantallen, ernst en kosten van rotavirus gastro-enteritis en het identificeren van eventuele specifieke doelgroepen voor vaccinatie noodzakelijk.

Dit proefschrift beoogt de frequentie van voorkomen (incidentie), de ziektelast en kosten van rotavirus gerelateerde ziekenhuisopnames, waartoe ook de nosocomiale rotavirus infecties worden gerekend, vast te stellen en potentiële risicogroepen te identificeren. Voorts zijn de bevindingen gebruikt voor een kosten-effectiviteits analyse van verschillende vaccinatie strategiën waarbij de Nederlands situatie het uitgangspunt is geweest.

Hoofdstuk 2 geeft een overzicht van de epidemiologie van rotavirus gastro-enteritis onder kinderen in Canada en Nederland, de twee landen waarop de studies in dit proefschrift betrekking hebben, op basis van reeds bestaande literatuur. Hoewel voor beide landen gegevens over rotavirus gerelateerde ziekenhuisopnames bestaan, is de kwaliteit van de gebruikte onderzoeksmethoden discutabel en bestaat er derhalve veel onzekerheid over de hoogte van de totale ziektelast. Systematisch onderzoek naar hoog-risicogroepen is in beide landen nog niet eerder gedaan.

In **Hoofdstuk 3** wordt een meta-analyse beschreven waarin de incidentie van nosocomiale rotavirus gastro-enteritis in landen van Noord-America en West-Europa is geëvalueerd. Resultaten uit gepubliceerde studies die voldeden aan gestelde kwaliteitscriteria werden middels statistische technieken van meta-analyse en meta-regressie samengevoegd, zodat een gemiddelde incidentie werd berekend en de invloed van seizoen en leeftijdsgroepen hierop kon worden bepaald. De gemiddelde incidentie van nosocomiale rotavirus gastro-enteritis was 0.4 per 100 ziekenhuisopnames onder kinderen (95% betrouwbaarheidsinterval: 0.1-2.1). De hoogste incidentie werd gevonden uit resultaten van studies onder 0-2 jarigen opgenomen tijdens de wintermaanden (incidentie: 8.1/100, (95% betrouwbaarheidsinterval: 6.4-9.9). De studie geeft daarmee inzicht in de mate en context waarin rotavirus een probleem is binnen ziekenhuizen.
Vergelijkbare resultaten worden genoemd in **Hoofdstuk 4** waarin een studie naar incidentie en ziektelast als gevolg van nosocomiale rotavirus gastro-enteritis in een tertiair kinderziekenhuis in Montreal wordt beschreven. De incidentie in deze studie bedroeg 0.30 nosocomiale rotavirus gastro-enteritis per 100 ziekenhuisopnames (95% betrouwbaarheidsinterval: 0.26, 0.35). Onder 214 onderzochte nosocomiale rotavirus infecties kreeg 46% (98 patiënten) vocht toegediend via infuus gedurende gemiddeld 3.3 dagen. Opvallend was verder dat bij 126 kinderen (56%) sprake was van een onderliggende chronische aandoening.

Hoofdstuk 5 en 6 beschrijven een studie onder 4 Nederlandse ziekenhuizen naar rotavirus gerelateerde ziekenhuisopnames waarin incidentie, ziektelast, kosten, patiënt-karakteristieken en rotavirus aandeel in kindergeneeskundige ziekenhuisopnames werd onderzocht. Hiertoe werden gegevens verzameld van alle kinderen met rotavirus infectie in een periode van 5 jaar evenals gegevens van algemene ziekenhuis-zorgstatistieken en bevolkingsregistraties. Rotavirus bleek verantwoordelijk voor 6.2% van alle kindergeneeskundige opnames in algemene ziekenhuizen (95% betrouwbaarheidsinterval: 5.3 – 7.1). Gedurende de wintermaanden, wanneer aantallen kindergeneeskundige opnames gemiddeld 30% hoger waren, bleek rotavirus verantwoordelijk voor 31% van deze stijging. Op basis van de gemeten incidentie zijn er in Nederland jaarlijks gemiddeld 4870 rotavirus gerelateerde ziekenhuisopnames (95% betrouwbaarheidsinterval: 4060 – 5680) waarbij het in 80% van gevallen kinderen onder de 2 jaar betreft. Vroeggeboorte, laag geboortegewicht en congenitale afwijkingen bleken significant vaker voor te komen bij deze kinderen dan in de algemene populatie (relatief risico: 1.6 tot 4.4).
Ook bleken deze kinderen vaker te worden opgenomen op een Intensive Care (relatief

risico: 4.2 tot 7.9), langer in het ziekenhuis te verblijven (1.5 tot 3.0 dagen langer) en hogere zorgkosten te hebben (€648 tot €1533 meer kosten). Aanvullende analyses toonden eveneens een verhoogd risico op nosocomiale rotavirus gastro-enteritis onder hoog-risico kinderen (odds ratio: 3.2 tot 3.6) en dat er zelfs sterfte optrad in deze groep (7 geobjectiveerde sterfgevallen). In hoofdstuk 6 wordt vervolgens een kosten-effectiviteitsanalyse beschreven waarin 3 vaccinatie-strategiën worden vergeleken voor Nederland: (1) de huidige situatie zonder vaccinatie, (2) rotavirus vaccinatie van alle zuigelingen (universele vaccinatie) en (3) vaccinatie van alleen hoog-risico kinderen (doelgroepen vaccinatie). Deze laatste strategie blijkt zeer kosten-effectief; alle geteste scenario's binnen doelgroepen vaccinatie resulteerden in een kosten/baten vehouding ver onder de in Nederland gehanteerde bovengrens van 20,000 euro per 'Quality Adjusted Life Year' (QALY), een in kosten-effectiviteits analyses gebruikte generieke maat voor gezondheidswinst. Universele rotavirus vaccinatie leidt welliswaar tot grotere gezondheidswinst, maar vereist ook hogere financiële investeringen resulterend in een verhouding van 60,000 euro/QALY.

In **Hoofdstuk 7** wordt een studie naar rotavirus gastro-enteritis onder patiënten met verminderde afweer (immuungecompromitteerd) beschreven. In deze studie werd zowel naar kinderen (259 rotavirus infecties) als volwassen patiënten met rotavirus gastro-enteritis (35) gekeken. Van hen waren respectievelijk 35 (12%) en 20 (57%) immuungecompromitteerd. Een aanzienlijk deel van deze patienten ondervond naast gastro-enteritis aanvullende problemen zoals leverfunctiestoornissen (46%), laag kaliumgehalte (41%), voedingsproblemen (31%) en, onder kinderen, langdurige diarree (> 14 dagen, 28%). Regelmatig toegepaste additionele interventies waren toediening van antibiotica (24%) of parenterale voeding (via infuus, 18%) en het aanpassen van onderhouds-medicatie of chemotherapie (31%). Ook bleek dat slechts in 12% van de episodes van gastro-enteritis onder volwassenen werd getest op rotavirus hetgeen forse onderrapportage van rotavirus suggereert.

Hoofdstuk 8 tenslotte bespreekt de belangrijkste bevindingen van dit proefstuk:
Ziekenhuisopnames als gevolg van rotavirus gastro-enteritis: Ons onderzoek heeft aangetoond dat in Nederland gemiddeld 1 op de 40 kinderen een keer wordt opgenomen in het ziekenhuis wegens rotavirus gastro-enteritis. Rotavirus heeft met bijna 5000 opnames per jaar een grote impact op de kindergeneeskundige zorg in Nederland. Met name tijdens de wintermaanden, wanneer rotavirus voornamelijk actief is, zorgt dit voor een grote toename van opnames op kinderafdelingen. Onder volwassenen lijkt sprake van forse onderrapportage van rotavirus en wordt diens rol in infectieuze gastro-enteritis onderschat.
Nosocomiale rotavirus gastro-enteritis: In westerse landen loopt gemiddeld 1 op de 250 opgenomen kinderen een rotavirus infectie op in het ziekenhuis. Het risico hierop is vooral groot onder kinderen onder de 2 jaar die tijdens de wintermaanden in het ziekenhuis verblijven. Deze infecties leiden veelal tot extra medische interventies en langduriger ziekenhuisopname.
Risicofactoren voor rotavirus gerelateerde ziekenhuisopname: Te vroeg geboren kinderen, kinderen met laag geboorte gewicht of met congenitale afwijkingen hebben een verhoogd risico om met rotavirus gastro-enteritis in het ziekenhuis te belanden of om een dergelijke infectie in het ziekenhuis op te lopen. Deze kinderen hebben vaker intensieve zorg nodig en liggen langer in het ziekenhuis. Ook waren enkele hoog-risico kinderen overleden aan de gevolgen van rotavirus gastro-enteritis. Onder immuungecompromitteerde patienten kent rotavirus gastro-enteritis een gecompliceerder beloop en noodzaakt tot aanvullende medische interventies. Vooral wanneer volwassen ziekenhuispatiënten een rotavirus gastro-enteritis doormaken betreft dit vaak immuungecompromitteerde patiënten.

Kosten-effectiviteit van rotavirus vaccinatie: Met de nieuwe inzichten in de ziektelast die rotavirus in Nederland veroorzaakt onder verschillende groepen blijkt vooral de kosten-effectiviteit van selectieve vaccinatie van hoog-risico groepen zeer gunstig. Geconcludeerd wordt derhalve dat ten minste het vaccineren van hoog-risico kinderen met prioriteit zou moeten worden ingevoerd.

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Abbreviations

RV	Rotavirus
GE	Gastroenteritis
RVGE	Rotavirus Gastroenteritis
CI	Confidence Interval
ICU	Intensive Care Unit
DBC	Dutch Diagnostic Codes
ICD	International Classification of Disease
nRV	Nosocomial Rotavirus
MCH	Montreal Children's Hospital
LBW	Low Birth Weight
RR	Relative Risk
OR	Odds Ratio
aOR	adjusted Odds Ratio
QALY	Quality Adjusted Life Year
DALY	Disability Adjusted Life Year
ICER	Incremental Cost-Effectiveness Ratio
GvHD	Graft versus Host Disease
NV	Norovirus

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Curriculum Vitae

Patricia Bruijning-Verhagen was born on December 4th 1974 in Maastricht. As a little girl she lived in Tanzania before the family moved back to the Netherlands where they settled in Hilversum. She finished high-school (VWO) at the Comenius College in Hilversum, studied French for one year in Grenoble and attended Medical School at the University of Groningen and subsequently at the Erasmus University in Rotterdam where she graduated in 2001. Following one year as junior house-officer at the Surgical Intensive Care of the Sophia Children's Hospital, Erasmus Medical Centre Rotterdam she did her residency training in pediatrics at the Leiden University Medical Center and the Juliana Pediatric Hospital, the Hague. In 2008 she completed her residency program with an elective training in Pediatric Infectious Diseases at the Montreal Children's Hospital. At this time she also started her research project on rotavirus at the department, supervised by dr. Caroline Quach and described in this thesis. In the same year she enrolled at McGill University in the Masters of Science Epidemiology Program. In 2009 she received the Maria Raiche Studentship Award for her research project. In 2010, after graduating from McGill and returning to the Netherlands she continued her PhD project on rotavirus at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht supervised by Professor Marc Bonten. After completing her thesis, she will continue working at the Julius Center with at partial cross-appointment at the National Institute for Public Health and the Environment (RIVM). Her research interests are focused on the prevention of and public health and economic impact of common childhood infections. She is currently involved in epidemiological research projects on rotavirus, upper respiratory tract infections and dengue.

Patricia is married to Martijn Bruijning. They live in Hilversum and have three children: Wessel (2006), Laurien (2007) and Lucas (2009).