Rotavirus vaccination for infants with medical risk conditions

Josephine van Dongen

Rotavirus vaccination for infants with medical risk conditions

Josephine van Dongen

Rotavirus vaccination for infants with medical risk conditions
PhD dissertation, Utrecht University, the Netherlands

Printing of this thesis is supported by DaklaPack, Annex Studios and UMC Utrecht

ISBN: 978-94-6416-643-9
DOI: https://doi.org/10.33540/647

Cover design by Tessa Dirken
Layout: Josephine van Dongen
Printed by Ridderprint

Rotavirus vaccination for infants with medical risk conditions

Rotavirus vaccinatie voor zuigelingen met medische risico aandoeningen
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. Dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 28 september 2021des ochtends te 10.15 uur

door

Josephine Alette Peihrien van Dongen

geboren 5 september 1989
te Amsterdam

Promotor:
Prof. dr. M.J.M. Bonten

Copromotor:
Dr. P.C.J.L. Bruijning-Verhagen

Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van ZonMw (836021024), GSK Biological SA (203108) en InnovatieFonds Zorgverzekeraars

Index

Chapter 1	General introduction	7
Chapter 2	Acute gastroenteritis disease burden among infants with medical risk conditions in the Netherlands	25
Chapter 3	Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting	51
Chapter 4	Rotavirus vaccine effectiveness among infants with medical risk conditions in the Netherlands	91
Chapter 5	Safety and tolerability of human rotavirus vaccination in medical risk infants in the Netherlands	117
Chapter 6	Non-specific effects of human rotavirus vaccination in medical risk infants in the Netherlands	141
Chapter 7	Evaluation of implementing a rotavirus vaccine program targeting high-risk infants in the Netherlands	159
Chapter 8	Summary and general discussion	185
Appendices		205
	Dutch summary/Nederlandse samenvatting	207
	Contributing authors	213
	List of publications and conference presentations	219
	Acknowledgements/Dankwoord	223
	Curriculum vitae	229

Chapter 1

General introduction

Partly adapted from: van Dongen, J.A.P. and Bruijning-Verhagen, P.C.J. Rotavirus infections and vaccination.

Dutch Journal of Clinical Microbiology, 2018

Introduction

In this general introduction, the background and relevance for the Risk-group Infant Vaccination Against Rotavirus (RIVAR) project are described. Based on the characteristics of rotavirus as a pathogen and the induced illness, it follows that vaccination is the only way to prevent disease. Reviewing the existing literature on rotavirus vaccination and its gaps, the aims of this thesis are described. Additionally, the outline of this thesis is presented.

Rotavirus disease

Rotavirus is the most common cause of acute gastroenteritis (AGE) in children.[1] Before the introduction of vaccination, rotavirus was the dominant cause of severe AGE leading to hospitalization and mortality.[2] Worldwide it was responsible for 40% of hospital admissions and 450.000 annual deaths among children.[3] In the Netherlands, the incidence rate of hospitalization due to rotavirus infection was estimated at approximately 500 per 100.000 child years for children below five years of age.[4] Since the introduction of rotavirus vaccinations in national immunization programs in Europe, pediatric rotavirus hospitalizations in those countries declined with 65 to 84%.[5] In the Netherlands no rotavirus vaccination program has been introduced, uptake of rotavirus vaccine in the private market is estimated to be low (less than one percent).

Genetics and viral characteristics

Rotaviruses are non-enveloped double-stranded RNA viruses. They have a complex structure of three outer layers surrounding a 11 segmented genome (**Figure 1**). The genome encodes for six structural proteins (viral protein 1,2,3,4,6,7) and six non-structural proteins (NSP1-6). Based on VP6, that defines the inner membrane of rotavirus, ten groups of rotaviruses can be distinguished, group A to J. Group A is most common in humans.[6] Further distinction in genotypes is based on outer membrane VP7 (glycoprotein G) and spike protein VP4 (defining protealysing protein P, see **figure 1**).[6,7] So far 36 different G types and 51 P types are defined.[8] Six of them represent 90% of circulating types of rotavirus among humans; G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8].9 G1P[8] is most common worldwide.[9] The virus is transmitted via the fecal-oral route. The viral density in feces of infected persons is estimated 10^{10} viral particles per gram stool and only a very limited number of virus particles (around 100) are needed to infect a susceptible host.[9,10] Infected surfaces enhance transmission; the virus remains infectious for several hours on hands and up to 60 days on inanimated surfaces.[11,12] Once infected, the virus infects and replicates in the enterocytes and entero-endocrine cells of the small intestines.[9,13] For binding to enterocytes the virus uses glycans on the cell surface. These glycans are part of the histoblood group antigen-complex (HBGAs).[9,14] The HBGA phenotype of the host defines, in part, how rotavirus genotypes bind to enterocytes. Diversity in HBGA phenotypes across populations worldwide can explain geographic differences in genotype dominance.[14]

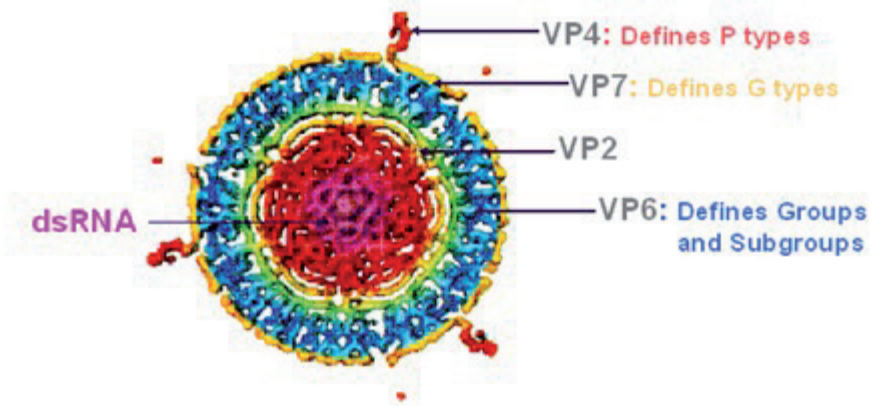


Figure 1. Structure of rotavirus. 2018 @NVMM
Abbreviations: dsRNA = double-stranded RNA, VP = viral protein.

Clinical characteristics

The clinical disease varies from asymptomatic to severe dehydration due to diarrhea, vomiting and fever. Incubation time of rotavirus is short, less than 48 hours. Two mechanisms explain the symptoms. First, rotavirus induces osmotic diarrhea as a consequence of cell damage, necrosis of enterocytes or villus atrophy and as a result of malabsorption. Secondly, NSP4, one of the non-structural proteins, generates secretory diarrhea and activation of the intestinal nerve system.[10] A rotavirus infection leads to fever and general malaise through pro-inflammatory cytokines, interleukins (IL-B and IL-6) and, tumor necrosis factor. The exact mechanism is not yet explained.[10] In addition, rotavirus can cause a systemic infection, rotavirus RNA has been detected in the liver, heart, bladder, lungs, kidneys, testicles and, central nerve system.[15]
Children are usually first infected between four and twenty-three months of age.[9] Presence of symptoms and severe disease course are most frequent during first infection.

Immune response

Immunity following rotavirus infection is primarily achieved through serum and mucosal antibodies against VP7 and VP4. Neutralizing antibodies offer protection against homotypic (against the same virus type) as well as against heterotypic (against a different virus type) rotavirus genotypes. This heterotypic immunity, also named cross-protection, increases with repeated rotavirus infection. The role of cellular immunity is still partly unexplained, however virus specific CD8+ cells potentially clear the infection and protect against disease.[9,16] Rotavirus immunity is highly protective against severe symptoms, however to a lesser extent against infection. Thus, re-infections with rotavirus are common and boost immunity against the virus.[17] A gradual decrease in CD4+ cells and neutralizing antibodies over time can account for incomplete immunity against re-infection.[6,13]

Epidemiology and disease burden

Rotavirus is a strong seasonal pathogen with a peak incidence between January and April in temperate climates.[18,19] Since 2014 there has been an unexplained decrease in rotavirus activity in the Netherlands and possibly a transition to a biennial instead of an annual epidemic pattern.[20,21] In 2014 and 2016 the number of rotavirus detections in the Dutch surveillance sentinel laboratories were approximately 60% lower compared to previous years.[22] During the alternating years 2015 and 2017 a normal rotavirus season was observed, but then 2018 and 2019 also had a normal rotavirus season.[23] In 2020, approximately half of the rotavirus detections were observed compared to the preceding year. The preventative measures (school closure and social distancing) implemented during the COVID-19 pandemic in that year potentially clarify the sharp decline in detections from April onwards.[24,25] Suggested explanations for the lower than expected rotavirus intensity in 2014 and 2016, are the mild winters, decreasing birth rate and the implementation of universal rotavirus vaccination in the surrounding countries.[21] Despite this changing epidemiology, the yearly number of hospitalizations due to rotavirus gastroenteritis in the Netherlands are estimated between 1900 and 3400 among children and five to six deaths occur.[26]

Prematurity, small for gestational age and, presence of severe congenital pathology are risk factors for a more severe and complicated rotavirus gastroenteritis.[27] This is reflected in increased hospitalization rates, prolonged hospital stay and increased mortality compared to healthy infants.[27–31] In the Netherlands, rotavirus related mortality almost exclusively occurs in this group of children.[28] Nosocomial infections in this population are particularly common, as these infants require prolonged (postnatal) hospitalization which predisposes them to hospital acquisition of rotavirus infection.[32] While the hospitalization and mortality burden in this group of infants with medical risk conditions (MRC) are well defined, the community disease burden is not. Due to the self-limiting character of rotavirus disease however, the majority of cases occur outside of the hospital,[33] and this burden could therefore be substantial.

Other risk-groups for severe rotavirus disease are immunocompromised patients and elderly.[9,18,34] About five percent of diarrhea outbreaks in geriatric care facilities are caused by rotavirus.[18] Up to 50% of parents experience mild to moderate complaints of gastroenteritis if their child is infected with rotavirus, indicating high transmissibility within households.[18,35]

Rotavirus vaccination

Based on rotavirus' pathogenesis and immune response, elimination is not considered a realistic goal. Hygiene and sanitary measures are unable to prevent transmission.[9] Vaccination against

rotavirus is therefore the most effective method to prevent disease.

Table 1. Currently available rotavirus vaccines

Product and manufacturer	Type of vaccine	Indication	License	Availability	Efficacy*
Rotarix (GlaxoSmith Kline Vaccines, Belgium)	Monovalent human G1P[8] strain, live-attenuated, oral	Infants >6 weeks of age, two doses	Global, since 2004	Worldwide	84.7% (95%CI 71.7; 92.4%)[36]
RotaTeq (Merck and Co, Inc., USA)	Pentavalent human-bovine G1, G2, G3, G4 and P[8] strains, live-attenuated, oral	Infants >6 weeks of age, three doses	Global, since 2006	Worldwide	98.0% (95%CI 88.3; 100%)[37]
Rotavac (Bharat Biotech, Hyderabad, India)	Monovalent neonatal G9P[11] strain, live-attenuated, oral	Infants >6 weeks of age, three doses	WHO prequalified in 2018, National since 2015	India, Palestine	56% (95%CI 37;70%)[38]
RotaSIIL (Serum Institute of India, PVT. LTD., Pune, India)	Pentavalent, bovine-hum-an reassort-ant G1, G2, G3, G4, G9 strains, live-attenuated, oral	Infants >6 weeks of age, three doses	WHO prequalified in 2018, National since 2017	India	33% (95%CI 12;49%)[38]
Rotavin-M1 (Center for Research and Production of Vaccines and Biologicals (POLY-VAC), Hanoi, Vietnam)	Monovalent human G1P[8] strain, live-attenuated, oral	Infants >6 weeks of age, two doses	National, since 2012	Vietnam	(73% sero-conversion)[38]
Lanzhou Lamb Rota-virus Vaccine (Lanzhou Institute of Biological Products Co., Ltd., Lanzhou, China)	Monovalent lamb G10P[12] strain, live-attenuated, oral	Once annually between 2 months and 3 years	National, since 2000	China	70.3% (95%CI 60.6;77.6)[39]
RV3-BB (PT BioFarma, Bandung, Indonesia)	Monovalent neonatal G3P[6] strain, live-attenuated, oral	Neonatal schedule (0–5 days, 8–10, and 14–16 weeks of age)	No	Phase 3	94% (95%CI 56;99%)[38]

Product and manufacturer	Type of vaccine	Indication	License	Availability	Efficacy*
P2-VP8-P[8] subunit (Walter Reed Army Institute of Research Pilot Bio-production Facility)	Non-replicating, monovalent, parental	To be determined	No	Phase 3	(>98% seroconversion)[38]
P2-VP8-P[4] P[6]P[8] subunit (Walter Reed Army Institute of Research Pilot Bio-production Facility)	Non-replicating, trivalent, parental	To be determined	No	Phase 3	Not available

*Efficacy against severe rotavirus acute gastroenteritis after vaccination in the first year of life. Abbreviations: CI = confidence interval, WHO = World Health Organization.

Current rotavirus vaccines

Four different rotavirus vaccines are currently licensed worldwide.[38] Two of these live-attenuated vaccines have been licensed in Europe and three additional vaccines are currently being evaluated.[38,40] More inactivated vaccine candidates are under development.[38] The characteristics of different rotavirus vaccines are presented in **table 1**.

The vaccines have been studied and developed exclusively for infants. Live-attenuated vaccines function by mimicking natural rotavirus infection. The live-attenuated virus type(s) contained in the vaccine infects the intestinal epithelium and induces an immune response, which is similar to a natural rotavirus infection. A complete vaccine course (multiple doses) provides a broad protection against diverse genotypes (i.e. both homotypic and heterotypic immunity).[41,42]

The two live-attenuated rotavirus vaccines that are globally available, RotaTeq and Rotarix, were investigated for efficacy and safety in large international phase III clinical trials with in total over 150.000 infants included. Highest efficacy for rotavirus vaccination was measured in Europe and North-America, 80 to 100%, against severe rotavirus gastroenteritis caused by diverse rotavirus genotypes.[36,37,43–45] Efficacy in developing countries yielded clearly lower estimates, 40 to 70%.[46,47] Proposed mechanisms for a lower efficacy are higher maternal antibodies, intestinal dysbiosis and a different host response.[48,49] There was a need for better rotavirus vaccines for developing countries. To address the problems of vaccine performance in these countries, other (parental) vaccines were developed. Vaccine efficacy for these newer vaccines in phase III trials seems indeed better, depicted in **table 1**.

Vaccine performance in medical risk infants (i.e. those born premature, with low birthweight

and/or congenital pathology) was studied in smaller trials for Rotarix and RotaTeq. Omenaca et al assessed Rotarix to be immunogenic in 228 stable premature infants.[50] The anti-rotavirus IgA seroconversion rate after two doses was 86% (95%CI 79;90%). Goveia et al proved efficacy of RotaTeq against rotavirus gastroenteritis in 153 healthy premature infants.[51] Clinical efficacy after three doses was 70% (95%CI 15;95%) against rotavirus (strain type G1-4) gastroenteritis of any severity. Both studies also report on safety; similar frequencies of adverse events after placebo versus rotavirus vaccination were described.

Vaccine effectiveness

Effectiveness studies examine the effects of vaccination on disease burden in a real-life setting. Overall, in high-income countries reports on vaccine effectiveness against severe rotavirus gastroenteritis have been consistently high, more than 80% after a full course of one of the globally available vaccines.[52–54] However, these estimates are mainly from studies in healthy infants. Based on the reassuring results from phase III trials, effectiveness of rotavirus vaccines in infants with medical risk conditions (MRC), until now, was assumed to be similar. This was corroborated by studies demonstrating high levels of post-vaccination seroconversion among infants with intestinal failure,[55] and effectiveness among infants on the neonatal care unit, including those with gastrointestinal pathology.[56] Countries that implemented infant rotavirus vaccination generally make no distinction in their recommendation between healthy infants and those belonging to the medical risk group (except for severe combined immunodeficiency).[57,58] Both globally available vaccines, RotaTeq and Rotarix, have been licenced for administration to premature infants (respectively, from 25 and 27 weeks of gestational age onwards).

In European countries, that implemented rotavirus vaccination for all infants, a decrease in hospital admissions for rotavirus infections from 65 to 84% has been observed.[5] This impact of rotavirus vaccination on rotavirus hospitalizations has also been reported for all-cause acute gastroenteritis admissions albeit to a lesser extent. A 54-57% reduction in hospitalized all-cause acute gastroenteritis was reported for Finland,[59,60] a 53% reduction for England[61] and 33% in Belgium.[62]

In addition, universal rotavirus vaccination provides a so-called herd effect. Herd effect is defined as ``the reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population''.[63] The achieved proportion of immunity in a population, dependent on vaccine coverage and efficacy, can lead to a decrease in symptomatic disease cases among unvaccinated individuals. This indirect vaccine effectiveness can be measured by comparing the risk of rotavirus infection among unvaccinated subjects in populations with and without infant rotavirus vaccination. A meta-analysis indicated that the indirect vaccine effectiveness of universal rotavirus vaccination on rotavirus hospitalization was 48% (95%CI 39;55%) in children under five years of age.[64] Reduction of transmission by a strong decrease in rotavirus infections among vaccinated infants benefits neonates and infants below six weeks of age, who

are too young to receive rotavirus immunization according to current licensures.[65] Reducing nosocomial infections is particularly important for intensive care unit inpatients to prevent severe rotavirus disease course.[67] For instance, in premature infants perinatal acquired rotavirus infection can lead to adverse neurological outcomes and cerebral damage.[67]

Beneficial non-specific effects are increasingly attributed to live-attenuated vaccines. The mechanism is not yet fully explained, but via trained or heterologous immunity vaccines seem to provide protection against non-target diseases. For vaccination with Bacillus Calmette-Guerin, measles, polio and Vaccinia such effects have been reported.[68] For the, relatively new, live-attenuated rotavirus vaccines the potency of inducing beneficial non-specific effects has not yet been established. After rotavirus vaccination, all-cause hospital admissions were observed to decrease compared to no vaccination in one study.[69] In this paper, an association with type 1 diabetes was studied and as a secondary outcome all-cause non rotavirus hospitalization was assessed. This hospitalization rate was reduced by 31% in the 60 days after rotavirus vaccination compared to an unvaccinated control group, however misclassification of untested acute gastroenteritis hospitalizations might have biased the outcome.

Adverse events

The globally available vaccines are generally well tolerated and have mild reactogenicity. Abdominal cramps and looser stools are the most common adverse events, occurring in one in 10 vaccinated infants. These estimates are based primarily on research in healthy infants. For medical risk infants, studies with small populations describe similar adverse event rates.[50,51,56,70,71] For this reason, the general consensus is that the benefits of preventing rotavirus disease outweigh the vaccine side effects for all infants.

Rotavirus vaccination has a severe, but rare known adverse event; intussusception. Intussusception is defined as acute invagination of intestines into each other with acute occlusion as result. Clinical signs and symptoms include bloody stools, severe abdominal pain and/or cramps and, in later stages, abdominal shock. Prolonged intussusception can lead to intestinal necrosis and requires surgical resection of the affected bowel segment. If intussusception is recognized timely and treated with hydrostatic reposition, it can resolve without the need of surgical intervention. The cause and pathophysiology of intussusception are not fully understood, neither is the mechanism of vaccine induced intussusception. The incidence of spontaneous intussusception increases with age from three months onwards and peaks around six to eight months.[72] A previous vaccine, RotaShield, was introduced in the United States and withdrawn within one year in 1999, after the association with intussusception, in one in 10.000 vaccinated infants, was demonstrated. This association was not detected in phase III clinical trials.[73] The current available vaccines were therefore extensively investigated with regard to this severe adverse event.[72] Based on the large-scale studies, intussusception is estimated to occur in 1.1 to 2.7 per 100.000 rotavirus vaccinated infants, primarily in the first seven days following the first dose.[74]

To reduce the risk of intussusception after vaccination, the current rotavirus vaccines should be administered early in life, preferably between six and nine weeks of age and no later than sixteen weeks of age for the first dose.
Following vaccination with live-attenuated rotavirus, shedding of vaccine type in the feces frequently occurs. Studies have demonstrated that shedding develops in 50 to 95% of vaccinated infants.[75–77] In general, shedding of live-attenuated rotavirus vaccine strain is highest after the first dose. Theoretically there is a risk of transmission of vaccine type rotavirus and infection of other individuals. Disease due to a rotavirus vaccine type in healthy subjects has so far been described in one case report, which occurred after reassortment of two vaccine types present in the pentavalent vaccine RotaTeq.[78] A study among premature infants receiving rotavirus vaccination at discharge showed that shedding did not lead to symptomatic transmission to household members.[79] In addition, the concentration of vaccine-derived shedding virus is much lower than of the vaccine itself and hygiene measures should prevent the risk of transmission.[80] The current generation rotavirus vaccinations are not considered to be an environmental risk.

Implementation of rotavirus vaccination programs
Since 2009, the World Health Organization (WHO) advises the implementation of rotavirus vaccination in all national immunization programs.[81] In the Netherlands rotavirus vaccination is currently not part of the national immunization program, but has been under consideration for years. Vaccine decision making is organised as follows; the Dutch Health Council advises the ministry of Health about potential new vaccines for the national immunization program. The minister then decides on implementation of vaccinations. The national institute of Health and Environment executes the national immunization program. Vaccine counselling and delivery is organized via youth healthcare providers in well-baby clinics. In 2007 the Dutch Health Council stated the importance of rotavirus vaccination and that they would make an advise based on future cost-effectiveness analyses and more evidence on prevalent serotypes.[82,83] Nonetheless, in 2013 no advise was given as there was still discussion concerning cost-effectiveness and whether rotavirus disease would qualify as a noteworthy preventable disease given the generally mild course of disease.[84]
For infants with MRC, disease course can however be worse due to (complications of) rotavirus and five to six annual deaths were estimated in this particular group. Furthermore, the results of a Dutch cost-effectiveness analysis indicated that a selective rotavirus vaccination strategy (targeting these medical risk infants exclusively) would be cost-effective and could reduce mortality.[28] However, there were concerns about the feasibility of a selective strategy. In the Netherlands there was no experience with such a strategy and good quality effectiveness data for these high-risk infants were also lacking. For these reasons, in anticipation of a new Health Council advise, the RIVAR project started in 2014.

Targeted versus universal rotavirus vaccination

Targeting a selective population is uncommon for rotavirus vaccination, only Croatia and Spain have implemented a selective rotavirus vaccination program for infants with gestational age before 33 weeks, infants with congenital heart- or metabolic pathologies, chronic liver or kidney disease and/or severe neurological damage.[85,86] No evaluation data about their vaccination program are made available. For the Netherlands it was estimated that a selective rotavirus vaccination program for infants with MRC (i.e. premature infants, low birthweight or with congenital disorders) would prevent the majority of rotavirus related infant deaths.

To select and immunize eligible medical risk infants, however, a selective vaccination program would require a novel infrastructure, separate from the existing Dutch national immunization program, involving secondary and tertiary neonatal care centers. In addition, the cost-effective analysis results were based on a vaccine effectiveness of at least 88% against severe disease among all, including medical risk, infants, but data to support this were largely lacking.

RIVAR project

In 2014, the lack of experience with targeted vaccination and uncertainties about the vaccine effectiveness in infants with MRC were reasons to initiate the Risk-group Infant Vaccination Against Rotavirus (RIVAR) project. In thirteen hospitals over 15 locations it provided an opportunity for infants born premature, small for gestational age and/or with a severe congenital pathology to receive immunization against rotavirus as part of routine medical care.[87] Throughout the RIVAR project we used the human rotavirus vaccination (Rotarix).

Aims of this thesis

The RIVAR project was designed to answer two main questions. First, what is the vaccine effectiveness of rotavirus vaccination in this specific medical risk population? And second, is a selective rotavirus vaccination program in second and third line care feasible? As secondary aims vaccine safety and, potential non-specific effects of rotavirus vaccination are assessed. These questions are answered, after first estimating the community burden of disease due to rotavirus in this population of infants with MRC and updating the cost-effectiveness analysis.

Outline of this thesis

Chapter 2 contains a description of the acute gastroenteritis disease burden among infants with MRC in the Netherlands. Based on observational data of the unvaccinated infant cohort in the RIVAR project we were able to quantify the full spectrum of community burden of rotavirus disease; incidence, severity, health care attendance and societal impact.

From 2014 onwards a change in rotavirus epidemiology is seen in the Netherlands, therefore we updated the previous cost-effectiveness analysis for universal and targeted rotavirus vaccination strategies. In **chapter 3,** we describe a health-economic evaluation of rotavirus vaccination

in the new endemic state, including a risk-benefit analysis.

In **chapter 4**, we compare a vaccinated and unvaccinated cohort of medical risk infants followed until 18 months of age for the occurrence of acute gastroenteritis. Vaccine effectiveness against severe rotavirus acute gastroenteritis will be assessed using time-to-event analysis. Vaccine impact on rotavirus hospitalization, vaccine effectiveness against rotavirus gastroenteritis of any severity and against all-cause acute gastroenteritis will also be determined. In order to guide clinical recommendations subgroup analyses are performed.

Safety and tolerability of human rotavirus vaccination among infants with MRC will be reported in **chapter 5**, based on active surveillance for (serious) adverse events following childhood vaccinations including against rotavirus. It is known that premature infants in particular can experience more frequent and specific adverse events. The analysis therefore focuses primarily on premature infants. Infants with other medical risk conditions are analysed separately.

In **chapter 6** the potential non-specific effects of rotavirus vaccination will be assessed by measuring effects on acute respiratory tract infections, atopy and all-cause hospitalization (excluding hospitalizations for acute gastroenteritis) within the RIVAR cohort.

We evaluate the feasibility of this selective rotavirus vaccination program implemented in secondary and tertiary pediatric care in **chapter 7**. Feasibility will be evaluated based on achieved vaccination coverage, and by exploring views and experiences of involved health care providers and parents of medical risk infants.

In **chapter 8** we synthesize the key findings of the RIVAR project and relate them to existing evidence. Furthermore, recommendations for further perspectives in research and clinical practice are provided.

References

1. Kotloff KL. The Burden and Etiology of Diarrheal Illness in Developing Countries. ***Pediatr Clin North Am.*** 2017;64(4):799-814. doi:10.1016/j.pcl.2017.03.006
2. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. ***Emerg Infect Dis***. Published online 2003. doi:10.3201/eid0905.020562
3. Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. ***Emerg Infect Dis.*** Published online 2006. doi:10.3201/eid1202.050006
4. Verberk JDM, Bruijning-Verhagen P, de Melker HE. Rotavirus in the Netherlands. National Institute for Public Health and the Environment (RIVM); 2017. https://core.ac.uk/download/pdf/80557731.pdf
5. Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006–2014. ***Vaccine.*** 2015;33(18):2097-2107. doi:10.1016/j.vaccine.2015.03.016
6. Matthijnssens J, Ciarlet M, Heiman E, et al. Full Genome-Based Classification of Rotaviruses Reveals a Common Origin between Human Wa-Like and Porcine Rotavirus Strains and Human DS-1-Like and Bovine Rotavirus Strains. ***J Virol.*** Published online 2008. doi:10.1128/JVI.02257-07
7. Matthijnssens J, Ciarlet M, Rahman M, et al. Recommendations for the classification of group a rotaviruses using all 11 genomic RNA segments. ***Arch Virol.*** Published online 2008. doi:10.1007/s00705-008-0155-1
8. Rotavirus Classification Working Group. List of Accepted Genotypes. Published 2019. Accessed February 8, 2021. https://rega.kuleuven.be/cev/%0Aviralmetagenomics/virus-classification/rcwg.
9. Crawford SE, Ramani S, Tate JE, et al. Rotavirus infection. ***Nat Rev Dis Prim.*** Published online 2017. doi:10.1038/nrdp.2017.83
10. Ward RL, Bernstein DI, Young EC, Sherwood JR, Knowlton DR, Schiff GM. Human rotavirus studies in volunteers: Determination of infectious dose and serological response to infection. ***J Infect Dis.*** Published online 1986. doi:10.1093/infdis/154.5.871
11. Abad FX, Pinto RM, Bosch A. Survival of Enteric Viruses. ***Appl Environ Microbiol***. 1994;60(10):3704-3710. doi:10.1128/aem.01248-06
12. Butz AM, Fosarelli P, Dick J, Cusack T, Yolken R. Prevalence of Rotavirus on High-Risk Fomites in Day-Care Facilities. ***Pediatrics***. 1993;92(2). Accessed November 23, 2018. http://pediatrics.aappublications.org/content/92/2/202
13. Mughini-Gras L, Pijnacker R, Heusinkveld M, et al. Societal Burden and Correlates of Acute Gastroenteritis in Families with Preschool Children. ***Sci Rep.*** Published online 2016. doi:10.1038/srep22144
14. Yang T-A, Hou J-Y, Huang Y-C, Chen C-J. Genetic Susceptibility to Rotavirus Gastroenteritis and Vaccine Effectiveness in Taiwanese Children. ***Sci Rep.*** 2017;7(1):6412. doi:10.1038/s41598-017-06686-y
15. Rivero-Calle I, Gómez-Rial J, Martinón-Torres F. Systemic features of rotavirus infection. ***J Infect***. Published online 2016. doi:10.1016/j.jinf.2016.04.029
16. Desselberger U, Huppertz HI. Immune responses to rotavirus infection and vaccination and associated correlates of protection. ***J Infect Dis.*** 2011;15(203):188-195. doi:10.1093/infdis/jiq031
17. Cortese MM, Haber P. Epidemiology and Prevention of Vaccine-Preventable Diseases - Rotavirus. 12th ed. The Pink Book Home; 2012. https://www.cdc.gov/vaccines/pubs/pink-

book/rota.html
18. Anderson EJ, Weber SG. Rotavirus infection in adults. ***Lancet Infect Dis.*** 2004;4:91-99.
19. Doorduyn Y, van Pelt W, Havelaar AH. The burden of infectious intestinal disease (IID) in the community: a survey of self-reported IID in The Netherlands. ***Epidemiol Infect.*** 2012;140(07):1185-1192. doi:10.1017/S0950268811001099
20. Hahné S, Hooiveld M, Vennema H, et al. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. ***Euro Surveill.*** 2014;19.
21. Van Gaalen RD, Van De Kassteele J, Hahné SJM, Bruijning-Verhagen P, Wallinga J. Determinants of rotavirus transmission: a lag non-linear time series analysis. ***Epidemiology.*** 2017;28(4):503-513. doi:10.1097/EDE.0000000000000654
22. Nederlandse Werkgroep voor Klinische Virologie. Virologische weekstaten. Accessed in Feb 2020. https://www.rivm.nl/virologische-weekstaten/recente-virologie-uitslagen
23. Schurink-van t Klooster TM, de Melker HE. The National Immmunisation Programme in the Netherlands: Surveillance and developments. ***Natl Inst Public Heal Environ***. Published online 2019:102-125. doi:10.1007/978-94-6265-282-8_2
24. Schurink-van t Klooster TM, de Melker HE. The National Immunisation Programme in the Netherlands - Surveillance and developments in 2019-2020. ***Natl Inst Public Heal Environ.*** Published online 2020. doi:10.21945/RIVM-2020-0077
25. Hungerford D, Cunliffe NA. Coronavirus disease (COVID-19) – impact on vaccine preventable diseases. ***Eurosurveillance.*** 2020;25(18):1-2. doi:10.2807/1560-7917.ES.2020.25.18.2000756
26. Moerkamp AH., van Gool WA, Dutch Health Institute. Note of Dutch Health Council and Institute of Health by Advices on Vaccination against Rotavirus.; 2017.
27. Verhagen P, Moore D, Manges A, Quach C. Nosocomial rotavirus gastroenteritis in a Canadian paediatric hospital: Incidence, disease burden and patients affected. ***J Hosp Infect.*** Published online 2011. doi:10.1016/j.jhin.2011.04.020
28. Bruijning-Verhagen P, Mangen M-JJ, Felderhof M, et al. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med***. 2013;11(112). doi:10.1186/1741-7015-11-112
29. Chang H, Zhang L, Ge Y, et al. A Hospital-Based Case-Control Study of Diarrhea in Children in Shanghai. ***Pediatr Infect Dis J.*** 2017;36(11):1057-1063. doi:10.1097/INF.0000000000001562
30. Dennehy PH, Cortese MM, Bégué RE, et al. A case-control study to determine risk factors for hospitalization for rotavirus gastroenteritis in U.S. children. ***Pediatr Infect Dis J.*** 2006;25(12):1123-1131. doi:10.1097/01.inf.0000243777.01375.5b
31. Newman RD, Grupp-Phelan J, Shay DK, Davis RL. Perinatal Risk Factors for Infant Hospitalization With Viral Gastroenteritis***. Pediatrics.*** 2004;103(1):e3-e3. doi:10.1542/peds.103.1.e3
32. Walther FJ, Bruggeman C, Daniels-Bosman MSM. Rotavirus infections in high-risk neonates. ***J Hosp Infect.*** 1984;(5):438-443. doi:10.1016/0195-6701(84)90014-8
33. Bányai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. Lancet. 2018;392(10142):175-186. doi:10.1016/S0140-6736(18)31128-0
34. Bruijning-Verhagen P, Nipshagen MD, de Graaf H, Bonten MJM. Rotavirus disease course among immunocompromised patients; 5-year observations from a tertiary care medical centre. J Infect. Published online August 2017. doi:10.1016/j.jinf.2017.08.006

35. Quee FA, de Hoog MLA, Schuurman R, Bruijning-Verhagen P. Community burden and transmission of norovirus and rotavirus gastroenteritis: A prospective household study. ***Lancet Infect Dis.*** 2019;20(Provisionally Accepted):598-606.
36. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis***. N Engl J Med***. 2006;354(1):11-22. doi:10.1056/NEJMoa052434
37. Vesikari T, Matson DO, Dennehy P, et al. Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine. ***N Engl J Med.*** 2006;354(1):23-33. doi:10.1056/NEJMoa052664
38. Burke RM, Tate JE, Kirkwood CD, Steele AD, Parashar UD. Current and new rotavirus vaccines. ***Curr Opin Infect Di***s. 2019;32(5):435-444. doi:10.1097/QCO.0000000000000572
39. Xia S, Du J, Su J, et al. Efficacy, immunogenicity and safety of a trivalent live human-lamb reassortant rotavirus vaccine (LLR3) in healthy Chinese infants: A randomized, double-blind, placebo-controlled trial. ***Vaccine.*** 2020;(xxxx). doi:10.1016/j.vaccine.2020.04.038
40. Seo H, Duan Q, Zhang W. Vaccines against gastroenteritis, current progress and challenges. ***Gut Microbes.*** 2020;11(6):1486-1517. doi:10.1080/19490976.2020.1770666
41. Matthijnssens J, Zeller M, Heylen E, et al. Higher proportion of G2P[4] rotaviruses in vaccinated hospitalized cases compared with unvaccinated hospitalized cases, despite high vaccine effectiveness against heterotypic G2P[4] rotaviruses. ***Clin Microbiol Infect.*** 2014;20(10):O702-O710. doi:10.1111/1469-0691.12612
42. Justino MCA, Linhares AC, Lanzieri TM, et al. Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for severe G2P[4] rotavirus gastroenteritis in Belém, Brazil. ***Pediatr Infect Dis J.*** Published online 2011. doi:10.1097/INF.0b013e3182055cc2
43. Itzler R, Koch G, Matson DO, et al. Robustness of the healthcare utilization results from the Rotavirus Efficacy and Safety Trial (REST) evaluating the human-bovine (WC3) reassortant pentavalent rotavirus vaccine (RV5). ***BMC Pediatr.*** 2010;10. http://www.biomedcentral.com/1471-2431/10/42
44. Vesikari T, Karvonen A, Korhonen T, et al. Safety and immunogenicity of RIX4414 live attenuated human rotavirus vaccine in adults, toddlers and previously uninfected infants. ***Vaccine.*** 2004;22(21):2836-2842. doi:10.1016/j.vaccine.2004.01.044
45. Vesikari T, Itzler R, Karvonen A, et al. RotaTeq??, a pentavalent rotavirus vaccine: Efficacy and safety among infants in Europe. ***Vaccine***. Published online 2009. doi:10.1016/j.vaccine.2009.10.041
46. Salinas B, Schael IP, Linhares AC, et al. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: A randomized, placebo-controlled trial in Latin American infants. ***Pediatr Infect Dis J.*** Published online 2005. doi:10.1097/01.inf.0000178294.13954.a1
47. Madhi SA, Cunliffe NA, Steele D, et al. Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants. ***N Engl J Med.*** 2010;362(4):289-298. doi:10.1056/NEJMoa0904797
48. Chella Sindhu KN, Babji S, Ganesan SK. Impact of rotavirus vaccines in low and middle-income countries. Curr ***Opin Infect Dis.*** Published online 2017. doi:10.1097/QCO.0000000000000397
49. Clarke E, Desselberger U. Correlates of protection against human rotavirus disease and the factors influencing protection in low-income settings. ***Mucosal Immunol.*** Published online 2015. doi:10.1038/mi.2014.114
50. Omenaca F, Sarlangue J, Szenborn L, et al. Safety, Reactogenicity and Immunogenicity of the Human Rotavirus Vaccine in Preterm European Infants: A Randomized Phase IIIb Study. ***Pediatr Infect Dis J.*** 2012;31(5). doi:10.1097/INF.0b013e3182490a2c
51. Goveia MG, Rodriguez ZM, Dallas MJ, et al. Safety and Efficacy of the Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine in Healthy Premature Infants. **Pediatr Infect Dis J.**

2007;26(12):1099-1104. doi:10.1097/INF.0b013e31814521cb
52. Burnett E, Parashar UD, Tate JE. Real-world effectiveness of rotavirus vaccines, 2006-19: a literature review and meta-analysis. **Lancet Glob Heal.** 2020;8(9):e1195-e1202. doi:10.1016/S2214-109X(20)30262-X
53. Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: Vaccines in use. **Cochrane Database Syst Rev.** 2019;2019(3). doi:10.1002/14651858.CD008521.pub4
54. Hungerford D, Smith K, Tucker A, et al. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. **BMC Infect Dis.** 2017;17. doi:10.1186/s12879-017-2613-4
55. Javid PJ, Sanchez SE, Jacob S, McNeal MM, Horslen SP, Englund JA. The safety and immunogenicity of rotavirus vaccination in infants with intestinal failure. **J Pediatric Infect Dis Soc**. Published online 2014. doi:10.1093/jpids/pit060
56. Fang AYW, Tingay DG. Early observations in the use of oral rotavirus vaccination in infants with functional short gut syndrome. **J Paediatr Child Health.** 2012;48(6):512-516. doi:10.1111/j.1440-1754.2011.02227.x
57. Public Health England. The Rotavirus Vaccination Programme: Information for Healthcare Professionals.; 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/770826/Rotavirus_vaccination_programme__information_document_Nov_2018.pdf
58. Department AGH. Australian Immunisation Handbook - Rotavirus. 20 September 2019. Published 2021. Accessed February 5, 2021. https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/rotavirus
59. Leino T, Ollgren J, Salo H, Tiihonen P, Kilpi T. First year experience of rotavirus immunisation programme in Finland. **Vaccine**. 2012;31(1):176-182. doi:10.1016/j.vaccine.2012.10.068
60. Hemming M, Räsänen S, Huhti L, Paloniemi M, Salminen M, Vesikari T. Major reduction of rotavirus, but not norovirus, gastroenteritis in children seen in hospital after the introduction of RotaTeq vaccine into the National Immunization Programme in Finland. **Eur J Pediatr.** 2013;172(6):739-746. doi:10.1007/s00431-013-1945-3
61. Marlow R, Muir P, Vipond B, Lyttle M, Trotter C, Finn A. Assessing the impacts of the first year of rotavirus vaccination in the United Kingdom. **Eurosurveillance.** 2015;20(48):1-7. doi:10.2807/1560-7917.ES.2015.20.48.30077
62. Raes M, Strens D, Vergison A, Verghote M, Standaert B. Reduction in pediatric rotavirus-related hospitalizations after universal rotavirus vaccination in belgium. **Pediatr Infect Dis J**. 2011;30(7):120-125. doi:10.1097/INF.0b013e318214b811
63. John TJ, Samuel R. Herd immunity and herd effect: New insights and definitions. **Eur J Epidemiol.** 2000;16(7):601-606. doi:10.1023/A:1007626510002
64. Rosettie KL, Vos T, Mokdad AH, et al. Indirect Rotavirus Vaccine Effectiveness for the Prevention of Rotavirus Hospitalization: A Systematic Review and Meta-Analysis. **Am J Trop Med Hyg.** Published online 2017. doi:10.4269/ajtmh.17-0705
65. Prelog M, Gorth P, Zwazl I, et al. Universal mass vaccination against rotavirus: Indirect effects on rotavirus infections in neonates and unvaccinated young infants not eligible for vaccination. **J Infect Dis.** Published online 2016. doi:10.1093/infdis/jiw186
66. Valentini D, Ianiro G, Di Bartolo I, et al. Hospital-acquired Rotavirus and Norovirus Acute Gastroenteritis in a Pediatric Unit, in 2014-2015; **J Med Virol**. Published online 2017. doi:10.1002/jmv.24866
67. de Vries LS. Viral Infections and the Neonatal Brain. Semin **Pediatr Neurol.** 2019;32:100769. doi:10.1016/j.spen.2019.08.005

68. de Bree LCJ, Koeken VACM, Joosten LAB, et al. Non-specific effects of vaccines: Current evidence and potential implications. **Semin Immunol.** 2018;39(April):35-43. doi:10.1016/j.smim.2018.06.002
69. Rogers MAM, Basu T, Kim C. Lower Incidence Rate of Type 1 Diabetes after Receipt of the Rotavirus Vaccine in the United States, 2001–2017. **Sci Rep**. 2019;9(1):7727. doi:10.1038/s41598-019-44193-4
70. Monk HM, Motsney AJ, Wade KC. Safety of Rotavirus Vaccine in the NICU. **Pediatrics**. 2014;133(6):e1555-e1560. doi:10.1542/peds.2013-3504
71. Van der Wielen M, Van Damme P. Pentavalent human-bovine (WC3) reassortant rotavirus vaccine in special populations: A review of data from the Rotavirus Efficacy and Safety Trial. **Eur J Clin Microbiol Infect Dis.** 2008;27(7):495-501. doi:10.1007/s10096-008-0479-5
72. Bines JE, Patel M, Parashar U. Assessment of Postlicensure Safety of Rotavirus Vaccines, with Emphasis on Intussusception. **J Infect Dis.** 2009;200. doi:10.1086/605051
73. Kassim P, Eslick GD. Risk of intussusception following rotavirus vaccination: An evidence based meta-analysis of cohort and case-control studies. **Vaccine**. 2017;35(33):4276-4286. doi:10.1016/j.vaccine.2017.05.064
74. Koch J, Harder T, von Kries R, Wichmann O. Risk of Intussusception After Rotavirus Vaccination. **Dtsch Aerzteblatt** Online. 2017;114:255-262. doi:10.3238/arztebl.2017.0255
75. Payne DC, Edwards KM, Bowen MD, et al. Sibling Transmission of Vaccine-Derived Rotavirus (RotaTeq) Associated With Rotavirus Gastroenteritis. **Pediatrics**. 2010;125(2). Accessed August 9, 2017. http://pediatrics.aappublications.org/content/125/2/e438
76. Anderson EJ. Rotavirus vaccines: viral shedding and risk of transmission. **Lancet Infect Dis.** 2008;8(10):642-649. doi:10.1016/S1473-3099(08)70231-7
77. Kaplon J, Cros G, Ambert-Balay K, et al. Rotavirus Vaccine Virus Shedding, Viremia an Clearance in Infants with Severe Combined Immune Deficiency. **Pediatr Infect Dis J**. 2015;34(3):326-328.
78. Sakon N, Miyamoto R, Komano J, Pediatr EJ. An infant with acute gastroenteritis caused by a secondary infection with a Rotarix-derived strain**. Eur J Pediatr.** Published online 2017. doi:10.1007/s00431-017-2963-3
79. Smith CK, McNeal MM, Meyer NR, Haase S, Dekker CL. Rotavirus shedding in premature infants following first immunization. **Vaccine.** 2011;29:8141-8146. doi:10.1016/j.vaccine.2011.08.028
80. Ladhani SN, Ramsay ME. Timely immunisation of premature infants against rotavirus in the neonatal intensive care unit. **Arch Dis Child Fetal Neonatal Ed.** 2014;99(6):F445-F447. doi:10.1136/archdischild-2013-305744
81. Weekly epidemiological record Relevé épidémiologique hebdomadaire. 2018;(1):1-8.
82. Toenders WGM. CFH-Rapport Beoordeling Rotavirus RIX4414 (Rotarix). Vol 3.; 2007.
83. Gezondheidsraad (Health Council of the Netherlands). De Toekomst van Het Rijksvaccinatieprogramma: Naar Een Programma Voor Alle Leeftijden.; 2007.
84. Gezondheidsraad (Health Council of the Netherlands). Het individuele, collectieve en publieke belang van vaccinatie. Published online 2013:1-86.
85. Tešović G. Childhood vaccinations in Croatia. **Period Biol.** 2012;114(2):149-166.
86. ECDC. Rotavirus infection: Recommended vaccination schedule. ECDC. Published 2021. Accessed February 24, 2021. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=32&SelectedCountryIdByDisease=-1
87. Bruijning-Verhagen PCJ. RIVAR study protocol. Published 2014. Accessed November 17, 2020. https://www.trialregister.nl/trial/5213

Chapter 2

Acute gastroenteritis disease burden among infants with medical risk conditions in the Netherlands

Josephine A.P. van Dongen, Elsbeth D.M. Rouers, Rob Schuurman, Marc J.M. Bonten, Patricia C.J. Bruijning-Verhagen. On behalf of the RIVAR study group.

The Pediatric Infectious Disease Journal, 2021

Abstract

Background

Infants with medical risk conditions are vulnerable to childhood infections including acute gastroenteritis (AGE). To guide prevention programs, we quantified AGE incidence, severity, and virus prevalence among medical risk infants in the Netherlands.

Methods

This prospective cohort-study was part of the RIVAR-project recruiting infants with prematurity, low birth weight or severe congenital conditions in 13 hospitals. Follow up included 18 monthly health questionnaires detailing AGE symptoms and healthcare usage. Parents were also instructed to notify when an infant developed AGE, to collect a stool sample and complete a daily severity score (MVS). Stool samples were analyzed by realtime PCR for rota- noro-, adeno- and astrovirus.

Results

Between November 2014 and October 2017, 631 infants participated during 9125 person-months of observation. In total 559 episodes were identified. The mean AGE IR was 73.5 per 100 person-years (PY) (95%CI: 67.6 - 79.9) and increased with age (IR: 48.3 (39.8-58.3) vs. 80.2 (73.0-88.1)/100PY for ages 1-5 vs. 6-18 months, respectively). Healthcare was attended for 38.1% (213/559) and 26.8% (68/254) were classified as severe based on the MVS. Stool samples were obtained from 254 AGE episodes. Norovirus was identified in 65 (25.6%) and rotavirus in 44 (17.7%). Adeno- and astrovirus together accounted for 8.3% (N=21). Severe AGE occurred most frequently in rotavirus positive episodes.

Conclusion

The observed AGE incidence, severity and healthcare usage among medical risk infants confirms substantial disease burden. Norovirus and rotavirus are the dominant pathogens and severe episodes occurred most frequently in children with rotavirus infection. AGE prevention in medical risk infants should be prioritized.

Introduction

Acute gastroenteritis (AGE) is a common infection with the highest incidence in young children.[1,2] The large majority of childhood AGE episodes are caused by enteric viruses, with rotavirus and norovirus being the dominant pathogens[1,3]. Premature birth (<36 weeks of gestation), low birthweight (<2500 grams) and/or presence of a congenital disorder are known risk factors for severe and complicated AGE, which is reflected in increased hospitalization rates, prolonged hospital stay and mortality compared to healthy infants[4–8].

As AGE is mainly a self-limiting disease, the majority of episodes occur outside of the hospital setting[9]. To quantify the disease burden in the community, several observational studies in Europe have evaluated AGE incidence and healthcare attendance among healthy children, adults or elderly and estimated the contribution of various enteric pathogens[10,11]. There is reason to assume that the community AGE burden is increased among infants with medical risk conditions, similar to what is observed for AGE hospitalizations. However, no studies have specifically addressed community AGE among medical risk infants. Such data on specific risk-groups are valuable to prioritize target-groups for preventive interventions and assess the cost-effectiveness of various vaccination strategies against rotavirus and, possibly in the future, norovirus[12,13].

Our aim is to quantify the all-cause AGE and virus specific community burden of disease in medical risk infants in the Netherlands, and to identify infants most at risk of severe disease.

Materials and methods

Study design

The Netherlands has not yet implemented rotavirus vaccination in the infant national immunization program (NIP). Uptake of rotavirus vaccine in the private market is less than one percent[14.]

This prospective cohort study is part of the Risk group Infant Vaccination Against Rotavirus (RIVAR) project. In brief, RIVAR pilots the implementation of a selective rotavirus vaccination program for medical risk infants organized in secondary pediatric care. Thirteen Dutch hospitals that host a Neonatal Intensive Care Unit or a neonatal post High/Intensive Care ward participated in the pilot and implemented rotavirus vaccination between May 2016 and October 2017. Implementation was combined with a before-after cohort study. All cohort participants were followed for the occurrence of AGE from enrollment between 6-14 weeks until 18 months of age. The current study uses data from the pre-implementation cohort only, recruitment ran from November 2014 to October 2017, when rotavirus vaccination was not yet routinely available in the hospitals.

Eligibility

All infants hospitalized in a participating hospital and aged less than 14 weeks were screened for eligibility, which includes infants with 1) one of the following diagnoses (i.e. medical risk conditions): preterm birth (gestational age < 36 weeks; low birthweight < 2500 grams; presence of a severe congenital disorder (**eFigure 1**), and 2) receiving care in a participating hospital between 6-14 weeks of postnatal age. Parents of eligible infants were approached for participation in the cohort study, and asked for informed consent (**eFigure 2**).

Data collection

For all eligible children, irrespective of cohort participation, we collected the following data: date of birth, gender, gestational age, birthweight, presence of congenital disorder and any contra-indications for rotavirus vaccination[15]. This allowed us to evaluate differences between participants and non-participants. Medical risk conditions were classified into; premature, SGA (based on the 10th percentile cut off for Dutch boys and girls[16,17]) and congenital disorder. Low, intermediate and high socioeconomic status (SES) was based on highest family educational level[18]. Ethnicity was defined by parental origin and divided into three categories, European, non-European and mixed[19.] Single parent households are combined in either of first two categories.

A baseline parental questionnaire detailed SES, ethnicity, household composition, pregnancy and labor, and was filled upon enrollment. Thereafter, parents received a monthly questionnaire until the end of follow up, at 18 months of age (**eFigure 2**). The monthly questionnaire contained the following items: occurrence of gastrointestinal and respiratory symptoms during the previous month, any doctor's visit or hospitalization, administration of vaccinations and occurrence of adverse events, type of feeding and daycare attendance.

For all cohort participants, medical charts were reviewed for additional data on hospitalizations, diagnoses, medication and other supportive therapy at 6 weeks, 5 months and 18 months of age.

Follow up for AGE

AGE was defined as acute watery or looser than normal stools, more than three times within in a 24 hour period, and/or acute forceful vomiting[20]. At enrollment, parents received verbal instructions concerning these AGE criteria, and on a plasticized instruction card. Parents of participants were instructed to instantly report if their child developed symptoms of AGE during the follow-up period. For each AGE episode, parents kept a standardized symptom 7-day diary, based on the Modified Vesikari Severity (MVS) Scale[21,22] (**eTable 1**). Parents were requested to collect a fecal sample, as soon as possible after AGE onset. Fecal samples were packed in biosafety envelopes and send by regular mail to the central laboratory for PCR testing (see supplement). On day 14 after AGE onset, an additional questionnaire was filled

by parents detailing healthcare usage, medication, total days with symptoms, lost parental work-days and daycare absenteeism. All monthly questionnaires and medical records were additionally checked for AGE symptoms that had not been reported to the study team. And identified as AGE episode if they met the AGE definition and no other cause for symptoms was provided. In this way, we were able to retrieve additional AGE episodes that had not been actively reported by parents. However these episodes were incomplete on pathogen and MVS severity information.

Outcomes

The primary aim was to quantify the AGE burden of disease in rotavirus unvaccinated medical risk infants until 18 months of age. This was based on 1) the incidence rate (IR) of all-cause and virus specific AGE, 2) the AGE related healthcare usage and, 3) the severity of AGE episodes, scored by the MVS scale (more detailed in supplement).

A secondary aim of our study was the societal burden, expressed as daycare absenteeism and parental work loss as well as secondary cases that occurred within the household. For these analyses, we used data from the 14-day AGE questionnaire.

To evaluate possible risk factors for severe AGE occurrence, we compared patient and household characteristics between infants with at least one AGE episode to those without any AGE during follow-up.

Statistical analysis

Descriptive statistics were performed using Chi-square or Fisher's Exact tests for categorical data, t-tests for normally distributed continuous data and non-parametric test (Mann-Whitney U) for non-normally distributed continuous data. A p-value < 0.05 was considered statistically significant.

The AGE IRs were calculated by dividing all AGE episodes by the total persontime of observation and corresponding 95% confidence intervals (95% CI) were computed using the Fisher's exact method. For virus specific IRs, estimates were adjusted for the proportion of AGE episodes for which no fecal sample was obtained. We used multiple imputation, by chained equations, for missing virus status of episodes without a stool sample collected (see supplement for specifications).

To further explore potential risk factors for severe AGE, we modeled the association between time to first severe AGE with baseline factors and AGE occurrence in seasonal months of known highest circulation of norovirus and rotavirus in the Netherlands (October – April)[23]. We used a Cox regression model with age as time axis. All potential covariates were tested univariate; those with a significant effect were used for the multivariate model. Model selection

was based on likelihood ratio test (LRT). Proportional hazard assumption was checked using the Schoenfelds' residuals. We applied multiple imputation to account for missings, as described in supplement.

As statistical software we used: SPSS IBM version 25, http://openepi.com and RStudio version 1.1.456.

Ethical approval

This study was reviewed by the Institutional Review Board of the University Medical Center Utrecht, which has declared it does not involve the Medical Research Involving Human Subjects Act.

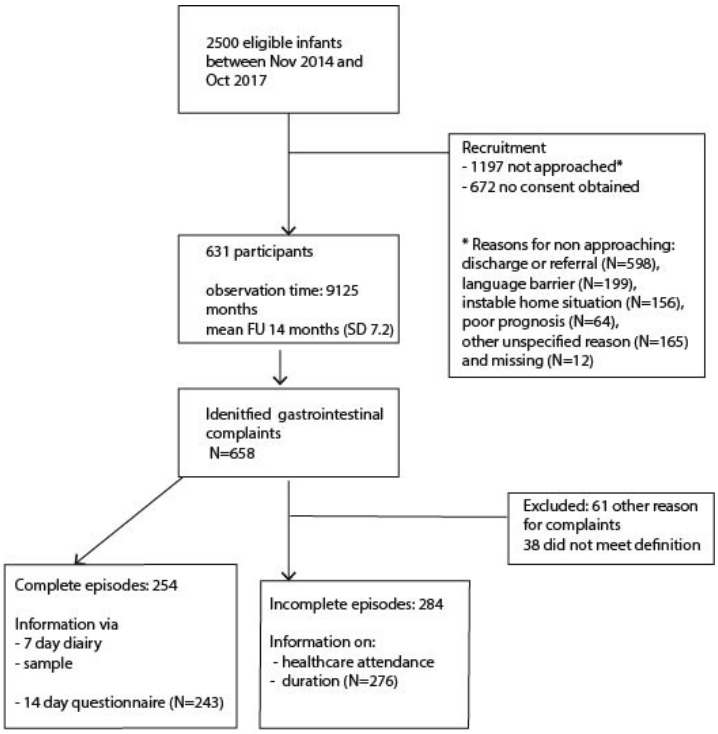


Figure 1. Study flowchart. Abbreviations: FU = follow up, SD = standard deviation, N = number.

Results

Between November 2014 and October 2017, 2500 medical risk infants met the RIVAR inclusion criteria across 13 participating hospitals (**Figure 1**). Mean gestational age was 33 weeks (SD ±4 weeks), 475 (19%) had a congenital disorder (cardiovascular 129, pulmonal 21, central nerve system 49, chromosomal 90, perinatal 70 and 199 other disorders) and 684 infants (27%) were small for gestational age.

Descriptive statistics

In total, 631 parents of medical risk infants consented to participate. Baseline characteristics of participants and non-participants were comparable (**eTable 2**). Follow up until 18 months of age was complete for 421 (67%) infants. Reasons for incomplete follow up were; dropped out (n=50), deceased (n=3) or loss to follow up (n=157) before 18 months of age. During participant follow-up, 559 AGE episodes occurred. In total 275 episodes were reported by parents, complete information was available for 254 of those, and an additional 284 AGE episodes were retrieved from monthly questionnaires and medical records (**Figure 1**).

Pathogen distribution

Of 254 AGE episodes a fecal sample was collected within 14 days of symptom onset. Of these 65 (25.6%) tested positive for norovirus and 44 (17.7%) for rotavirus. Co-infections for norovirus and rotavirus were present in four AGE episodes, 21 samples were adenovirus- and/or astrovirus positive (8.3%). AGE episodes with a stool sample collected had a longer duration but less frequent healthcare attendance compared to those without a stool sample (**eTable 3**).

AGE disease burden

The IR for all-cause AGE up to 18 months of age was 73.5 per 100 PY, IR increased with older age from 48.3 per 100 PY <6 months of age to 80.2 per 100 PY for infants 6-18 months of age (**Table 1**). No differences were observed in IRs between subgroups of medical risk infants. The AGE IR demonstrated a clear seasonal pattern with highest rates in months January to April and October to December, **eFigure 3**. Comparing the seasonal months to out-of-season months, the mean incidence was higher during seasonal months. After multiple imputation, the estimated IR for norovirus- and rotavirus positive episodes was not significantly different.

Table 1. Community AGE incidence for medical risk infants

AGE	Subgroup	IR (per 100 PY)	95% CI	p-value
All cause		73.5	67.6 - 79.9	-
Age	< 6 months	48.3	39.8 – 58.3	-
	6-12 months	85.7	75.3 – 97.1	0.00
	> 12 months	79.3	68.4 – 90.1	0.43
Medical risk type	Preterm (GA < 36 weeks)	75.9	68.0 – 84.6	-
	Preterm and SGA	64.0	52.4 – 77.2	0.13
	Presence of congenital disorder	66.9	51.5 – 86.8	0.44
Season	Jan-Oct	94.5	85.6 – 104.1	-
	May-Sept	45.0	38.0 -53.0	0.00
Pathogen#	Rotavirus	14.6	12.1 – 17.1	-
	Norovirus	14.2	11.7 – 16.7	0.89
	Pan negative	31.7	28.6 – 34.8	0.00

Estimated with correction for pathogen under detection based on multiple imputation for missing AGE samples. Abbreviations: AGE = acute gastroenteritis, IR = incidence rate, PY = person years, CI = confidence interval, GA = gestational age, SGA = small for gestational age, Jan = January, Dec = December.

Healthcare was attended for 213 out of 559 of AGE episodes (38.1%, 95% CI 34 - 43%), 42 infants were admitted to the hospital for their AGE episode (7.5%). The proportion of episodes requiring healthcare was twice as high for rotavirus- and norovirus positive episodes compared to pan negative episodes, p-value 0.00 (see **Table 2**). Nosocomial infections (based on acquiring infection during hospital stay) occurred in six patients.

Table 2. Severity and social impact per pathogen

AGE episodes	Severe	MVS	Dura-tion	Health care attended	Hospitalization	Parental work loss	Daycare absenteeism	Transsion within household	Secondary household member(s)
All cause	68 (27%)	8 (3-13)	5 (1-9)	213 (38%)	42 (7.5%)	73 (30%)	67 (28%)	107 (44%)	2 (1-3)
Pan negative	26 (22%)	8 (4-12)	5 (2-8)	20 (18%)	4 (4%)	9 (7%)	15 (13%)	30 (26%)	2 (1-3)
Norovirus positive	17 (27%)	8 (3-13)	5 (2-8)	23 (40%)	4 (7%)	25 (40%)	19 (29%)	39 (67%)	2 (1-3)
Rotavirus positive	18 (43%)	10 (6-14)	5 (3-7)	17 (42%)	2 (10%)	17 (38%)	20 (44%)	27 (68%)	2 (1-3)
Adenovirus positive	8 (32%)	9 (3-15)	5 (0-10)	12 (48%)	1 (4%)	9 (36%)	10 (40%)	11 (44%)	1 (0-2)
Astrovirus positive	6 (40%)	10 (5-15)	7 (3-11)	4 (27%)	0	5 (33%)	6 (40%)	8 (53%)	1 (1-1)

Denominator changes for all variables and all groups of AGE episodes, because of missing data. Percentages are given for episodes with complete information. For continuous variables medians with interquartile ranges (IQR) are shown. Abbreviations: MVS=Modified Vesikari Score.

Of 254 AGE episodes with a MVS-score available, 68 were classified as severe (26.8%, 95% CI 22 - 33%). Rotavirus- and norovirus positive infections were severe in 18 out of 43 (41.9%) and 17 out of 65 (26.2%) of cases, respectively. Differences for infections per pathogen are listed in **Table 2**; this information was only available for complete episodes.

Secondary outcomes

Any paid parental work loss due to illness of the infant was reported in 73 out of 244 AGE episodes, with a median duration of 1.75 days (interquartile range (IQR) 0.75-2.75). Daycare absenteeism was reported for 67 out of 236 AGE episodes , with a median of 1.5 days (IQR 0.5-2.5). In 32.8% - 49.2% of AGE episodes, families were unable to proceed with regular

activities, like grocery shopping, cleaning or leisure activities (**Table 2**).

Risk factors for (severe) AGE

312 participants (49%) had at least one AGE episode during follow up and multiple episodes (varying from two-seven) were reported in 88 infants (14%), differences in their characteristics are shown in **eTable 4.** The most important differences between the groups were more frequent daycare attendance and higher family education among infants with at least one AGE episode. Infants with severe AGE did not differ from those with non-severe AGE.

Mean age for first severe AGE episode was 8.3 months (95% CI 7.2-9.5) and 14.2 months (95% CI 13.5-14.8) for non-severe AGE. The multivariate Cox regression analysis resulted in a final model with only seasonal months and daycare attendance statistically significantly associated with severity (**Table 3**).

Table 3. Risk factors associated with time to first severe AGE episode

Risk factor	Univariate HR	Multivariate HR*	95% CI	Adjusted HR after MI*	95% CI
Seasonal months (Oct-April)	27.01	27.12	(10.60-69.39)	27.24	(12.96-57.26)
Sibling	0.77	0.42	(0.17-1.02)	0.76	(0.41-1.41)
Breastfed	2.55	1.28	(0.46-3.56)	2.25	(1.18-4.30)
Born in seasonal months	0.92	0.62	(0.28-1.42)	0.82	(0.43-1.48)
Daycare	5.72	4.05	(1.35-12.17)	1.24	(0.43-3.55)

Abbreviations: HR = hazard ratio, CI = confidence interval, MI = multiple imputation, RV = rotavirus, Jan = January. * Adjusted for seasonal months, siblings, breastfed, born in seasonal months and daycare attendance.

Because of potential non-random missing information of risk factors, we compared complete cases versus those with at least one missing covariate, and found that complete cases were more frequently older at AGE episode or when censored. They less often had an older sibling in their household, attended daycare from six months onwards and had an episode in season (**eTable 5**). The estimates after multiple imputation account for the missing not at random.

Discussion

In this prospective cohort study we quantified the AGE disease burden among infants with medical risk conditions on several items; incidence, severity, healthcare attendance and family impact. For community AGE we found an IR of 73.5 per 100 PY, translating to at least one AGE episode in the first 18 months of life in medical risk infants. One in three AGE episodes required a doctor visit and one in thirteen required hospitalization. One third of episodes were classified as severe. In addition to the AGE disease burden incurred by the infant, we observed substantial societal burden. In 30% parents and ill infants were absent from paid work or daycare, respectively, in 40% families couldn't fulfill their normal activities. Rotavirus and norovirus accounted for one third of all AGE episodes and rotavirus positive AGE was associated with more severe disease. In line with this, AGE episodes occurring during seasonally active months for rotavirus and norovirus were associated with more severe disease.

We hypothesized that the burden of disease of AGE in medical risk infants is higher compared to healthy infants, because it is suggested that severe childhood infections are more prevalent[24,25] and harm these infants more [26]. However, the overall AGE IR found in our study is in line with reported IRs for healthy infant populations in the Netherlands. De Wit and colleagues found an IR of 74 per 100 PY in a population based setting for 0-1 year olds, and of 90 per 100 PY for 1-4 year olds[27]. Another Dutch community study (RotaFam) even found a three times higher all-cause AGE IR (301/100 PY in children up to two years of age)[28], but this study was conducted during the high epidemic months only (January-May). In our study, the incidence of AGE was also twice higher during the seasonal months compared to the off-season months. Furthermore, the RotaFam study used an interactive mobile application to monitor real-time AGE symptoms, which may have yielded higher case-ascertainment than in our study which relied on active reporting by parents and recording on monthly questionnaires. These IR comparisons suggest that medical risk infants do not have higher IRs compared to healthy infants.

Compared to studies among healthy infants, we found that AGE healthcare attendance and severity appear to be increased among medical risk infants. In our study, 51% of infants required healthcare related to AGE, whereas this proportion was only 18% in a Dutch community study among 1523 healthy infants[10]. Moreover, 7.5% of AGE episodes among medical risk infants required hospitalization in our study, compared to 3.4% and 1.6% respectively, in British and Dutch studies among healthy infants with AGE[10,29]. Similarly, our findings suggest increased severity and prolonged duration of symptoms among medical risk infants with 27% of episodes classifying as severe compared to 8% in healthy infants and a median symptom duration of 5 days versus 3-4 days in healthy infants[28,30,31]. These findings are in contrast with the statement recently published by the European Academy of Pediatrics[32], suggesting no accountable evidence on increased severity in specific risk groups. Based on our study we conclude that the disease burden of AGE among medical risk infants is substantially increased relative to healthy infants.

In the absence of therapeutic interventions for AGE, prevention is the approach to decrease the burden of disease in this vulnerable patient population. In the Netherlands a targeted rotavirus vaccine program would be cost-effective as suggested by two previous studies[5,14]. However due to changing epidemiology[33,34] the effectiveness of a selected vaccine strategy might be modified. Other European countries have implemented rotavirus vaccination in their national immunization program, thereby creating herd immunity (indirect protection)[35,36.] Our study results suggest that these infants with medical risk conditions would benefit from AGE prevention.

As strengths, this study covers the full burden of disease by combining incidence rate, severity, healthcare attendance and family impact of AGE in infants with medical risk conditions. Furthermore, this vulnerable patient population is generally not studied. Therefore this study provides unique information on community disease burden of AGE. By comparing participants and non-participants, it appeared that the study population is representable for the group of infants with medical risk conditions in the Netherlands.

This study has several limitations. First, data on pathogen and MVS scale were missing for about half of the AGE episodes, because parents failed to take a stool sample and complete the diaries. To reduce bias, we used multiple imputation in calculating pathogen specific IRs and in the analysis on risk factors for severe AGE. While this method accounts non-random missing data and thereby adjusts for bias by complete case analysis, it also has limitations by assuming (too much) variance in outcome variables based on the imputation procedure[37,38.] However, with multiple imputation the sample size is maintained and it yields unbiased standard errors[37,38]. Proportion of missing data is not a guide for using multiple imputation, as with correct specified imputation procedures estimates obtained will be less biased than by complete case analysis[39].

Furthermore we checked for differential missingness and showed the results of complete case and imputed data analyses together. The high rate of missing data in community studies on AGE could be overcome by using modern interactive technologies to monitor participants[28]. In the RotaFam study, symptom data was in 97% complete and stool samples were obtained from 87% of AGE episodes, compared to 45% in our study.

Secondly, in our study 33% of participants were lost to follow up before 18 months of age. Possibly, because parents taking care of a child with special medical needs were overburdened and thereby limited in their capacity to adhere to study procedures, illustrated by the median days of hospitalization (35 days, range 3-439). Still, the mean follow up was 14 months. In addition, the survival analysis is used to consider loss to follow up and observation time[40].

In conclusion, the observed AGE incidence, severity and healthcare usage among medical risk infants confirms substantial disease burden with increased severity and healthcare usage compared to what has been observed in healthy infants. Norovirus and rotavirus are the dominant pathogens and rotavirus is most frequently severe. AGE prevention in medical risk infants should be prioritized.

Acknowledgements

We would like to thank the all RIVAR participants and their parents or guardians, the study team, all principal investigators and research nurses of the different study sites for their contribution to this project.

The RIVAR study team: Zwart L.M.; Tims-Polderman C.; Beurden, van M.; Bont, L.J. ; Norbruis O.J.; Hemels, M.; Well, van G.T.J.; Vlieger, Arine; Sluijs, van der J.; Stas, H.G.; Tramper-Stranders, G.; Kleinlugtenbeld, E.A.; Kempen, van A.A.M.W.; Wessels, M.; Rossum, van M. ; Dassel, C.; Houten, van M.; Pajkrt, D.

The RIVAR study is funded by ZonMw, Innovatiefonds Zorgverzekeraars, GlaxoSmithKline and UMC Utrecht.

References

1. Svraka S, Duizer E, Vennema H, et al. Etiological role of viruses in outbreaks of acute gastroenteritis in The Netherlands from 1994 through 2005. ***J Clin Microbiol.*** 2007;45(5):1389-1394. doi:10.1128/JCM.02305-06

2. De Wit MAS, Koopmans MPG, Kortbeek LM, Van Leeuwen NJ, Bartelds AIM, Van Duynhoven YTHP. Etiology of gastroenteritis in sentinel general practices in the Netherlands. ***CID.*** 2001;7(1):280-288. doi:10.3201/eid0701.010113

3. Hartman S, Brown E, Loomis E, Russell HA. Gastroenteritis in Children. ***Am Fam Physician.*** 2019;99(3):159-165. Accessed February 4, 2019. https://www.aafp.org/afp/2019/0201/p159.html#.XFgt3nAuZnM.mendeley

4. Verhagen P, Moore D, Manges A, Quach C. Nosocomial rotavirus gastroenteritis in a Canadian paediatric hospital: Incidence, disease burden and patients affected. ***J Hosp Infect.*** Published online 2011. doi:10.1016/j.jhin.2011.04.020

5. Bruijning-Verhagen P, Mangen M-JJ, Felderhof M, et al. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med***. 2013;11. doi:10.1186/1741-7015-11-112

6. Newman RD, Grupp-Phelan J, Shay DK, Davis RL. Perinatal Risk Factors for Infant Hospitalization With Viral Gastroenteritis. ***Pediatrics***. 2004;103(1):e3-e3. doi:10.1542/peds.103.1.e3

7. Chang HGH, Glass RI, Smith PF, Cicirello HG, Holman RC, Morse DL. Disease burden and risk factors for hospitalizations associated with rotavirus infection among children in New York State, 1989 through 2000. ***Pediatr Infect Dis J.*** 2003;22(9):808-814. doi:10.1097/01.inf.0000086404.31634.04

8. Dennehy PH, Cortese MM, Bégué RE, et al. A case-control study to determine risk factors for hospitalization for rotavirus gastroenteritis in U.S. children. ***Pediatr Infect Dis J.*** 2006;25(12):1123-1131. doi:10.1097/01.inf.0000243777.01375.5b

9. Bányai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. ***Lancet.*** 2018;392(10142):175-186. doi:10.1016/S0140-6736(18)31128-0

10. Mughini-Gras L, Pijnacker R, Heusinkveld M, et al. Societal Burden and Correlates of Acute Gastroenteritis in Families with Preschool Children. ***Sci Rep***. Published online 2016. doi:10.1038/srep22144

11. Tam CC, Rodrigues LC, Viviani L, et al. Longitudinal study of infectious intestinal disease in the UK (IID2 study): Incidence in the community and presenting to general practice. ***Gut.*** 2012;61(1):69-77. doi:10.1136/gut.2011.238386

12. International Vaccine Access Center. Current Rotavirus Vaccine Intro status. Bloom Sch Public Heal. 2018;([cited 2019]). http://www.view-hub.org/viz/

13. Hallowell BD, Parashar UD, Hall AJ. Epidemiologic challenges in norovirus vaccine development. ***Hum Vaccines Immunother.*** 2019;15(6):1279-1283. doi:10.1080/21645515.2018.1553594

14. Bruijning-Verhagen P, van Dongen JAP, Verberk JDM, et al. Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-

endemic setting. ***BMC Med.*** Published online 2018. doi:10.1186/s12916-018-1134-3

15. Cortese MM, Parashar UD. Prevention of Rotavirus Gastroenteritis Among Infants and Children Recommendations of the Advisory Committee. MMWR Recomm Reports. 2009;58:1-25.

16. Hoftiezer L, Dijs-Elsinga J, van Dillen J, et al. Perined population curves. Published online 2018. https://www.perined.nl/publicaties1/geboortegewichtcurven

17. Hoftiezer L, Hof MHP, Dijs-Elsinga J, Hogeveen M, Hukkelhoven CWPM, van Lingen RA. From population reference to national standard: new and improved birthweight charts. ***Am J Obstet Gynecol***. 2019;220(4):383.e1-383.e17. doi:10.1016/j.ajog.2018.12.023

18. Dutch Public Health care. Social economic status. Published online 2019. https://www.volksgezondheidenzorg.info/onderwerp/sociaaleconomische-status/cijfers-context/samenhang-met-gezondheid#definities

19. World population by Country 2020. https://worldpopulationreview.com/continents/capitals/europe

20. Ruuska T, Vesikari T. Rotavirus Disease in Finnish Children: Use of Numerical Scores for Clinical Severity of Diarrhoeal Episodes. ***Scand J Infect Dis.*** 1990;22(3):259-267. doi:10.3109/00365549009027046

21. Schnadower D, Tarr PI, Gorelick MH, et al. Validation of the modified vesikari score in children with gastroenteritis in 5 US emergency departments. ***J Pediatr Gastroenterol Nutr.*** 2013;57(4):514-519. doi:10.1097/MPG.0b013e31829ae5a3

22. Freedman SB, Eltorky M, Gorelick M. Evaluation of a Gastroenteritis Severity Score for Use in Outpatient Settings. ***Pediatrics***. 2010;125(6):e1278-e1285. doi:10.1542/peds.2009-3270

23. Nederlandse Werkgroep voor Klinische Virologie. Virologische weekstaten. Accessed in Feb 2020.

24. Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. ***Arch Dis Child.*** 2006;91(11):929-935. doi:10.1136/adc.2005.086306

25. Asad A. Common Queries about Immunization in preterm infants. ***Pediatr Ann.*** 2018;1(47):147-153.

26. Steiner L, Diesner SC, Voitl P. Risk of infection in the first year of life in preterm children: An Austrian observational study. ***PLoS One***. 2019;14(12):1-11. doi:10.1371/journal.pone.0224766

27. de Wit M, Koopmans M, Kortbeek L, et al. Sensor, a population-based cohort study on gastroenteritidis in the Netherlands, incidence and etiology. ***Am J Epidemiol.*** 2001;154(7):666-674.

28. Quee FA, de Hoog MLA, Schuurman R, Bruijning-Verhagen P. Community burden and transmission of norovirus and rotavirus gastroenteritis: A prospective household study. ***Lancet Infect Dis.*** 2019;(Provisionally Accepted).

29. Walker JL, Andrews NJ, Atchison CJ, et al. Effectiveness of oral rotavirus vaccination in England against rotavirus-confirmed and all-cause acute gastroenteritis. ***Vaccine*** X. 2019;1(July 2013):100005. doi:10.1016/j.jvacx.2019.100005

30. Vissing NH, Chawes BL, Rasmussen MA, Bisgaard H. Epidemiology and risk factors of infection in early childhood. ***Pediatrics.*** 2018;141(6). doi:10.1542/peds.2017-0933

31. Edelstein M, Merk H, Deogan C, Carnahan A, Wallensten A. Quantifying the incidence and cost of acute gastrointestinal illness in Sweden, 2013–2014. ***Epidemiol Infect.*** 2016;(144):2831-2839. doi:10.1017/S0950268816000467

32. Dornbusch HJ, Vesikari T, Guarino A, LoVecchio A, Hadjipanayis A, Koletzko B. Rotavirus vaccination for all children or subgroups only? Comment of the European Academy of Paediatrics (EAP) and the European Society for Paediatric Infectious Diseases (ESPID) recommendation group for rotavirus vaccination. ***Eur J Pediatr.*** 2020;179(9):1489-1493. doi:10.1007/s00431-020-03608-5

33. Verberk JDM, Pijnacker R, Bruijning-Verhagen P, et al. Biennial Pattern of Rotavirus Gastroenteritis in The Netherlands and a Shifting Age Distribution Following a Low Rotavirus Season, 2010-2016 Abbreviated Title: Biennial Rotavirus Pattern in The Netherlands in Absence of Rotavirus Vaccination Running Head: ***Pediatr Infect Dis J.*** Published online 2017. doi:10.1097/INF.0000000000001880

34. Hahné S, Hooiveld M, Vennema H, et al. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. ***Euro Surveill Eur Commun Dis Bul***l. Published online 2014.

35. Solastie A, Leino T, Ollgren J. Success of rotavirus vaccination in Finland, a register based study measuring impact beyond overall effectiveness. ***Vaccine***. 2020;38(21):3766-3772. doi:10.1016/j.vaccine.2020.03.022

36. Panozzo CA, Becker-Dreps S, Pate V, et al. Direct, indirect, total, and overall effectiveness of the rotavirus vaccines for the prevention of gastroenteritis hospitalizations in privately insured us children, 2007-2010. ***Am J Epidemiol.*** Published online 2014. doi:10.1093/aje/kwu001

37. Mukaka M, White SA, Terlouw DJ, Mwapasa V, Kalilani-Phiri L, Faragher EB. Is using multiple imputation better than complete case analysis for estimating a prevalence (risk) difference in randomized controlled trials when binary outcome observations are missing? ***Trials.*** 2016;17(1):1-12. doi:10.1186/s13063-016-1473-3

38. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. ***J Clin Epidemiol.*** 2006;59(10):1087-1091. doi:10.1016/J.JCLINEPI.2006.01.014

39. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. ***J Clin Epidemiol.*** 2019;110:63-73. doi:10.1016/j.jclinepi.2019.02.016

40. Kleinbaum D, Klein M. Survival Analysis - A Self-Learning Text. 2012;(Third Edition).

Supplementary material

Laboratory analysis

AGE stool samples were send to the central laboratory at the University Medical Center Utrecht and tested by multiplex realtime PCR for presence of rota-, noro-, adeno(type 40/41)- and astrovirus. Briefly, RNA and DNA were isolated from the samples using the MagnaPura96® (Roche Diagnostics, Pleasanton, CA USA) and amplified by ABI75000 realtime PCR system® (Thermofisher Scientific, Foster City, CA, USA). Prior to extraction, a non-human internal control was spiked into the lysis buffer of the samples to monitor for sample inhibition. Positive and negative controls for each pathogen were tested in every run. Samples tested negative for all four viruses are defined as pan negative. Fecal samples collected within fourteen days of symptom onset were defined as AGE samples.

Primary outcome definitions

1) To calculate IRs we used the total number of AGE episodes identified. IRs were calculated for the total cohort, per age-category (< 6 months, 6-11 months and 12-17 months), by subgroup of medical risk condition and by virus type. Given the strong seasonality of viral AGE, we also calculated IRs by month of the year.

2) Healthcare attendance was defined as the proportion of episodes for which healthcare was required and was stratified into doctor visit or hospitalization. Healthcare usage was also assessed per virus-type.

3) The AGE severity based on the MVS[1,2] was calculated from the daily symptom-score completed for the seven days following AGE onset and classified into mild (0-8 points), moderate (9-10 points) or severe (≥11 points). Severity was assessed for all-cause and virus specific AGE.

Missing data and multiple imputation

Because of a moderate to large proportion of missing information, we applied multiple imputation by chained equation. The imputation model included variables with infant, household and AGE characteristics which contains auxiliary information, the 22 imputed datasets were combined to obtain IR estimates and 95% CI accounting for uncertainty and the imputation procedure. By using auxiliary variables the imputation model can make use of more information than used for analyses[3]. In this case, seven variables, not included in the analysis, containing information related to missing covariates were added to the multiple imputation dataset. For the multiple imputation procedure, we used R package mice, with m=22 and maxit=10. The proportion of missing in this observational data was up to 50% for some of the variables. The fraction of missing information (FMI) is a quantification of the loss of information in a dataset

while considering information maintained by other variables[4]. FMI in our dataset was around 37%. Then, multiple imputation was repeated, 22 new datasets were created for covariates used for survival analyses, again including auxiliary information.

We used the STROBE Statement Checklist for reporting of cohort studies. http://www.strobe-statement.org

References

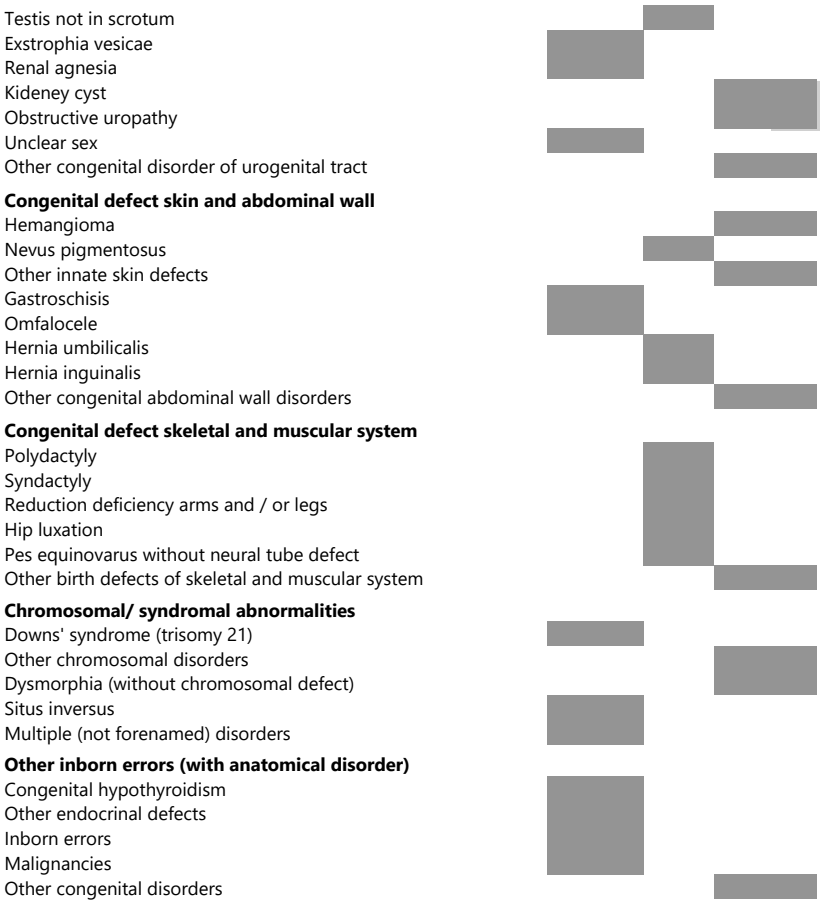
1. Freedman SB, Eltorky M, Gorelick M. Evaluation of a Gastroenteritis Severity Score for Use in Outpatient Settings. ***Pediatrics.*** 2010;125(6):e1278-e1285. doi:10.1542/peds.2009-3270

2. Schnadower D, Tarr PI, Gorelick MH, et al. Validation of the modified vesikari score in children with gastroenteritis in 5 US emergency departments. ***J Pediatr Gastroenterol Nutr.*** 2013;57(4):514-519. doi:10.1097/MPG.0b013e31829ae5a3

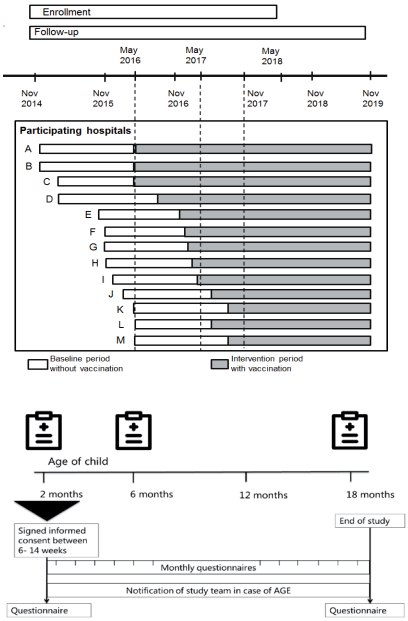
3. Hardt J, Herke M, Leonhart R. Auxiliary variables in multiple imputation in regression with missing X: A warning against including too many in small sample research. ***BMC Med Res Methodol***. 2012;12:1-13. doi:10.1186/1471-2288-12-184

4. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. ***J Clin Epidemiol.*** 2019;110:63-73. doi:10.1016/j.jclinepi.2019.02.016

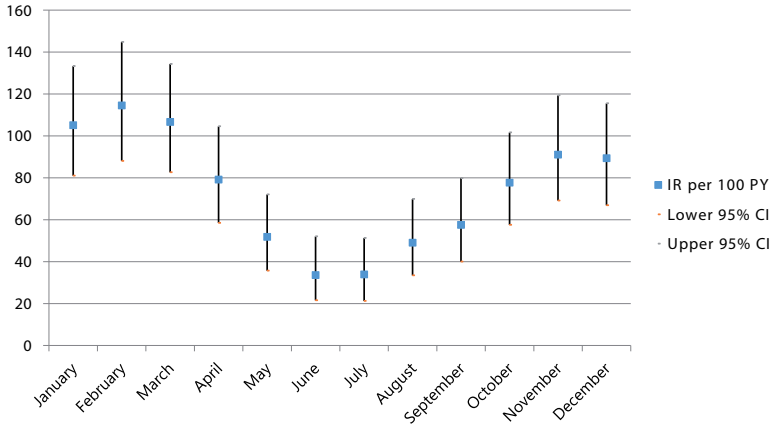
CONGENITAL DISORDERS ACCORDING TO ICD-10	Qualifies as eligible		
	Yes	No	Sometimes
Congenital malformation central nervous system and senses			
Anencephaly	■		
Microcephaly		■	
Spina bifida and meningo(myeleo)cele	■		
Encephalocele			■
Neuromuscular disease	■		
Hydrocephalus/holoprosencephaly without neural tube defect			■
Other congenital CNS malformation			
Congenital defect in senses		■	
Microphthalmia			
Other congenital eye disorders			
Inborn errors of the ears			
Other innate sense abnormalities			
Congenital anomaly cardiovascular			
Lack of umbilical cord artery		■	
Transposition of the large vessels	■		
Tetralogy of Fallot			
Ventricle septum defect			■
Hypoplastic left heart syndrome	■		
Coarctation of the aorta			
Tricuspidis atresia / stenosis			
Complicated heart defect			
Other birth defects of heart and blood vessels			■
Congenital anomaly digestive system			
Cleft lip with or without cleft palate		■	
Split palate without cleft lip	■		
Esophagus atresia/stenosis/fistula			
Intestinal/anal atresia			
Hirschsprungs' disease			
Malrotation/volvulus			
Other congenital disorder of digestive tract			■
Congenital respiratory abnormality			
Choanal atresia	■		
Tracheal disorder			
Lung hypoplasia			
Lobar emphysema			
Hydro/chylo thorax			
Diaphragmatic hernia			■
Relaxation of diaphragm	■		
Other congenital respiratory disorders			■
Congenital malformation urogenital system			
Hypospadias and/or epispadias		■	



eFigure 1. List of eligible congenital disorders. Abbreviations: ICD-10 = international code of diseases 10th edition. Qualifying conditions are those that last longer than 12 months, involve multiple organ systems and/or are expected to require pediatric specialty care. Defined into categories: A. Cardiovascular, B. Pulmonal, C. Central Nerve System, D. Chromosomal, E. Perinatal and F. Other.



eFigure 2. Schematic outline of study data collection. Abbreviations: Nov = November, AGE = acute gastroenteritis.



eFigure 3. Incidence rate per month. Abbreviations: IR = incidence rate, PY = person years, CI = confidence interval.

eTable 1. Modified Vesikari Score (MVS) scale

	0 Points	1 Point	2 Points	3 Points
Diarrhea duration, d	0	1–4	5	≥6
Maximal no. of diarrheal stools per 24-h period	0	1–3	4–5	≥6
Vomiting duration, d	0	1	2	≥3
Maximal no. of vomiting episodes per 24-h period	0	1	2–4	≥5
Maximal recorded fever, rectal, °C	<37.0	37.1–38.4	38.5–38.9	≥39.0
Health care provider visits	None		Outpatient[a]	ED[b]
Treatment	None	Rehydration	Hospitalization	

[a] Community-based health care provider visit related to vomiting, diarrhea, fever, or fluid refusal.
[b] ED health care provider visit related to vomiting, diarrhea, fever, or fluid refusal.

Modified Vesikari Score (MVS):

0-8 mild

9-10 moderate

 Abbreviations: d= days, 24-h = 24 hour, ED = emergency department.

eTable 2. Participants versus non-participants

Characteristic		Participant N=631	Non-participant N=1869	p-value
Gender, n male (%)		361 (57.2)	975 (52.4)	0.04
Gestational age, mean weeks +days (SD)		32+4 (3+6)	33+1 (4+0)	0.00
Birthweight, median grams (IQR)		1847.5 (708.5-2986.5)	1910 (855-2965)	0.26
SGA, n yes (%)		161 (25.5)	523 (28.0)	0.23
Congenital disorder, n any (%)		126 (20.0)	349 (18.7)	0.48
	A. Cardiovascular	41 (32.5)	88 (25.2)	0.08
	B. Pulmonal	5 (4.0)	16 (4.6)	0.88
	C. Central nerve	8 (6.3)	41 (11.7)	0.15
	D. Chromosomal	23 (18.3)	67 (19.2)	0.94
	E. Perinatal	14 (11.1)	56 (16.0)	0.31
	F.Other[#]	56 (44.4)	143 (40.9)	0.33
Twin status, n yes (%)		158 (25)	439 (23.5)	0.43

[#]Infants can have multiple congenital disorders, in category "Other" there are duplicates. Abbreviations: N = number in group, n = number with characteristic, SD = standard deviation, IQR = interquartile range.

eTable 3. Sampled versus non sampled AGE episodes

Characteristic		Sampled AGE (N=252)	Unsampled AGE (N=274)	p-value
Duration, n days[#] (%)	One day	10 (4.1)	40 (14.8)	0.00
	Two-seven	184 (76.0)	184 (68.1)	
	Eight–fourteen	48 (19.8)	40 (14.8)	
	> Fourteen	0	6 (2.2)	
Healthcare attendance, n yes (%)*		68 (27.9)	127 (46.4)	0.00
Age at AGE, n months (%)	Younger than six months	49 (20.5)	53 (19.3)	0.89
	Six-eleven months	103 (43.1)	116 (42.3)	
	12 months and older	87 (36.4)	105 (38.3)	

[#]Missing in 14 cases (3%). * Missing in 8 cases (2%). Abbreviations: AGE = acute gastroenteritis, N = number in group, n = number with characteristic.

eTable 4. Infants with ≥ 1 AGE episode versus no AGE episode

Characteristic	≥ 1 AGE episode N=312			No AGE episode N=252*	p-value^
		Any severe episode N=58§	Non severe episode N=111§		
Gender, n male (%)	184 (60.4)	34 (58.6)	63 (56.8)	147 (58.3)	0.88
Gestational age, mean weeks+days (SD)	32+4 (3+6)	32+6 (3+3)	33+0 (3+4)	32+2 (4+0)	0.44
Birthweight, median grams (IQR)	1910 (673-3147)	2037 (1061-3013)	1979 (606-3352)	1760 (680-2840)	0.46
SGA, yes (%)	80 (25.6)	15 (25.9)	24 (21.6)	58 (23.0)	0.47
Congenital disorder, n yes (%)	63 (20.2)	7 (12.1)	21 (18.9)	48 (19.0)	0.73
Twin status, n yes (%)	65 (20.8)	15 (25.9)	21 (18.9)	69 (27.4)	0.07
Daycare attendance,					
n yes (%)#	171 (60.6)	38 (67.9)	75 (70.8)	70 (39.8)	0.00
Highest family education, n high (%)	236 (76.4)	46 (82.1)	91 (82.0)	159 (65.7)	0.02
Older sibling in household, n yes (%)#	98 (36.4)	18 (39.1)	39 (39.8)	87 (44.2)	0.09
Sibling attending daycare, n yes (%)#	57 (22.8)	10 (23.3)	28 (30.4)	46 (25.7)	0.50

*No information on AGE episodes for 67 infants. # Missing information in more than 100 cases (17.7%), §For 143 AGE episodes severity unknown, ^based on comparison between any versus no AGE. Abbreviations: N = number in group, n = number with characteristic present, SD = standard deviation.

eTable 5. Complete cases versus incomplete cases for survival analysis

Characteristic	Complete cases (N=191)	At least one missing value (N=226)	p-value
Sibling, n	69 (36.1%)	71/149 (47.7%)	0.03
Age (>12 months), n	153 (80.1%)	121 (53.5%)	0.00
Attending daycare, n	102 (53.4%)	93/133 (69.9%)	0.00
Episode in season, n	32 (16.8%)	34/153 (22.2%)	0.20
Born in season, n	134 (59.3%)	115 (60.2%)	0.85
Breastfed, n	20 (10.5%)	31/221 (14.0%)	0.07

Chapter 3

Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting

P. Bruijning-Verhagen, J. A. P. van Dongen, J. D. M. Verberk, R. Pijnacker, R. D. van Gaalen, D. Klinkenberg, H. E. de Melker & M.-J. J. Mangen

BMC Medicine, 2018

Abstract

Background and objective

Since 2013, a biennial rotavirus pattern has emerged in the Netherlands with alternating high and low endemic years and a nearly 50% reduction in rotavirus hospitalization rates overall, while infant rotavirus vaccination has remained below 1% throughout. As the rotavirus vaccination cost-effectiveness and risk-benefit ratio in high-income settings is highly influenced by the total rotavirus disease burden, we re-evaluated two infant vaccination strategies, taking into account this recent change in rotavirus epidemiology.

Methods

We used updated rotavirus disease burden estimates derived from (active) surveillance to evaluate (1) a targeted strategy with selective vaccination of infants with medical risk conditions (prematurity, low birth weight, or congenital conditions) and (2) universal vaccination including all infants. In addition, we added herd protection as well as vaccine-induced intussusception risk to our previous cost-effectiveness model. An age- and risk-group structured, discrete-time event, stochastic multi-cohort model of the Dutch pediatric population was used to estimate the costs and effects of each vaccination strategy.

Results

The targeted vaccination was cost-saving under all scenarios tested from both the healthcare payer and societal perspective at rotavirus vaccine market prices (€135/child). The cost-effectiveness ratio for universal vaccination was €51,277 at the assumed vaccine price of €75/child, using a societal perspective and 3% discount rates. Universal vaccination became cost-neutral at €32/child. At an assumed vaccine-induced intussusception rate of 1/50,000, an estimated 1707 hospitalizations and 21 fatal rotavirus cases were averted by targeted vaccination per vaccine-induced intussusception case. Applying universal vaccination, an additional 571 hospitalizations and < 1 additional rotavirus death were averted in healthy children per vaccine-induced intussusception case.

Conclusion

While universal infant rotavirus vaccination results in the highest reductions in the population burden of rotavirus, targeted vaccination should be considered as a cost-saving alternative with a favorable risk-benefit ratio for high-income settings where universal implementation is unfeasible because of budget restrictions, low rotavirus endemicity, and/or public acceptance.

Introduction

In recent years, the Netherlands has seen an unexpected change in rotavirus epidemiology, while infant rotavirus vaccination coverage (the vaccine has been licensed since 2006) has remained below 1%. Annual epidemics were observed until 2013; thereafter, an alternating pattern of high- and low epidemic years emerged (**Fig. 1**). During low endemic years, rotavirus detections in virological surveillance decreased by 58% (2014) and 52% (2016) compared to an average of the years before 2013, and a delayed start of rotavirus seasons was observed[1, 2]. Similarly, general practice (GP) consultation rates for acute gastroenteritis (AGE) during the winter months in children under 5 years old were reduced[3], and the prevalence of asymptomatic rotavirus observed in daycare attendees was significantly lower in 2014 (prevalence rate 0.6%) compared to 2011–2013 (prevalence rate 6.8–11.2%)[4]. Rotavirus detections and seasonal GP consultation rates during the alternating years 2015 and 2017 were comparable to pre-2014 numbers[3, 5]. Due to this changing epidemiology, the overall incidence of rotavirus disease in the Dutch pediatric population has reduced substantially. To our knowledge, a similar change in epidemic pattern has not been observed in any other European country without a national infant rotavirus vaccination program.

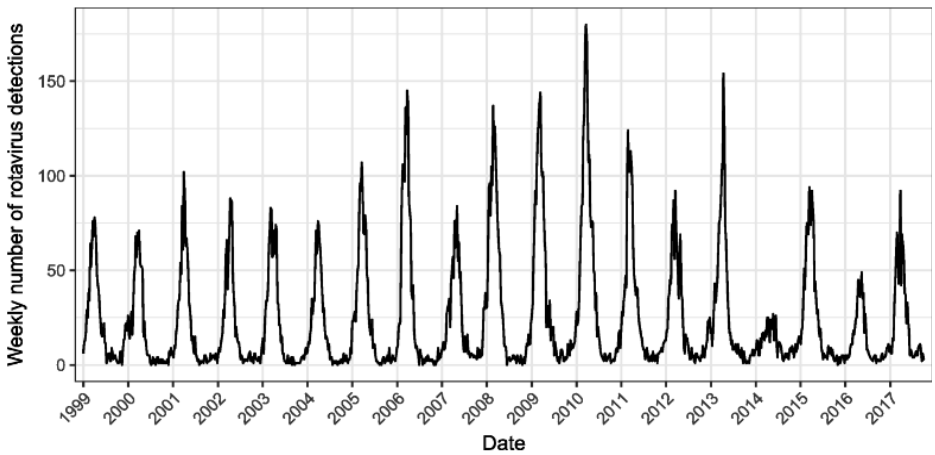


Fig. 1 Weekly number of rotavirus detections in sentinel laboratory surveillance (for 2017 only up to week 40)

Although the driving factors for this change in epidemic pattern are currently unknown, it has been suggested that, apart from a declining birth rate and temperature fluctuations, rotavirus dynamics in the Netherlands may also be influenced by vaccination policies in neighboring countries[6]. Universal rotavirus vaccination programs have been implemented in all three neighboring countries of the Netherlands (Belgium in 2006, Germany in 2013, the UK in 2013), with coverage varying between 78% and 94% [7-9]. Implementation in these countries was

followed by a sustained reduction in rotavirus detections of 44–75%[10]. This reduced circulation of rotavirus may have influenced the number of rotavirus introductions into the Netherlands.

We previously evaluated the cost-effectiveness of infant rotavirus vaccination in the Netherlands and considered three potential vaccination strategies: "no vaccination," "universal vaccination," and "targeted vaccination" [11]. The targeted vaccination strategy is a selective vaccination program, including only infants with medical risk conditions predisposing to severe or complicated rotavirus AGE, including prematurity, low birth weight, and severe congenital pathology[10]. No decision has been made yet on the preferred strategy for the Netherlands. Assuming the observed biennial pattern in rotavirus epidemics represents a new epidemiological equilibrium, a re-assessment of the national rotavirus disease burden and the cost-effectiveness of each of these infant rotavirus vaccination strategies is therefore required to inform policy makers. In addition, it is now widely recognized that rotavirus vaccination induces a small but increased risk of intussusception (IS). Because of this serious side effect, an evaluation of risk-benefit ratios has become an integral part of the decision-making process on rotavirus vaccination policy.

Our aim was to update our previous model-based health economic evaluation of rotavirus vaccination in the Netherlands by both taking into account the present, lower endemic state, and expanding the analysis by including risk-benefit calculations.

Methods

Updated rotavirus disease burden

The original economic evaluation[11] used data from three observational studies conducted in the Netherlands: (1) the Sensor cohort study on community AGE[12] and (2) the Netherlands Institute of Primary Health Care (NIVEL) study on AGE in primary care[13] were conducted in 1999 and provided age-stratified data on AGE incidence and the proportion rotavirus attributed; (3) the RoHo study quantified rotavirus community-acquired hospitalizations and nosocomial infections in children 0–15 years old for the years 2006–2010 with separate estimates for healthy children and those with medical risk conditions[11,14]. Incidence estimates by disease category (rotavirus in the community, GP visits, community-acquired hospitalizations, and nosocomial infections) and by risk status (healthy vs medical risk group) were derived from these studies and used as input for the original cost-effectiveness model. To represent the average rotavirus disease burden over the period 2013–2016, covering two high and two low epidemic seasons, we updated these input parameters using the data sources and methodology as discussed in the following sections.

Rotavirus community incidence

Virological laboratory surveillance in the Netherlands collects weekly numbers of rotavirus detections from 17 to 21 sentinel laboratories serving primary care, hospitals, and long-term

care facilities[5]. Time series analyses have confirmed that these surveillance data correlate well with rotavirus disease activity in the population[15, 16]. Rotavirus surveillance data were used to scale the community incidence of rotavirus AGE as originally measured in 1999 (Sensor study[12]) to the average for the years 2013–2016. We calculated the scaling factor as follows: 1 minus ([mean]annual rotavirus detections between 2013 and 2016/annual rotavirus detections in 1999). We kept the original rotavirus age distribution and the age-specific proportion of cases visiting primary care, as no updated estimates were available. The scaled incidence estimates were applied to the 2016 population size to obtain the annual expected total number of community cases and GP visits; see **Table 1**[17].

Table 1. Parameters for model input

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
Birth cohort n (%)	171,387	157,847 (92.1%)	13,540 (7.9%)	Fixed	Statistics Netherlands [46, 47]	Birth cohort size 2016. Prevalence of high-risk conditions, same as in Bruijning et al. [11]
Rotavirus incidence	***Most likely value (minimum–maximum)***					
Population: < 1 year	15,188 (10,161-21,597)	Calculated		Pert	Community-based cohort study[12]; virologi-cal rotavirus surveillance data[5]	Incidence based on simulations from original study data (for details see [17]), scaled to the years 2013–2017. Distribution among non-target and target groups based on relative size of each category in birth cohort
Population: 1–4 years	35,756 (21,805-54,972)					
Population: 5–14 yearsa	7897 (1426-26,004)					

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
GP visits < 1 year	21.5% (12.8–29.1%)			Pert	GP-based cohort study[13]	Percentage of rotavirus cases based on simulations from original study data (for details see[17])
GP visits 1–4 years	18.5% (16.3–20.8%)					
GP visits 5–14 years	6.4% (4.8–7.3%)					
Community-acquired (CA) hospitalization	2024 (1789 – 2256)	82.8% (82.7–82.9%) of total	Calculated (total minus non-target)	Pert	RoHo study[14]; indirect estimated annual hospitalizations 2; RIVAR AGE surveillance[18]	Incidence based on original study data (for details see[11]) and scaled to the years 2013–2016. Distribution over non-target and target groups and over CA and nosocomial cases based on active AGE surveillance in 2014–2016
Nosocomial infections per CA case	Calculated	0.21 (0.206–0.213)	0.89 (0.88–0.90)	Pert	RIVAR AGE surveillance[18]	
Mortality rate/1000 hospitalizations	Calculated	0.00 (0.00; 0.04)	0 81 (0.36; 1.46)	Pert	RoHo study[14]; External dataset Sophia Children's hospital	For details see[11]
Age distribution of hospitalizations and fatal cases	See Additional file 1: Table S2 in Bruijning et al. [11]				RoHo study[14];	Same as[11]
Intussusception (IS) incidence						
Vaccine-induced IS risk	1/50,000 vaccinated children			Fixed	[32- 35]	Calculated from[36]: 56 with resection out of 1176 IS cases in infants < 12 months
Complicated (with intestinal resection)	4.8% of induced IS cases			Fixed	[36]	

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
Utilities rotavirus AGE	QALY loss					
Mild (no medical care)	0.0011			Fixed	GP study in Canada[48]	50% of estimate for moderate, similar to[11, 17, 31, 49]
Moderate (GP visit only)	0.0022			Fixed	GP study in Canada[48]	
Severe (hospitalization)	0.0034			Fixed	Emergency-department study in UK[20]	
Nosocomial	Calculated	Calculated	Calculated		RoHo study[14]	Based on severity distribution, same as in[10]
Rotavirus fatal cases	Calculated	81.5 minus patient age at rotavirus infection	Simulated, assuming LE of 1; 20; 41.3 minus patient's age with probability of 1/3 each	Uni¬form	Statistics Netherlands [46]; Expert panel[11]	For non-target group, based on average LE in the Netherlands. For target group, same as Bruijning et al.[11]
Utilities intussception	QALY loss					
Uncomplicated IS	0.0037			Fixed	Based on Reyes et al.[37]	
Complicated IS	0.0111			Fixed	Assumption	Assuming three times more severe than uncomplicated IS; see Additional file 1
Healthcare costs rotavirus AGE						
No medical care	€0			Fixed		

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
Standard GP visit (€/unit)	€33				Dutch reference prices[22]	If GP attend-ance; home visit: Pert (0; 0.1; 0.1), standard GP visit: Pert (0.9; 0.9; 1.0), and GP telephone con-sultation: Pert (0; 0.97; 0.97); same as in[11, 17] Average cost/episode including antibiotics, oral rehydration solutions, and other prescribed drugs/ GP consultation (home or standard GP visit) Additional GP consultations for hospitalized cases same as[11], based on[50]
GP home visit (€/unit)	€50					
GP telephone consultation (€/unit)	€17				Based on cohort studies[12, 13, 51]	
Drug costs incl. Prescription fee (€/unit)	€43					
Laboratory costs (€/unit)	€78				Expert elicitation	10% with laboratory test[52]
Ambulance (€/unit)	€618.6			Fixed	Dutch reference price[22]; hospi-tal-based observational study[50]	1% of hospital-ized cases transported by ambulance[50]

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
Rotavirus hospitalization (€/hospitalization)	Calculated	€2417 (2248–2584)	€2828 (2782–4000)	Pert	RoHo study[11]	Weighted estimates from original study data (see additional file in[11])
Nosocomial rotavirus (€/hospitalization)	Calculated	€2413 (1378–3048)	€2361 (1334–3388)			
Uncomplicated IS (€/hospitalization)	€1423	Fixed	Hospital administrative data (see Additional file 1); Valk et al. [53]			Average LOS for Dutch IS cases = 2.11 days + costs of diagnostics (i.e., abdominal X-ray, ultrasonography)
Complicated IS (€/hospitalization)	€6759			Fixed	Assumption	3× LOS for uncomplicated IS, whereof 1 day in ICU, and additional procedures (i.e., ileo-cecal resection, abdominal X-ray, ultrasonography). See Additional file 1
Patient and family costs for rotavirus AGE[b]						
Without medical care	Additional diapers			Uniform	Assumption	For details see[11, 17]
Requiring GP visit	Additional diapers and travel costs			Pert	Assumptions and guidelines for health economic evaluation[22]	
Hospitalization	Travel costs					
Nosocomial rotavirus	Not applicable					

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
Productivity losses caregiver						
Cost per hour paid work loss	€32				Statistics Netherlands[54] and guidelines for health economic evaluation[22]	
Hours of paid work loss per episode:						
Without medical care	1 day (~8 h) in 5% of episodes			Beta	RotaFam (see Additional file 1)	For children >10 years of age work loss estimates were reduced by 50%
Requiring GP visit	0.5–2 days in 25% of episodes			Beta; uniform	RotaFam (see Additional file 1)	
Hospitalization	26.40				Based on[50]	For details see[17]
Nosocomial AGE	24.58				Based on[50]	For details see[7]
Uncomplicated IS	4.93			Fixed	Estimated based on LMR data (see Additional file 1) and Statistics Netherlands[54]	Based on LOS and applying average care-giver employment of 16.4 h/week (similar to Mangen et al.[38])[d]
Complicated IS	14.79			Fixed		
Vaccine coverage	Universal vaccination			Targeted vaccination		
Vaccine coverage	86.2%	86.2%		Fixed	Discrete choice experiment[28]	
Vaccine efficacy	Table 2 in Bruijning et al.[11]			Pert	Vaccine trials[55-57]	
Herd protection	See Table 2	Not applicable		Fixed	Published estimates, see Table 2	Only for universal vaccination scenarios

Parameter	Total population	Non-target group	Target group	Distribution	Data source	Method
Vaccination costs						
Vaccine costs/infants	€75	€135.32		Fixed	Free market price for targeted vaccination[29]; for universal vaccination based on assumption as in[11,31]	
Application and administration costs	€12.36	€12.36		Fixed	[30]	
Start-up cost first year	€233,760			Fixed	[17]	

LOS length of hospital stay, LE life expectancy, RIVAR Risk-Group Infant Vaccination Against Rotavirus, LMR Netherlands National Medical Registry

a Of which 80% is aged 5–9 years and 20% is aged 10–14 years

b Note, we did not consider any patient and family costs for IS cases

c Reported vaccine costs exclude costs for spillage; 2% spillage costs was added in the model

d Based on population statistics for the year 2014 [54], the most recent year available, we calculated similarly as in Mangen et al. [38] the average working hours/week for a primary caregiver. For this we assumed that, except for single-father households, the female is the primary caregiver taking care of a sick child. In 2014 73.4% of primary caregivers had paid employment, for an average of 22.3 h/week. For an average primary caregiver in the Netherlands this corresponds to 16.4 h/week.

Rotavirus hospitalizations

A similar approach was used to scale the annual number of community-acquired and nosocomial rotavirus hospitalizations from the RoHo study (2006–2010) to the average for the years 2013–2016. To calculate the scaling factor, we used virological surveillance data on annual rotavirus detections and annual AGE hospitalization data derived from inpatient primary and secondary discharge diagnoses collected by the Dutch National Medical Registry (LMR, national coverage around 90%). The anonymized discharge diagnoses were coded according to the 9th International Classification of Diseases (ICD-9) from 2001 up to 2012 and according to ICD-10 from 2013 onwards. Using an indirect method[15], the proportion of AGE-coded hospitalizations attributable to rotavirus (including community-acquired and nosocomial infections) was calculated for each year in children younger than 5 years. A scaling factor was then calculated from the indirectly estimated annual rotavirus hospitalizations comparing the mean of 2006–2010 (RoHo-study years) to the mean of 2013–2016. This scaling factor was applied to the mean annual number of rotavirus hospitalizations used in the original model (**Table 1**).

The proportion of rotavirus hospitalizations attributable to nosocomial or community-acquired infections and also the ratio of healthy vs risk-group children were originally derived from the RoHo study. Proportions were updated based on results from active AGE surveillance conducted in 12 Dutch hospitals between November 2014 and November 2016 18, 19. Collected data include age, sex, rotavirus presence in stool, type of infection (community-acquired or nosocomial), and the presence of medical risk conditions. As the active surveillance only included children < 2 years of age, proportions for older children were kept consistent to what was found in the RoHo study.

Other parameter updates

Each model input parameter and assumption was checked for potential updates by screening the literature and checking available data from ongoing surveillance. As we outline in this section, this yielded new and improved data on the impact of rotavirus disease and vaccination, and we updated our parameters accordingly.

A recent UK study estimated the quality-adjusted life year (QALY) loss due to severe rotavirus AGE[20]. These estimates were applied as QALY loss for community-acquired rotavirus hospitalizations (**Table 1**).

For rotavirus episodes without medical care and those requiring GP visits, we updated our previous estimates on parental productivity losses due to work absence based on results from a prospective household study on AGE among 289 Dutch families with young children conducted between January and May 2016[21]. (See **Table 1** and Additional file 1 for details.)

All costs — healthcare costs, patient and family costs, and productivity losses — were updated to 2016 cost prices using Dutch consumer price indexes and recent reference prices (**Table 1**)[22].

Herd protection as a result of infant rotavirus vaccination, where rotavirus AGE in unvaccinated children is reduced, has been widely observed post-implementation in high-income, high-coverage settings [23-27]. We therefore incorporated herd-protection effects in our base case for universal infant rotavirus vaccination. We stratified herd-protection levels by age and by vaccinated vs unvaccinated cohorts (Additional file 1: **Table S1**). Unvaccinated age cohorts were assumed to be ineligible for vaccination based on age at the time of implementation, but may still benefit from herd effects. The available studies on herd-protection levels used historical pre-vaccination cohorts as a comparator in settings where annual rotavirus epidemics occurred [23-27]. To account for the presence of a biennial epidemic pattern in the current pre-vaccination setting in the Netherlands, we lowered study estimates by 50% for our analysis. This assumes that relevant reductions due to herd effects only occur every other year. We assumed no effect on adult rotavirus infections from any of the infant vaccination strategies[11] and no herd effects for targeted vaccination, as this would result in a maximum vaccine coverage of 8% in the infant

population[11].

Further parameter updates included changing the vaccination coverage for both targeted and universal vaccination from 88% (vaccine coverage Belgium[11]) to 86% based on a recent assessment of willingness to vaccinate among Dutch parents[28], changing the vaccine costs for a targeted vaccination strategy to the current market price of €135.32 per child[29] and changing the application costs to €12.36 per dose[30]. Vaccine costs for a universal vaccination within the national immunization program were kept at €75 per child, which assumes that tender processes will lower vaccine prices by almost 50%[11,31].

Intussusception

Our previous model[11] was extended to include the risk of developing IS following rotavirus vaccination. Based on the available literature, we assumed a vaccine-induced IS rate of 1:50,000 [32-35], whereof 4.8% would result in complications ([36], **Table 1**). The associated QALY loss for uncomplicated IS was 0.0037[37], and costs were based on the average length of stay (LOS; 2.11 days) for IS in the Netherlands (**Table 1**, see Additional file 1 for details). Threefold higher estimates, representing the 95% percentile of the LOS distribution, were used for complicated IS cases (see Additional file 1 for details). Parental work loss was based on LOS, and we assumed that an average caregiver works 16.4 h/week, based on the mean weekly workhours among the primary caregivers according to Statistics Netherlands in 2014[38].

Model

The model has been described previously[11]; see **Fig. 2**. In brief, we used an age- and risk-group structured, discrete-time event, stochastic multi-cohort model of the Dutch pediatric population. The model used separate estimates for the number, and the costs of, community-acquired and nosocomial rotavirus cases, stratified by risk stratus into healthy vs medical risk conditions, the latter qualifying for targeted vaccination (**Table 1**). The effect of either targeted or universal infant vaccination was modeled as a reduction in rotavirus AGE and associated health outcomes in vaccinated and non-vaccinated age cohorts between 0 and 15 years old, stratified by risk status. Time steps of 1 month were used for ages 0 to 11 months and time steps of 1 year for ages 1 to 15. A time horizon of 20 years was used with year 1 being the start of either vaccination program.

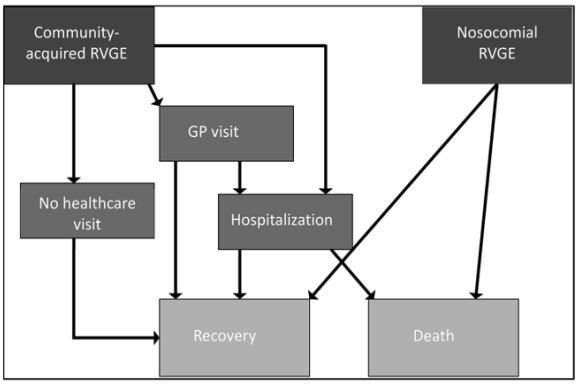


Fig. 2 Rotavirus outcome tree and different healthcare paths considered in model. With permission from Bruijning-Verhagen et al.[11]

Cost-effectiveness and risk-benefit analyses

The model was built in Microsoft Excel with the add-in software @Risk, version 7.5 (Palisade). For all three vaccination strategies ("no vaccination," "targeted vaccination," and "universal vaccination"), the model estimates the number of rotavirus cases in the population, GP visits, hospitalizations, rotavirus-related deaths, QALYs, and life years. The model further estimates the number of vaccine-induced IS cases and associated QALYs. Net costs (i.e., net social costs and net healthcare costs), life years gained (LYG), and QALYs gained were calculated by summing all costs, life years, and QALYs over the 20-year time horizon. For each simulation, 5000 runs were conducted using Monte Carlo sampling, accounting for the uncertainty of the model parameters (**Table 1**).

The incremental cost-effectiveness ratios (ICERs) were calculated by dividing the net cost differences between each vaccination strategy, compared to no vaccination, by either QALYs gained or LYG. Our primary perspective was societal (i.e., including non-healthcare costs such as caregiver work loss), and the healthcare payer perspective was included in the sensitivity analysis. Costs are expressed in 2016 euros. A discount rate of 3% was used for both costs and effects[39].

Risk-benefit ratios were calculated by dividing the number of severe outcomes averted by vaccination, which included rotavirus hospitalizations or rotavirus fatal cases, by (1) the estimated number of vaccine-induced IS cases and (2) the estimated number of vaccine-induced complicated IS cases. The calculated ratios were used to obtain the benefit per vaccine-induced IS case and per vaccine-induced complicated IS case, respectively. Risk-benefit ratios were calculated both for the total population and for each risk group, since the risk of severe outcomes due to rotavirus differs between children with and without medical risk conditions.

Sensitivity and scenario analyses

Univariate sensitivity analysis was conducted to identify critical parameters driving our results. In short, parameter variations included 25% lower and 25% higher rotavirus hospitalization rates and hospitalizations costs; vaccine-induced IS rates of 1:20,000 and 1:100,000 (base case 1:50,000)[32-35], and IS complication rates of 0% and 9.6% (base case 4.8%). We also included slightly higher QALY losses based on the sensitivity analysis of Marlow et al. (for hospitalizations 0.0039 vs 0.0030 and for GP visits 0.0030 vs 0.0022)[20]) As caregiver work-loss estimates for rotavirus AGE are influenced by local employment conditions and parental leave plans, they can vary substantially by country. Our sensitivity analysis therefore also included 100% higher caregiver productivity losses. Subsequently, we tested the impact of old vs new parameter estimates including caregiver work loss for mild and moderate rotavirus cases[4] and QALY losses for hospitalized cases[11]. We applied various discount rates: 2% and 4% for both costs and effects (3% in the baseline), as well as the Dutch discount rates (1.5% for effects and 4% for costs[10]). Extensive sensitivity analyses were conducted on vaccine costs to determine the thresholds at which the vaccination strategies would become cost-saving under base-case assumptions.

Additionally, strategy-specific scenarios included the following: a lower vaccination coverage of 75% for "targeted vaccination" (baseline 86%); decreased or increased herd protection, or no herd protection at all in case of universal vaccination. Because a shift to a biennial rotavirus epidemic pattern could theoretically increase the average age of first infection as a result of the reduced force of infection, we assessed the impact of an "older" age when first infected. To this end, we simulated scenarios where 50% or 75% of the 0–1 years old patients with rotavirus from baseline were 1–2 years old instead, and consequently had lower probabilities of seeking medical care, both GP and hospitalization. Finally, an "alternative universal vaccination" scenario was also analyzed where we assumed that "universal vaccination" would be recommended, but not covered by the publicly funded national immunization program. Instead, vaccines would be individually purchased for each infant with or without partial reimbursement from health insurance. For this scenario, we assumed a coverage of 60%, no herd protection due to the lower coverage, and the actual market price (i.e., €135.32/child). For more details see also Additional file 2: **Tables S2 and S3**.

Results

The updated rotavirus disease burden estimated a reduction in the number of rotavirus AGE episodes in the Netherlands by 13% compared to 1999, and in the number of hospitalizations by 45% compared to 2006–2010. The 2014–2016 active surveillance data identified a somewhat higher proportion of children with medical risk conditions (26% vs 16%) among those < 2 years of age hospitalized for rotavirus and a higher proportion of nosocomial infections (28% vs 11%) compared to the RoHo study[11].

Without vaccination and over a 20-year time horizon, an estimated 1.25 million rotavirus AGE episodes (62,500 annually), 54,000 hospitalizations (2700 annually), and 110 fatal rotavirus cases (5.5 annually) in children 0–15 years old would occur in the Netherlands, resulting in 2597 QALYs lost (130 annually) or 1309 life years lost (65.45 annually), and in societal costs of €180 million (€9 million annually; see **Table 2**).

Table 2 Rotavirus disease and cost burden in children < 15 years old (mean (95% credibility interval) and incremental results from targeted or universal infant rotavirus vaccination based on a 20 years' time horizon

Disease and cost burden	AGE episodes (× 1000)	Hospitalizations[a] (× 1000)	Fatal cases	Vaccine-induced IS	QALYs lost[b]	Life years lost[b]	Net societal costs[b] (mio €)	
No vaccination	1251 (903–1627)	54 (48–60)	110 (59–175)	NA	2597 (1681–3727)	1309 (471–2372)	180 (153–218)	
Targeted vaccination	1208 (871–1573)	46 (41–51)	12 (5–23)	4.61	1458 (1057–1890)	195 (18–463)	163 (139–199)	
Universal vaccination	586 (407–789)	14 (12–16)	7 (4–11)	58.40	689 (477–923)	105 (5–245)	278 (268–294)	
Incremental results from vaccination	Averted AGE episodes (× 1000)	Averted hospitalizations (× 1000)	Averted fatal cases	Additional IS	Incremental QALYs gained	Incremental life years gained	Δ net societal costs (in mio €)[c]	ICER €/QALY gained
Targeted vaccination vs no vaccination								
Absolute change	433 (32–55)	8 (7–9)	99 (54–153)	4.61	1139 (426–2022)	1114 (399–2004)	-−17[c] (−21 to −13.6)[c]	cost-saving (costsaving-costsaving)

Disease and cost burden	AGE episodes (× 1000)	Hospitalizations[a] (× 1000)	Fatal cases	Vaccine-induced IS	QALYs lost[b]	Life years lost[b]	Net societal costs[b] (mio €)	
Percent reduction	3.4% (2.9–4.0%)	14.7% (13.9–15.3%)	89.8% (86.7–92.2%)	NA	42.7% (23.0–57.7%)	85.6% (72.3–97.2%)	9.4% (8.0–11.0%)	NA
Percent reduction	53.2% (48.1–58.4%)	74.4% (71.9-76.5%)	93.9% (92.7–94.8%)	NA	72.9% (63.0–81.1%)	92.1% (82.5–99.3%)	NA	NA
Universal vaccination vs targeted vaccination[d]								
Absolute change	622 (451–810)	32 (28–36)	4 (1–12)	53.79	769 (561–1003)	90 (9–239)	115 (94–131)	149,282 (101,101 220,113)
Percent reduction	51.5% (46.5–56.7%)	70% (67.4–72.3%)	39.5% (26.9–53.4%)	NA	52.8% (47.6–58.8%)	48.2% (25.4–88.6%)	NA	NA

[a]Including nosocomial infections [b]Using a 3% discount rate for effects (QALYs/life years) and costs

[c]Negative costs are savings [d]Comparing universal vaccination to targeted vaccination in order to obtain the incremental results of extending targeted vaccination to universal vaccination

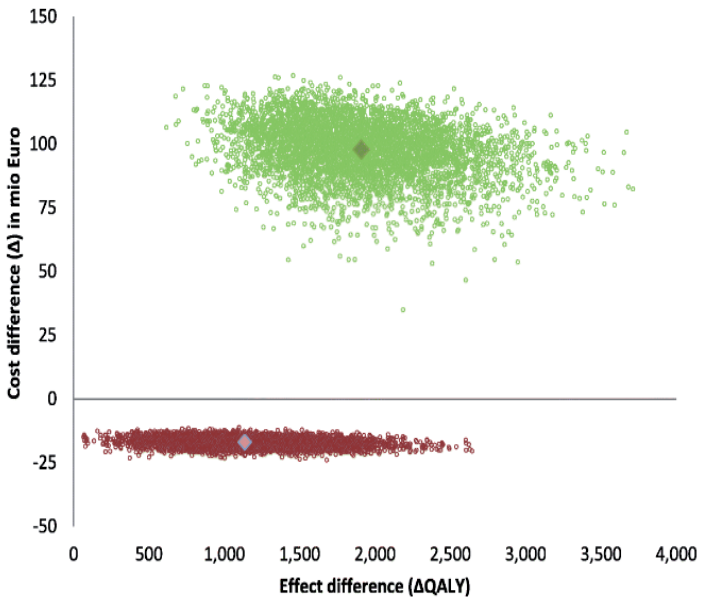


Fig. 3 Cost-effectiveness plane for targeted vaccination (depicted in red) and universal vaccination (depicted in green) using a societal perspective and a 3% discount rate

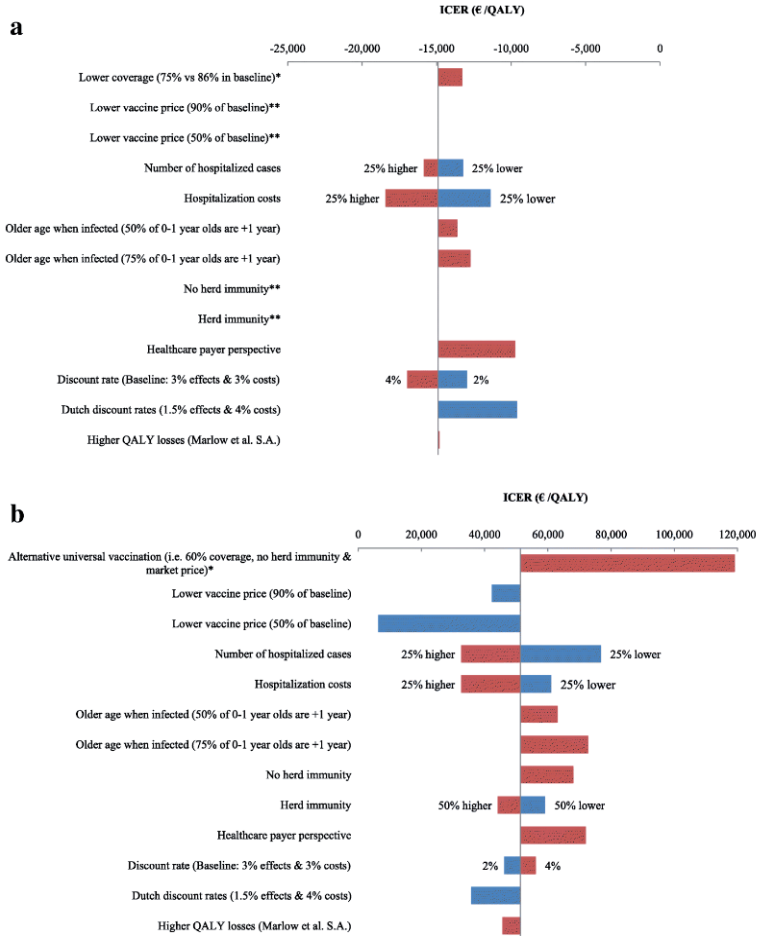


Fig. 4 Tornado diagram showing one-way and multi-way sensitivity and scenario analyses results for a a targeted vaccination strategy and b a universal vaccination strategy

Note1: The x-axis shows the effect of changes in selected variables on the mean incremental cost-effectiveness ratio (ICER) for the base-case taking a societal perspective. The y-axis shows the model parameter that was varied. The bars indicate the mean change in the ICER caused by changes in the value of the indicated variable holding all other parameters similar, whereby a blue bar indicates a lower value of the selected variable(s) as in the baseline and a red bar a higher value of the selected variable(s). Sensitivity analyses with less than 5% changes are not shown. Detailed results are presented in **Table S2** in Additional file 2 for targeted vaccination and in **Table S3** in Additional file 2 for universal vaccination.

Note2: All scenarios for targeted vaccination were cost-saving and health gaining. This results in negative ICERs.

*Some of the sensitivity analyses were only applicable to universal vaccination (i.e. alternative universal vaccination strategy), and others were only to target vaccination (i.e. lower coverage in the target population).

**No S.A. on vaccine price was performed for targeted vaccination as this was already cost-saving at the current market price; No S.A. on herd immunity, as a population vaccine coverage of 7% will not induce herd protection.

We first compared targeted vaccination to no vaccination over a 20-year time horizon. With annual vaccination costs of €0.64 million, targeted vaccination would avert on average 43,000 rotavirus AGE episodes and 99 fatal cases, and would induce 4.6 IS cases, of which 0.22 would be complicated cases. The targeted vaccination strategy would result in 1139 QALYs gained and €17 million savings (**Table 2**). Targeted vaccination was cost-saving in all simulations (**Fig. 3**) and remained cost-saving in all conducted sensitivity analyses (**Fig. 4a** and Additional file 2: **Table S2**).

We then compared the no vaccination strategy to universal vaccination, which would cost €15 million annually. Over a 20-year time horizon universal vaccination would avert 665,000 rotavirus AGE episodes and 103 fatal cases and would induce 58.4 IS cases, of which 2.8 would be complicated. Universal vaccination would result in 1907 QALYs gained and €98 million additional costs (**Table 2**) at an ICER of €51,280/QALY gained (**Fig. 2** and Additional file 2: **Table S3**). When universal vaccination was compared to targeted vaccination, the ICER increased to €149,280/QALY gained. Sensitivity analyses revealed that vaccine costs, presence and level of herd protection, the perspective chosen (i.e., healthcare costs only vs societal costs), the number of annual rotavirus hospitalizations, the costs per hospitalization, older age at first infection, and productivity losses were most influential on cost-effectiveness results (**Figs. 4, 5** and Additional file 2: **Table S3** and **Figure S1**).

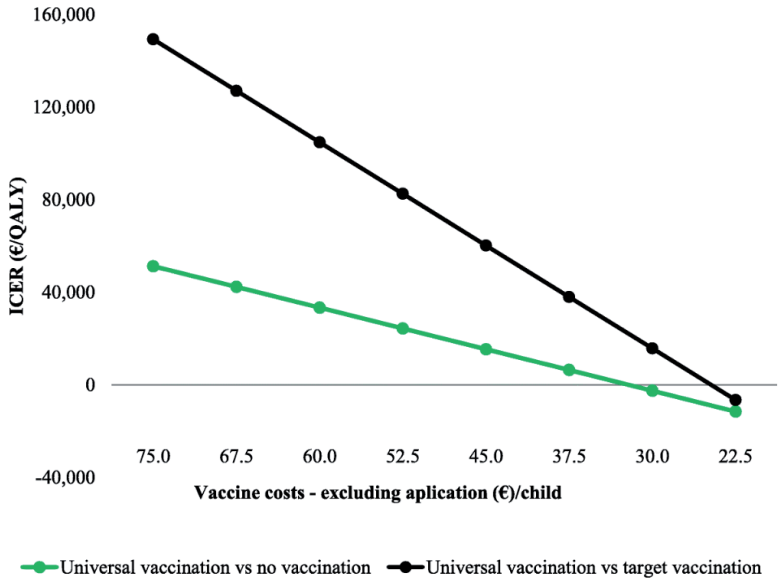


Fig. 5 Mean ICER (cost per QALY gained) for universal vaccination vs no vaccination (green line/dots), and for universal vaccination vs targeted vaccination (black line/dots) using a societal perspective and assuming a discount rate of 3%, for different vaccine costs. Results are also presented in **Table S3** in Additional file 2 (universal vaccination vs no vaccination) and in **Table S4** in Additional file 2 (universal vaccination vs targeted vaccination).

Under base-case assumptions and using a societal perspective, universal vaccination would become cost-saving at vaccine costs of €32 per child when compared to a strategy with no vaccination, or at €24.5 per child when compared to a strategy with targeted vaccination. The alternative universal vaccination scenario, where the vaccine would not be covered by the publicly funded national immunization program but purchased individually at market prices, was not considered cost-effective at an ICER of €119,191/QALY (95% credibility interval (CI) €70,488/QALY–€244,692/QALY) (see **Fig. 3** and Additional file 2: **Table S3**).

Vaccination averts fatal rotavirus cases and hospitalization (benefits), but at the costs (risk) of inducing IS cases. The risk-benefit ratio differed by health status of the vaccinated child (**Table 3**). Among infants with medical risk conditions, we estimated a benefit of 21 prevented fatal rotavirus cases and 1707 prevented rotavirus hospitalizations for every vaccine-induced IS case. In healthy children the estimated risk-benefit ratio resulted in 0.05 prevented fatal cases and 571 hospitalized cases for every vaccine-induced IS case.

Table 3 Risk-benefit ratios for rotavirus vaccination

	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases	Induced complicated IS: prevented fatal cases	Induced complicated IS: prevented hospitalized cases
All children				
Targeted vaccination	1:21 (1:12–1:33)	1:1707 (1:1494–1:1920)	1:445 (1:244–1:691)	1:35,564 (1:31,126–1:39,995)
Universal vaccination	1:1.8 (1:1.0–1:2.8)	1:685 (1:603–1:767)	1:37 (1:20–1:59)	1:14,267 (1:12,566–1:15,974)
Targeted group				
Targeted vaccination	1:21 (1:12–1:33)	1:1707 (1:1494–1:1920)	1:445 (1:244–1:691)	1:35,564 (1:31,126–1:39,995)
Universal vaccination	1:22 (1:12–1:34)	1:2012 (1:1773–1:2252)	1:455 (1:250–1:706)	1:41,913 (1:36,942–1:46,921)
Healthy children				
Targeted vaccination	NA	NA	NA	NA
Universal vaccination	1:0.05 (1:0.00–1:0.16)	1:571 (1:503–1:639)	1:1.0 (1:0.03–1:3.24)	1:11,896 (1:10,475–1:13,319)

Discussion

Our results show that, in a high-income and relatively low rotavirus endemic setting, targeted rotavirus vaccination of infants with medical risk conditions is a cost-saving strategy and has the most favorable risk-benefit ratio. This finding remains robust in all of our sensitivity analyses. This strategy would also nearly eliminate rotavirus-related mortality in high-income settings, where fatal rotavirus cases among otherwise healthy children are extremely rare. Yet, the impact of targeted vaccination on the rotavirus disease burden in the pediatric population is limited, with only a 3.4% reduction in AGE episodes and a 14.7% reduction in hospitalizations (**Table 2**).

Universal rotavirus vaccination has the potential to reduce the population rotavirus disease burden in children by >50% and avert nearly 75% of hospitalizations (**Table 2**). However, in a low-endemic setting and at assumed vaccine costs of €75 per child, the ICER for universal rotavirus vaccination at €51,280/QALY for the societal perspective and at €72,021/QALY for the healthcare perspective is not considered a cost-effective intervention according to most internationally accepted willingness-to-pay thresholds[40,41,42]. Further reductions in vaccine prices are therefore needed to improve cost-effectiveness. Universal vaccination could become cost-saving when vaccine costs are reduced to €32 per child or less. Importantly, even in a low-endemic setting, the risk-benefit ratio for healthy children vaccinated under a universal vaccination strategy can still be considered favorable at 571 averted hospitalizations for every vaccine-induced case of IS.

Our analysis also showed that the alternative universal vaccination scenario, i.e., no publicly funded program but vaccines individually purchased, is the least favorable strategy due to higher vaccine costs per child (no price reductions generated through tender processes) and absence of herd protection because of moderate vaccine uptake. Yet, this or comparable strategies are currently in use in several high- or middle-income countries[43]. Health authorities may therefore wish to reconsider one of the alternative, more cost-effective vaccination strategies.

Healthcare budget restrictions and prioritization may be an important reason why a publicly funded universal vaccination program is unfeasible. In this situation, a publicly funded targeted vaccination program can form a suitable alternative, as it results in cost savings both from the societal and healthcare payer perspective, while protecting the most vulnerable infants. Concerns about vaccine safety of the currently licensed vaccines and public acceptance may be another reason for not implementing universal vaccination. For instance, in France several reports on severe and even fatal IS cases following rotavirus vaccination resulted in public concern and the decision by health authorities to withdraw the recommendation for routine infant rotavirus vaccination[44]. A recommendation for targeted vaccination could offer an acceptable solution because of the more favorable risk-benefit ratio.

Our study has several limitations. The model input was largely based on epidemiological data as well as healthcare and non-healthcare cost estimates from the Netherlands. Differences in rotavirus endemicity, population demographics, caregiver employment, and cost prices may limit the generalizability of our findings to other high-income settings. However, we have performed extensive sensitivity analyses to evaluate the robustness of our ICER estimates and the most influential parameters. As targeted vaccination remained cost-saving under all scenarios tested, we are confident that this strategy will be cost-saving to other high-income settings. The ICER for universal vaccination, however, may be more variable, and for some high-income countries it may be better represented by one of the alternative scenarios from our sensitivity analysis.

Our model did not include dynamic simulation of herd effects following introduction of universal vaccination. Given the unusual pre-vaccination biennial rotavirus pattern in the Netherlands, observations on herd-protection levels from other countries may not be representative. Therefore, we chose to lower the herd-protection estimates extracted from studies in Europe and North America by 50% for our analysis. We considered this the most likely scenario, but the accuracy of these adjusted estimates remains uncertain. Our sensitivity analysis showed that a 50% change in herd effects from baseline would result in a 15% change in ICER. Another limitation of our static, rather than a dynamic model, is that we could not explore how universal rotavirus vaccination affects the timing and pattern of rotavirus epidemic peaks. Sudden spikes in incidence put additional pressure on hospital capacity, and this may be especially relevant if these coincide with circulation of respiratory viruses in winter months. The periodicity and timing of rotavirus epidemics may therefore be important for bed capacity planning. Available rotavirus dynamic models so far suggest that high-coverage rotavirus vaccination in temperate climates results in a biannual pattern and a shift of the epidemic peak to April/May[45].

Finally, it is currently uncertain whether the biennial rotavirus pattern in the Netherlands will be sustained in future years. If conditions affecting rotavirus epidemiology change in the future, disease levels could return to those pre-2014. Naturally, this would change the ICERs for the different vaccination strategies analyzed and the threshold for cost-saving vaccine prices.

Conclusion

While universal infant rotavirus vaccination results in the highest reductions in the population burden of rotavirus, targeted vaccination should be considered as a cost-saving alternative with the most favorable risk-benefit ratio for high-income settings where universal implementation is unfeasible for reasons of budget restrictions, low rotavirus endemicity, and/or public acceptance.

Acknowledgements

We thank Wilfrid van Pelt for providing historical data on rotavirus detections in the Netherlands from virological surveillance.

Funding

PB-V has received funding from the Netherlands Organization for Health Research and Development for conduct of the RotaFam study (ZonMw number 016.166.158) and Risk-Group Infant Vaccination Against Rotavirus (RIVAR) study (ZonMw number 80–83600–98-20129).

References

1. Hahne S, Hooiveld M, Vennema H, van Ginkel A, de Melker H, Wallinga J, van Pelt W, Bruijning-Verhagen P. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. ***Euro Surveill***. 2014;19(43).

2. Verberk JDM, Bruijning-Verhagen P, de Melker HE. Rotavirus in the Netherlands; background information for the Health Council. In: RIVM Report. Bilthoven: National Institute of Public Health and the Environment; 2017. p. 1–70.

3. National Institute for Public Health and the Environment. State of Infectious Diseases in the Netherlands, 2016. http://www.rivm.nl/dsresource?objectid=bce6439b-ce72-49d3-b7ed-e0c42348c8c5&type=pdf&disposition=inline.

4. Enserink R, Scholts R, Bruijning-Verhagen P, Duizer E, Vennema H, de Boer R, Kortbeek T, Roelfsema J, Smit H, Kooistra-Smid M, et al. High detection rates of enteropathogens in asymptomatic children attending day care. ***PLoS One.*** 2014;9(2):e89496.

5. Rijksinstituut voor Volksgezondheid en Milieu. RIVM Virologische Weekstaten, Open Rapportages [http://www.rivm.nl/Onderwerpen/V/Virologische_weekstaten/Rapportages/Open_rapportages_virologische_weekstaten/Virologische_uitslagen_per_week_sinds_2006_grafieken].

6. van Gaalen RD, van de Kassteele J, Hahne SJM, Bruijning-Verhagen P, Wallinga J. Determinants of rotavirus transmission: a lag nonlinear time series analysis. ***Epidemiology.*** 2017;28(4):503–13.

7. Braeckman T, Theeten H, Lernout T, Hens N, Roelants M, Hoppenbrouwers K, Van Damme P. Rotavirus vaccination coverage and adherence to recommended age among infants in Flanders (Belgium) in 2012. ***Euro Surveill***. 2014;19(20:pii=20806)

8. Rieck T, Wichmann O, Siedler A. Aktuelles aus der KV-Impfsurveillance; Impfquoten der rotavirus-, Masern-, HPV- und Influenza-Impfung in Deutschland. ***Epidemiologisches Bulletin.*** 2017;2017(1)

9. Public Health England. National rotavirus immunisation programme update: preliminary vaccine coverage for England, February 2016 to July 2016. In: Infection Report. vol. 10 Number 32: ***Health Protection Report***; 2016.

10. de Hoog MLA, Vesikari T, Giaquinto C, Huppertz HI, Martinon-Torres F, Bruijning-Verhagen P. Report of the 5th European expert meeting on rotavirus vaccination (EEROVAC). ***Hum Vaccin Immunother.*** 2018;14(4):1027–34.

11. Bruijning-Verhagen P, Mangen MJ, Felderhof M, Hartwig NG, van Houten M, Winkel L, de Waal WJ, Bonten MJ. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med***. 2013;11:112.

12. de Wit MA, Koopmans MP, Kortbeek LM, Wannet WJ, Vinje J, van Leusden F, Bartelds AI, van Duynhoven YT. Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. ***Am J Epidemiol***. 2001;154(7):666–74.

13. de Wit MA, Koopmans MP, Kortbeek LM, van Leeuwen NJ, Bartelds AI, van Duynhoven YT. Gastroenteritis in sentinel general practices, The Netherlands. ***Emerg Infect Dis.*** 2001;7(1):82–91.

14. Bruijning-Verhagen P, Sankatsing V, Kunst A, van den Born C, Bleeker E, Thijsen S, Ijzerman EP, van der Velden VH, Bonten MJ. Rotavirus-related hospitalizations are responsible for high seasonal peaks in all-cause pediatric hospitalizations. ***Pediatr Infect Dis J***. 2012;31(12):e244–9.

15. National Institute for Public Health and the Environment. The National Immunisation Programme in the Netherlands: developments in 2009 [http://www.rivm.nl/bibliotheek/rapporten/210021012.pdf].

16. Schurink-van' t Klooster TM, de Melker HEE. The national immunisation programme in the Netherlands: surveillance and developments in 2015-2016. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu; 2016.

17. Mangen MJ, van Duynhoven YT, Vennema H, van Pelt W, Havelaar AH, de Melker HE. Is it cost-effective to introduce rotavirus vaccination in the Dutch national immunization program? ***Vaccine.*** 2010;28(14):2624–35.

18. van Dongen F, Schuurman R, Bonten MJM, Study-Group ObotR. Rotavirus hospitalizations in the absence of rotavirus vaccine in 2015–2016 in the Netherlands. In: 5th European Expert Meeting on Rotavirus Vaccination: March 20-22nd, 2017 2017; Utrecht; 2017. p. 85.

19. RIVAR-project: Risk-Group Infant Vaccination Against Rotavirus. [http://portal.juliuscentrum.nl/research/nl-NL/cohortsandprojects/cohortsprojects/rivar.aspx].

20. Marlow R, Finn A, Trotter C. Quality of life impacts from rotavirus gastroenteritis on children and their families in the UK. ***Vaccine***. 2015;33(39):5212–6.

21. Quee F, de Hoog MLA, Schuurman R, Bruijning-Verhagen P. A comparison of incidence, transmission and burden of norovirus and rotavirus infections among young families in the Netherlands. In: 5th European Expert Meeting on Rotavirus Vaccination: March 20-22nd, 2017 2017; Utrecht; 2017. p. 83–4.

22. ZIN. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland (ZIN); 2015. Geactualiseerde versie 2015

23. Prelog M, Gorth P, Zwazl I, Kleines M, Streng A, Zlamy M, Heinz-Erian P, Wiedermann U. Universal mass vaccination against rotavirus: indirect effects on rotavirus infections in neonates and unvaccinated young infants not eligible for vaccination. ***J Infect Dis***. 2016;214(4):546–55.

24. Atchison CJ, Stowe J, Andrews N, Collins S, Allen DJ, Nawaz S, Brown D, Ramsay ME, Ladhani SN. Rapid declines in age group-specific rotavirus infection and acute gastroenteritis among vaccinated and unvaccinated individuals within 1 year of rotavirus vaccine introduction in England and Wales. ***J Infect Dis.*** 2016;213(2):243–9.

25. Krishnarajah G, Demissie K, Lefebvre P, Gaur S, Sheng Duh M. Clinical and cost burden of rotavirus infection before and after introduction of rotavirus vaccines among commercially and Medicaid insured children in the United States. ***Hum Vaccin Immunother.*** 2014;10(8):2255–66.

26. Kaufman HW, Chen Z. Trends in laboratory rotavirus detection: 2003 to 2014. Pediatrics. 2016;138(4):e20161173.

27. Sabbe M, Berger N, Blommaert A, Ogunjimi B, Grammens T, Callens M, Van Herck K, Beutels P, Van Damme P, Bilcke J. Sustained low rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014. ***Euro Surveill.*** 2016;21

28. Veldwijk J, Lambooij MS, Bruijning-Verhagen PC, Smit HA, de Wit GA. Parental preferences for rotavirus vaccination in young children: a discrete choice experiment. ***Vaccine.*** 2014;32(47):6277–83.

29. Zorginstituut Nederland. Medicijnkosten.nl. [https://www.medicijnkosten.nl/databank?artikelId=7083&hoeveelheid=1,00].

30. Nederlandse Zorgautoriteit. Toedieningskosten per vaccinatie - H006: neventarief 0 tot 5 jarige - Nederlandse Zorgautoriteit Rekenstaat 2014 tariefbeschikking. Utrecht: Nederlandse Zorgautoriteit; 2014.

31. Rozenbaum MH, Mangen MJ, Giaquinto C, Wilschut JC, Hak E, Postma MJ, Consensus Group on Dutch Rotavirus V. Cost-effectiveness of rotavirus vaccination in the Netherlands; the results of a consensus model. ***BMC Public Health***. 2011;11:462.

32. Leino T, Ollgren J, Stromberg N, Elonsalo U. Evaluation of the intussusception risk after pentavalent rotavirus vaccination in Finnish infants. ***PLoS One***. 2016;11(3):e0144812.

33. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: a self-controlled case-series evaluation. ***Vaccine.*** 2016;34(32):3684–9.

34. Rha B, Tate JE, Weintraub E, Haber P, Yen C, Patel M, Cortese MM, DeStefano F, Parashar UD. Intussusception following rotavirus vaccination: an updated review of the available evidence. ***Expert Rev Vaccines.*** 2014;13(11):1339–48.

35. Oberle D, Jenke AC, von Kries R, Mentzer D, Keller-Stanislawski B. Rotavirus vaccination: a risk factor for intussusception? ***Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.*** 2014;57(2):234–41.

36. Palupi-Baroto R, Lee KJ, Carlin JB, Bines JE. Intussusception in Australia: epidemiology prior to the introduction of rotavirus vaccine. ***Aust N Z J Public Health***. 2015;39(1):11–4.

37. Reyes JF, Wood JG, Beutels P, Macartney K, McIntyre P, Menzies R, Mealing N, Newall AT. Beyond expectations: post-implementation data shows rotavirus vaccination is likely cost-saving in Australia. ***Vaccine.*** 2017;35:345–52.

38. Mangen MJ, Bouwknegt M, Friesema IH, Haagsma JA, Kortbeek LM, Tariq L, Wilson M, van Pelt W, Havelaar AH. Cost-of-illness and disease burden of food-related pathogens in the Netherlands, 2011. ***Int J Food Microbiol.*** 2015;196:84–93.

39. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, Murray CJL. WHO guide to cost-effectiveness analysis. Geneva: World Health Organization; 2003.

40. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. [https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making].

41. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for costeffectiveness in health care health technology assessment (HTA). Brussels: Belgian Health Care Knowledge Centre; 2008.

42. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. ***N Engl J Med***. 2014;371(9):796–7.

43. Parez N, Giaquinto C, Du Roure C, Martinon-Torres F, Spoulou V, Van Damme

P, Vesikari T. Rotavirus vaccination in Europe: drivers and barriers. ***Lancet Infect Dis***.

2014;14(5):416–25.

44. Publique HCdlS. Infections à rotavirus : suspension des recommandations de vaccination des nourrissons [rotavirus infections; recommendation for infant vaccination suspended]. In: Avis et rapports de HCSP. Paris: Haut Conseil de la Sante Publique (HCSP); 2015. p. 1–5.

45. Pitzer VE, Atkins KE, de Blasio BF, Van Effelterre T, Atchison CJ, Harris JP, Shim E, Galvani AP, Edmunds WJ, Viboud C, et al. Direct and indirect effects of rotavirus vaccination: comparing predictions from transmission dynamic models. ***PLoS One***. 2012;7(8):e42320.

46. CentraalBureau voor de Statistiek. Levensverwachting; geslacht, leeftijd (per jaar en periode van vijf jaren). [http://statline.cbs.nl/Statweb/

47. Global Health Data Exchange. Perinatal care in the Netherlands 2008. 2008.

48. Brisson M, Sénécal M, Drolet M, Mansi JA. Health-related quality of life lost to rotavirus-associated gastroenteritis in children and their parents: a Canadian prospective study. ***Pediatr Infect Dis J.*** 2010;29(1):73–5.

49. Jit M, Mangen MJ, Melliez H, Yazdanpanah Y, Bilcke J, Salo H, Edmunds WJ, Beutels P. An update to "The cost-effectiveness of rotavirus vaccination: comparative analyses for five European countries and transferability in Europe". ***Vaccine.*** 2010;28(47):7457–9.

50. Friesema IH, Lugner AK, van Duynhoven YT, Group GEW. Costs of gastroenteritis in the Netherlands, with special attention for severe cases. Eur J Clin Microbiol Infect Dis. **2012;31(8):1895–900.**
51. van den Brandhof WE, De Wit GA, de Wit MA, van Duynhoven YT. Costs of gastroenteritis in the Netherlands. ***Epidemiol Infect***. 2004;132(2):211–21.

52. Haagsma JA, Geenen PL, Ethelberg S, Fetsch A, Hansdotter F, Jansen A, Korsgaard H, O'Brien SJ, Scavia G, Spitznagel H, et al. Community incidence of pathogen-specific gastroenteritis: reconstructing the surveillance pyramid for seven pathogens in seven European Union member states. ***Epidemiol Infect***. 2013;141(8):1625–39.

53. van der Valk ME, Mangen MJ, Leenders M, Dijkstra G, van Bodegraven AA, Fidder HH, de Jong DJ, Pierik M, van der Woude CJ, Romberg-Camps MJ, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF therapy: results from the COIN study. ***Gut***. 2014;63(1):72–9.
54. (Statistiek) SNCBvd: Beroepsbevolking; kerncijfers naar geslacht en andere kenmerken 1996–2014. 13 Februar 2015 edn; 2015.
55. Vesikari T, Dennehy P, Matson D, Itzler R, Dallas M, Goveia M, DiNubile M, Heaton P, Lawrence J, Ciarlet M. Efficacy of Rotateq®, the pentavalent rotavirus vaccine, between doses: potential benefits of early protection [abstract]. ***Arch Dis Child***. 2008;93:pw 70.
56. Vesikari T, Itzler R, Karvonen A, Korhonen T, Van DP, Behre U, Bona G, Gothefors L, Heaton PM, Dallas M, et al. RotaTeq, a pentavalent rotavirus vaccine: efficacy and safety among infants in Europe. ***Vaccine.*** 2009;28(3):345–51.
57. Vesikari T, Karvonen A, Ferrante SA, Ciarlet M. Efficacy of the pentavalent rotavirus vaccine, RotaTeq(R), in Finnish infants up to 3 years of age: the Finnish Extension Study. ***Eur J Pediatr.*** 2010;169(11):1379–86.

Supplementary Material

Additional file 1: Model Input Data

Table S1 – Assumed herd protection effects for vaccinated and unvaccinated age cohorts

	Vaccinated			Unvaccinated		
Age group	Study estimates	Source	Model input	Study estimates	Source	Model input
<2-3 months	61%	[1,2]	30%	NA		0
3 mo -1 year	37-65%*	[3]	25%	NA	[1-5]	0
1-2 years	37-65%*		25%	33-72%		28%
2-3 years	37-65%*		25%	38-62%		28%
3-4 years	37-65%*		25%	36-65%		28%
4-5 years	37-65%*		25%	25-65%		28%
6-10 years	NA		0	39-61%		25%
10-14 years	NA		0	50-55%		25%

* age-group not specified, average of ages < 5

Intussusception length of hospital stay

Administrative hospital discharge data were retrospectively collected from the Dutch National Medical Registration (LMR) database. The LMR database covers around 90% of the total Dutch population of 17 million people. It contains anonymized data on hospital admissions, outpatient consultation and emergency department visits including discharge diagnoses according to the International Classification of Diseases (ICD) codes, date of admission and discharge, patient age and gender. For diagnostic coding, the Ninth Revision (ICD-9) was used up to 2012 and ICD-10 thereafter. A validation study showed high accuracy of coding and concluded that the discharge data are generally of high quality[6].

For the period from 1 January 2008 to 31 December 2012, we extracted all cases with a primary or secondary discharge diagnosis of intussusception (ICD-9 CM code 560.0) in children aged between 0 and 12 months (i.e. children aged 0–35 months). A total of 276 cases were retrieved. The average length of stay was 2.11 days and 95% of patients were discharged within 6 days of hospitalization. For the complicated IS cases, we assumed their hospital stay represented the upper 5% of the length of stay distribution which was > 6 days, 3 times more than the average length of stay. We thus assumed a three times longer hospital stay for complicated IS cases, compared to uncomplicated IS cases. A similar assumption was applied for utility losses, such that QALY losses for complicated IS were three times that of uncomplicated IS.

RotaFam study

This is a prospective community-based household study on AGE occurrence and transmission[7]. Households with at least one child aged less than two years were randomly selected from municipal registries and invited to participate in the study. Participating households kept a digital symptom diary by means of an interactive smartphone App for each household member during ten consecutive weeks between January and May 2016 or 2017. Occurrence of AGE, which was detected based on symptom entries through built-in algorithms in the App, triggered additional disease questionnaires and a stool sample request for virological examination. The disease questionnaires included a severity score, items on healthcare usage and parental work-loss. All samples were tested by multiplex PCR for presence of norovirus, rotavirus, astrovirus and adenovirus 40/41. Data from the 2016 season on rotavirus AGE episodes in children were used to estimate parental productivity losses due to work-absence for community (i.e. mild) and GP attended (i.e. moderate) episodes.

We identified 28 community episodes of rotavirus AGE in children < 15 years. Of these, eight were GP attended. In three episodes (11%), a caregiver took time off from work varying between 0.5 and 2 days. These sick children were aged < 2 years and two had also attended the GP.

Thus, in one out of 20 episodes without medical care a caregiver took time off from work (ie. 1 day in 5% of cases). For two out of eight GP-attended episodes, a caregiver took time off from work (ie. 0.5-2 days in 25% of cases).

Additional file 2: Additional results

Table S2 – Targeted vaccination compared to no vaccination: Baseline assumptions and applied sensitivity and scenario analyses

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY) - Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Baseline	1139 (426-2022)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY) - Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Sensitivity and scenario analyses: w.r.t. assumed intussusception (IS) risk (in baseline 1:50,000) and complicated IS (in baseline 4.8%)								
IS risk: 1:20,000	1139 (426-2022)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	11.53/0.55	1:9 (1:5-1:13)	1:683 (1:598-1:768)
IS risk: 1:100,000	1139 (426-2022)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	2.31/0.11	1:43 (1:23-1:66)	1:3414 (1:2988-1:3840)
Complicated IS 0%	1139 (426-2022)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	4.61/0.00	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
Complicated IS 9.6%	1139 (426-2022)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	4.61/0.44	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
w.r.t. assumed hospitalization rate								
Lower hospitalization rate (*75%)	870 (283-1561)	-11.5(-14.5--8.9)	cost-saving (cs-cs)	-6.9 (-9.2--4.8)	cost-saving (cs-cs)	4.61/0.22	1:16 (1:9-1:25)	1:1,260 (1:1121-1:1440)
Higher hospitalization rate (*125%)	1414 (566-2482)	-22.4 (-18.3--27.1)	cost-saving (cs-cs)	-15.3 (-11.9--19.2)	cost-saving (cs-cs)	4.61/0.22	1:27 (1:15-1:41)	1:2134 (1:1868-1:2400)
w.r.t. hospitalization costs								
Lower hospitalization costs (*75%)	1139 (426-2022)	-13.0 (-16.0--10,2)	cost-saving (cs-cs)	-7.1 (-9.4--5.0)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
Higher hospitalization costs (*125%)	1139 (426-2022)	-21.0 (-25.5--17.0)	cost-saving (cs-cs)	-15.1(-19.0--11.7)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY) - Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
w.r.t. productivity losses								
Caregiver work absence as in[8] [b]	1139 (426-2022)	-16.8 (-20.5--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
w.r.t. assumed QALY losses (in baseline: 0.0011, 0.0022, 0.0034 and 0.0026 for mild, moderate, severe and nosocomical infections, respectively)								
QALY losses as in[8] [c]	1134 (421-2017)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
higher QALY losses[9] [d]	1146 (433-2029)	-17.0 (-20.8--13.6)	cost-saving (cs-cs)	-11.1 (-14.2--8.4)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
w.r.t. assumed discount rate (3% for costs and effects in baseline)								
Discount rate: 0% effects & costs	2385 (792-4363)	-22.6 (-27.6--18.2)	cost-saving (cs-cs)	-14.8 (-18.9--11.2)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
Discount rate: 2% effects & costs	1435 (528-2560)	-18.6 (-22.7--14.9)	cost-saving (cs-cs)	-12.2 (-15.6--9.2)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
Discount rate: 4% effects & costs	916 (349-1615)	-15.5 (-19.0--12.5)	cost-saving (cs-cs)	-10.1 (-13.0--7.6)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)
Dutch Discount rates (ef-fects (1.5%) & costs (4%))[10]	1620 (583-2909)	-15.5 (-19.0--12.5)	cost-saving (cs-cs)	-10.1 (-13.0--7.6)	cost-saving (cs-cs)	4.61/0.22	1:21 (1:12-1:33)	1:1707 (1:1494-1:1920)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY) - Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
w.r.t. older age at first infection and consequently slightly lower probability of seeking medical care[e]								
50% of 0-1 year olds were assumed to be 1-2 years old when infected	1052 (383-1873)	-14.3 (-17.8 - -11.3)	cost-saving (cs-cs)	-9.0(-11.9- -6.5)	cost-saving (cs-cs)	4.61/0.22	1:20 (1:11-1:31)	:1532 (1:1340-1:1725)
75% of 0-1 year olds were assumed to be 1-2 years old when infected	9968 (335-1773)	-12.7 (-15.9- -9.8)	cost-saving (cs-cs)	-7.7 (-10.4--5.4)	cost-saving (cs-cs)	4.61/0.22	1:19 (1:10-1:29)	1:1420 (1:1239-1:1602)
w.r.t. assumed vaccine coverage (in baseline: 86% coverage)								
Vaccine coverage: 75%	1113 (406-1987)	-14.8 (-18.1--11.8)	cost-saving (cs-cs)	-9.6 (-12.4--7.3)	cost-saving (cs-cs)	4.02/0.19	1:24 (1:13-1:37)	1:1707 (1:1494-1:1920)

CI: confidence interval; cs: cost-saving; (cs-cs): 95%CI limits both cost-saving; IS: intussusception; S.A.: Sensitivity analysis or scenario analysis.

a)Note: negative costs are savings

b)In the earlier model the assumed hours of work loss for mild cases were: 0.93; 1.36; 0.84 days for ages 0 to 4; 5 to 9 and 10 to 14 years respectively, versus in the baseline: 1 day (~8 hours) in 5% of episodes for children under the age of 10 and for children > 10 years of age work loss estimates were reduced by 50%. In the earlier model the assumed hours of work loss for moderate cases were: 1.35; 1.98; 1.23 for ages 0 to 4; 5 to 9 and 10 to 14 years respectively, versus in the baseline: 0.5 - 2 days in 25% of episodes for children under the age of 10 and for children > 10 years of age work loss estimates were reduced by 50%.

c)Bruijning et al. [8] used 0.0011, 0.0022, 0.0022 and 0.0020 for mild, moderate, severe and nosocomial infections, respectively.

d)We included slightly higher QALY losses based on the sensitivity analysis of Marlow et al. (for hospitalizations 0.0039 vs 0.0030 in the baseline and for GP visits 0.0030 vs 0.0022 in the baseline)[9])

e)On average 21.5% of the 0-1 years old would require a GP visit, whereas only 18.5% of 1-4 years old (**Table 1**). As the GP has a gatekeeper function in the Netherlands, we modelled that on average 27.6% of the 0-1 year olds visiting a GP would require hospitalization, whereas this would be only 16.4% if 1-4 years old. These averages were derived from the baseline simulations results.

Table S3 – Universal vaccination compared to no vaccination: Baseline assumptions and applied sensitivity and scenario analyses

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY)- Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Baseline	1907 (1114-2915)	98 (74-116)	51,277 (29,259-94,686)	137 (126-148)	72,021 (45,102-126,919)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Sensitivity and scenario analyses: w.r.t. assumed intussusception (IS) risk (in baseline 1:50,000) and complicated IS (in baseline 4.8%)								
IS risk: 1:20,000	1907 (1114-2915)	98 (74-116)	51,350 (29,302-94,814)	137 (126-148)	72,090 (45,144-127,054)	146.0/7.0	1:0.7 (1:0.4-1:1.1)	1:274 (1:241-1:307)
IS risk: 1:100,000	1908 (1114-2916)	98 (74-116)	51,253 (29,245-94,643)	137 (126-148)	71,998 (45,088-126,874)	29.0/1.4	1:3.5 (1:1.9-1:5.6)	1:1370 1:1206-1:1533
Complicated IS 0%	1908 (1114-2915)	98 (74-116)	51,270 (29,255-94,674)	137 (126-148)	72,014 (45,098-126,906)	58.4 / 0.0	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Complicated IS 9.6%	1907 (1114-2915)	98 (74-116)	51,284 (29,263-94,697)	137 (126-148)	72,027 (45,106-126,931)	58.4 / 5.6	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
w.r.t. assumed hospitalization rate								
Lower hospitalization rate (*75%)	1608 (949-2419)	124 (101-140))	76,831 (47,406-135,892)	157 (148-166)	97,654 (63,262 - 169,264)	58.4 / 2.8	1:1.3 (1:0.7-1:2.1)	1:514 (1:452-1:575)
Higher hospitalization rate (*125%)	2213 (1262-3435))	72 (47-93)	32,581 (16,434-63,943)	118 (104-131)	53,214 (32,257-96,889)	58.4 / 2.8	1:2.2 (1:1.2-1:3.5)	1:856 (1:754-1:958)
w.r.t. hospitalization costs								
Lower hospitalization costs (*75%)	1907 (1114-2915)	116 (94-133)	61,023 (36,124-110,191)	156 (147-165)	81,767 (51,898-142,952)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY)- Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Higher hospitalization costs (*125%)	1907 (1114-2915)	79 (54-100)	41,531 (22,321-79,488)	119 (105-132)	62,275 (38,511-111,246)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
w.r.t. productivity losses								
Higher proucitvity losses (* 200%)	1907 (1114-2915)	60 (20-88)	31,659 (9,010-65,904)	137 (126-148)	72,027 (45,106-126,931)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Caregiver work loss as in[8] [b]	1907 (1114-2915)	99 (83-114)	51,746 (30,863-94,173)	137 (126-148)	72,021 (45,102-126,919)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
w.r.t. assumed QALY losses (in baseline: 0.0011, 0.0022, 0.0034 and 0.0026 for mild, moderate, severe and nosocomical infections, respectively)								
QALY losses as in[8] [c]	1875 (1083-2882)	98 (74-116)	52,165 (29,599-97,158)	137 (126-148)	73,268 (45,633-130,334)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
higher QALY losses[9] [d]	2144 (1332-3179)	98 (74-116)	45,620 (26,919-80,560)	137 (126-148)	64,075 (41,500-106,594)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
w.r.t. assumed discount rate (3% for costs and effects in baseline)								
Discount rate: 0% effects & costs	3525 (1715-5891)	126 (95-150)	35,747 (18,828-77,207)	178 (163-192)	50,537 (29,130-104,921)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Discount rate: 2% effects & costs	2294 (1279-3612)	106 (80-126)	46,192 (25,696-88,889)	149 (137-161)	65,025 (39,734-119,999)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Discount rate: 4% effects & costs	1612 (976-2416)	91 (69-108)	56,223 (32,908-101,064)	127 (117-137)	78,785 (50,448-133,670)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY)- Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Dutch Discount rates (ef-fects (1.5%) & costs (4%))[10]	2534 (1382-4041)	91 (69-108)	35,773 (19,780-70,545)	127 (117-137)	50,128 (30,299-94,832)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
w.r.t. older age at first infection and consequently slightly lower probability of seeking medical care[e]								
50% of 0-1 year olds were assumed to be 1-2 years old when infected	1785 (1029-2742)	113 (90-130)	63,147 (37,271-115,558)	148 (138-158)	83,144 (52,799-146,342)	58.4 / 2.8	1:1.6 (1:0.9-1:2.6)	:598 (1:528-1:669)
75% of 0-1 year olds were assumed to be 1-2 years old when infected	1706 (984-2608)	124 (102-141)	72,777 (44,198-131,290)	157 (148-166)	92,015 (58,897-161,918)	58.4 / 2.8	1:1.5 (1:0.8-1:2.4)	1:528 (1:465-1:592)
w.r.t. assumed herd immunity (in baseline herd immunity was considered)								
No herd immunity	1690 (916-2680)	115 (96-131)	68,092 (39,790-131,501)	148 (138-158)	87,833 (53,677-166,304)	58.4 / 2.8	1:1.7 (1:0.9-1:2.8)	1:603 (1:527-1:678)
Lower herd immunity (*50%)	1798 (1016-2800)	106 (85-124)	59,188 (34,260-111,126)	143 (132-153)	79,465 (49,224-144,298)	58.4 / 2.8	1:1.8 (1:0.9-1:2.8)	1:644 (1:566-1:722)
Higher herd immunity (*150%)	2017 (1212-3045)	89 (64-109)	44,204 (24,791-81,325)	132 (120-143)	65,356 (41,380-112,987)	58.4 / 2.8	1:1.8 (1:1.0-1:2.9)	1:726 (1:640-1:812)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)[a]	ICER (€/QALY)- Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
for an alternative universal vaccination (in baseline: vaccine coverage of 86% & herd immunity & vaccine costs of €75/child)								
Vaccine coverage 60% & no herd immunity & market price (€135.3/child)	1480 (730-2443)	176 (163-188)	119,191 (70,488-244,692)	200 (193-207)	134,920 (80,702-275,744)	40.8/2.0	1:2.4 (1:1.3-1:3.8)	1:603 (1:527-1:678)
w.r.t. vaccine cost per child, excluding application costs (in baseline vaccine costs of €75/child)								
Vaccine costs of €67.5	1907 (1114-2915)	81 (57-99)	42,304 (23,270-79,865)	120 (109-131)	63,048 (39,266-111,667)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €60.0	1907 (1114-2915)	64 (40-82)	33,331 (16,809-64,499)	103 (92-114)	54,075 (33,482-96,411)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €52.5	1907 (1114-2915)	46 (23-65)	24,358 (9,958-49,675)	86 (75-97)	45,102 (27,586-81,051)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €45.0	1907 (1114-2915)	29 (6-48)	15,385 (2,750-34,992)	69 (58-80)	36,129 (21,511-66,081)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €37.5	1907 (1114-2915)	12 (-11-31)	6,412 (cs - 21,296)	52 (41-63)	27,156 (15,467-50,957)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €30.0	1907 (1114-2915)	-5 (-28 - 14)	cost-saving (cs - 2,561)	35 (23-45)	18,183 (9,298-36,179)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €22.5	1907 (1114-2915)	-22 (-46 - -3)	cost-saving (cs- cs)	18 (6-28)	9,209 (2,758-21,476)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)
Vaccine costs of €15.0	1907 (1114-2915)	-39 (-63 - -21)	cost-saving (cs - cs)	0.5 (-11 - 11)	236 (cs – 7,623)	58.4 / 2.8	1:1.8 (1:1.0-1:2.8)	1:685 (1:603-1:767)

Used abbreviations: CI: confidence interval; cs: cost-saving; (cs-cs): 95%CI limits both cost-saving; IS: intussusception; S.A.: Sensitivity analysis or scenario analysis.

a)Note: negative costs are savings

b)In the earlier model the assumed hours of work loss for mild cases were: 0.93; 1.36; 0.84 days for ages

0 to 4; 5 to 9 and 10 to 14 years respectively versus in the baseline: 1 day (~8 hours) in 5% of episodes for children under the age of 10 and for children > 10 years of age work loss estimates were reduced by 50%. In the earlier model the assumed hours of work loss for moderate cases were: 1.35; 1.98; 1.23 for ages 0 to 4; 5 to 9 and 10 to 14 years respectively versus in the baseline: 0.5 – 2 days in 25% of episodes for children under the age of 10 and for children > 10 years of age work loss estimates were reduced by 50%.

c)Bruijning et al[8] used 0.0011, 0.0022, 0.0022 and 0.0020 for mild, moderate, severe and nosocomial infections, respectively.

d)We included slightly higher QALY losses based on the sensitivity analysis of Marlow et al. (for hospitalizations 0.0039 vs 0.0030 in the baseline and for GP visits 0.0030 vs 0.0022 in the baseline)[9]).

e) On average 21.5% of the 0-1 years old would require a GP visit, whereas only 18.5% of 1-4 years old (**Table 1**). As the GP has a gatekeeper function in the Netherlands, we modelled that on average 27.6% of the 0-1 year olds visiting a GP would require hospitalization, whereas this would be only 16.4% if 1-4 years old. These averages were derived from the baseline simulations results.

Table S4 – Universal vaccination compared to target vaccination: Baseline assumptions and applied sensitivity and scenario analyses

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)	ICER (€/QALY)- Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Baseline	769 (561-1003)	115 (94-131)	149,282 (101,101 - 220,113)	148 (139-157)	193,084 (142,802 - 271,403)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Sensitivity and scenario analyses: w.r.t. vaccine cost per child, excluding application costs (in baseline vaccine costs of €75/child)								
Vaccine costs of €67.5	769 (561-1003)	98 (77-114)	127,021 (82,989-190,334)	131 (122-140)	170,823 (125,657 - 241,489)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Vaccine costs of €60.0	769 (561-1003)	81 (59-97)	104,760 (65,365-161,065)	114 (105-123)	148,562 (108,357 - 211,313)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Vaccine costs of €52.5	769 (561-1003)	63 (42-79)	82,500 (47,090-131,537)	97 (88-106)	126,301 (91,196-181,116)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Vaccine costs of €45.0	769 (561-1003)	46 (25-62)	60,239 (28,385-101,948)	80 (71-89)	104,040 (73,947-151,104)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)

Scenario	Δ QALY	Δ societal cost (in mio. €)[a]	ICER (€/QALY) - Societal perspective	Δ healthcare cost (in mio. €)	ICER (€/QALY)- Healthcare payer perspective	Induced IS/complicated IS cases	Induced IS: prevented fatal cases	Induced IS: prevented hospitalized cases
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Vaccine costs of €37.5	769 (561-1003)	29 (8-45)	37,978 (9,277-73,241)	63 (54-72)	81,779 (56,779-120,988)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Vaccine costs of €30.0	769 (561-1003)	19 (-9-28)	15,717 (cs - 44,867)	46 (37-55)	59,519 (39,427-90,783)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Vaccine costs of €22.5	769 (561-1003)	-5 (-26-11)	cost-saving (cs -16,466)	29 (20-37)	37,528 (21,440-61,339)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)
Vaccine costs of €15.0	769 (561-1003)	-22 (-43 - -6)	cost-saving (cs -cs)	12 (2-20)	14,997 (2,738-32,159)	53.8/ 2.6	1:0.09 (1:0.02-1:0.2)	1:597 (1:526-1:668)

Used abbreviations: CI: confidence interval; cs: cost-saving; (cs-cs): 95%CI limits both cost-saving; IS: intussusception.

a)Note: negative costs are savings

Note2: No sensitivity analyses on vaccine costs were applied for the target vaccination strategy, as this scenario was already cost-saving at current market prices of €135.32, for both perspectives. By lowering the vaccine costs, the savings would become larger.

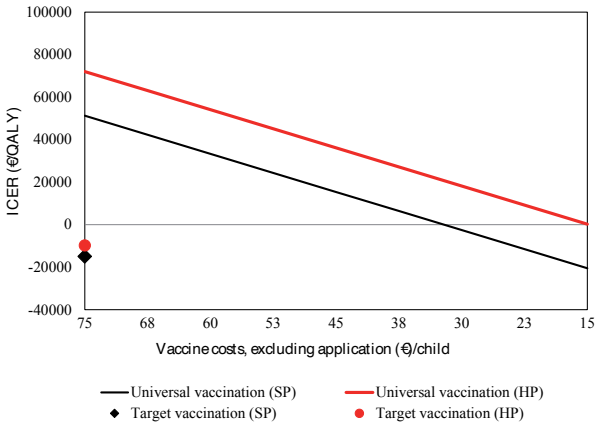


Figure S1: Mean ICER for targeted* and universal vaccination using a societal perspective (black square/black line) and healthcare payer perspective (red dots/red line), for different vaccine costs.

*No sensitivity analyses on vaccine costs were applied for the targeted vaccination strategy, as this scenario was already cost-saving at current market prices of €135.32, for both perspectives. By lowering the vaccine costs, the savings would become larger.

Note: In case of universation vaccination strategy is vaccination cost-saving at vaccine costs of €32/child using a societal perspective (SP) and at €14.8/child using a healthcare payer perspective (HP). For full details see **Table S3**.

References

1. Prelog M, Gorth P, Zwazl I, Kleines M, Streng A, Zlamy M, Heinz-Erian P, Wiedermann U: Universal Mass Vaccination Against Rotavirus: Indirect Effects on Rotavirus Infections in Neonates and Unvaccinated Young Infants Not Eligible for Vaccination. ***J Infect Dis*** 2016, 214(4):546-555.
2. Atchison CJ, Stowe J, Andrews N, Collins S, Allen DJ, Nawaz S, Brown D, Ramsay ME, Ladhani SN: Rapid Declines in Age Group-Specific Rotavirus Infection and Acute Gastroenteritis Among Vaccinated and Unvaccinated Individuals Within 1 Year of Rotavirus Vaccine Introduction in England and Wales. ***J Infect Dis*** 2016, 213(2):243-249.
3. Krishnarajah G, Demissie K, Lefebvre P, Gaur S, Sheng Duh M: Clinical and cost burden of rotavirus infection before and after introduction of rotavirus vaccines among commercially and Medicaid insured children in the United States. ***Hum Vaccin Immunother*** 2014, 10(8):2255-2266.
4. Kaufman HW, Chen Z: Trends in Laboratory Rotavirus Detection: 2003 to 2014. ***Pediatrics*** 2016, 138(4).
5. Sabbe M, Berger N, Blommaert A, Ogunjimi B, Grammens T, Callens M, Van Herck K, Beutels P, Van Damme P, Bilcke J: Sustained low rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014. ***Euro Surveill*** 2016, 21(27).
6. Paas G, Veenhuizen K: Onderzoek naar de betrouwbaarheid van de Landelijke Medische Registratie (LMR). [Research on the reliability of the National Medical Registration (LMR)]. In. Utrecht: Prismant; 2002: 1-22.
7. Quee F, de Hoog MLA, Schuurman R, Bruijning-Verhagen P: A comparison of incidence, transmission and burden of norovirus and rotavirus infections among young families in the Netherlands. In: 5th European Expert Meeting on Rotavirus Vaccination: March 20-22nd, 2017 2017; Utrecht; 2017: 83-84.
8. Bruijning-Verhagen P, Mangen MJ, Felderhof M, Hartwig NG, van Houten M, Winkel L, de Waal WJ, Bonten MJ: Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med 2013***, 11:112.
9. Marlow R, Finn A, Trotter C: Quality of life impacts from rotavirus gastroenteritis on children and their families in the UK. ***Vaccine*** 2015, 33(39):5212-5216.
10. ZIN: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. In., vol. Geactualiseerde versie 2015: Zorginstituut Nederland (ZIN); 2015.

Chapter 4

Rotavirus Vaccine Effectiveness among Infants with Medical Risk Conditions in the Netherlands

Josephine A.P. van Dongen, Elsbeth D.M. Rouers, Rob Schuurman, Marlies A. van Houten, Louis J. Bont, Obbe F. Norbruis, Marieke A.C. Hemels, Gijs T.J. van Well, Arine M. Vlieger, Jacqueline van der Sluijs, Helene G. Stas, Gerdien Tramper-Stranders, Elly A. Kleinlugtenbeld, Anne A.M.W. van Kempen, Margreet Wessels, Maaike C. van Rossem, Carin A.C.M. Dassel, Dasja Pajkrt, Marc J.M. Bonten, and Patricia C.J. Bruijning-Verhagen. On behalf of the RIVAR study team.

Under review, revisions submitted

Abstract

Objective

Rotavirus vaccination has 87-100% effectiveness against severe rotavirus acute gastroenteritis (AGE), in healthy infants in high-income countries. Little is known whether infants with medical risk conditions (MRC) are equally protected. We conducted a quasi-experimental prospective multicenter before-after cohort-study to assess the vaccine effectiveness (VE) of the human rotavirus vaccine (HRV) among MRC infants.

Methods

HRV was implemented in routine care for MRC infants in 13 Dutch hospitals. Participants in the before and after cohort, HRV unvaccinated and vaccinated respectively, were followed for occurrence of (rotavirus) AGE. VE of at least one dose was estimated using time-to-event analysis for severe rotavirus AGE. Vaccine impact on rotavirus hospitalizations comparing pre- and post-implementation periods was also assessed.

Results

631 and 851 high-risk infants with MRC participated in the before and after cohorts, respectively. In total, 1302 infants were premature (88.3%), 447 small for gestational age (30.2%) and 251 had at least one congenital disorder (17.0%). VE against severe rotavirus AGE was 30% (95%CI -36;65%) and -2% (95%CI -50;31%) against rotavirus AGE of any severity. Overall, the observed number of rotavirus hospitalizations was low and not significantly different between the cohorts (2 and 2, respectively).

Conclusion

In contrast to previous findings among healthy term infants, the routine use of human rotavirus vaccine in vulnerable medical risk infants offers limited protection against severe rotavirus gastroenteritis. Our study highlights the importance of studying vaccine performance in subgroups of medical risk infants separately.

Introduction

Rotavirus is a frequent cause of acute gastroenteritis (AGE) in children below five years of age.[1] Since the global introduction of vaccines against rotavirus in 2006, hospitalizations for rotavirus AGE have decreased substantially.[2] Worldwide, over 98 countries have now included rotavirus vaccination in their national immunization program.[3] The majority of countries use one of two globally licensed live-attenuated oral rotavirus vaccines; Rotarix© or RotaTeq©. In high income countries, high rotavirus vaccine effectiveness (VE) against severe rotavirus AGE has been consistently reported for both vaccines with overall VE of more than 80% for a full series of either vaccine.[4–6] Yet, these estimates are primarily based on results from healthy infants.[4–6] There is however limited data on the performance of rotavirus vaccines in infants with underlying medical conditions that may influence their vaccine response and/or their risk of severe rotavirus AGE. These include premature infants, infants born small for gestational age and those with severe congenital disorders. There is reason to assume, vaccine responsiveness may be attenuated in these infants because of immaturity or conditions compromising immune responses to some extent due to their MRC.[7–9]

Infants diagnosed with one or more of these medical risk conditions (MRC) represent eight percent of the Dutch birth cohort.[10] An earlier study showed these infants are at increased risk of severe or complicated rotavirus AGE.[10] In the absence of universal rotavirus vaccination in the Netherlands we started a pilot with rotavirus vaccination implemented in routine neonatal/infant care for MRC infants. The human rotavirus vaccine (HRV, Rotarix©) was used throughout the project. This implementation was combined with a before-after cohort study to evaluate rotavirus VE of at least one dose in high-risk infants with one or more MRC, with a focus on premature infants.

Patients and methods

The RIVAR (Risk group Infant Vaccination Against Rotavirus) project piloted the implementation of a selective rotavirus vaccination program for MRC infants in pediatric secondary and tertiary care hospitals. The primary objectives of the RIVAR project were 1) to assess the feasibility of implementing and executing this selective rotavirus vaccination program in routine hospital and outpatient care for MRC infants and, 2) to determine vaccine effectiveness (VE) against severe rotavirus AGE in MRC infants.

Here, we describe the results of the step-wedge before-after cohort study that was designed to assess the primary endpoint of VE. The study protocol was registered in the Dutch trial registry.[11]

Study setting

Dutch hospitals with a neonatal intensive care unit (NICU) or post-intensive care (IC)/High Care (HC) ward were invited to participate in the project. Hospitals could participate if they were willing to 1) implement rotavirus vaccination for MRC infants in their routine neonatal care and, 2) recruit and enroll eligible infants in the before-after cohort study.

Thirteen Dutch hospitals, at 15 locations, with a NICU or post-IC/HC unit participated in the RIVAR study. Hospitals enrolled in a stepped-wedge order. The first hospitals enrolled in November 2014 and the last in April 2016.

Implementation of a hospital-based selective rotavirus vaccination program

Following enrollment, each hospital entered a preparatory pre-implementation year during which local operational procedures were developed for patient selection, rotavirus vaccine delivery, administration and, documentation. In the second year, rotavirus vaccination was locally implemented, at different time-points, for all infants with a qualifying MRC and was continued throughout the study.

At the start of the pre-implementation year, the participating site initiated screening of all hospitalized infants less than 14 weeks of age for prematurity (gestational age before 36 weeks), low birthweight (LBW, under 2500 grams) and/or, presence of a severe congenital disorder (for qualifying conditions, see figure S1 in appendix). Infants still hospitalized or receiving outpatient care between six to 14 weeks of postnatal age (corresponding with the age-window for first dose rotavirus vaccination) were eligible. Following implementation, the human rotavirus vaccine (HRV, containing attenuated human rotavirus G1P8 genotype, licensed by GSK, Belgium, since 2006) was used throughout the project and given as two oral doses.

Before-after cohort study

Parents of eligible infants were approached for participation in the cohort study with active follow-up for occurrence of AGE until 18 months of age. Enrollment started early in the pre-implementation year and continued in each hospital until 12-18 months after implementation of the selective rotavirus vaccination program. The 'before' cohort thus included infants who received standard of care only. The 'after' cohort included infants who were routinely offered rotavirus vaccination. Throughout follow-up, next to monthly questionnaires and medical chart review, parents were asked to notify the study team whenever symptoms of AGE developed in their child. Parents were instructed to collect a fecal sample from their child as soon as possible and to complete a symptom diary for seven days and a questionnaire on healthcare attendance. For a schematic overview of the study outline and procedures, see **figure 1**.

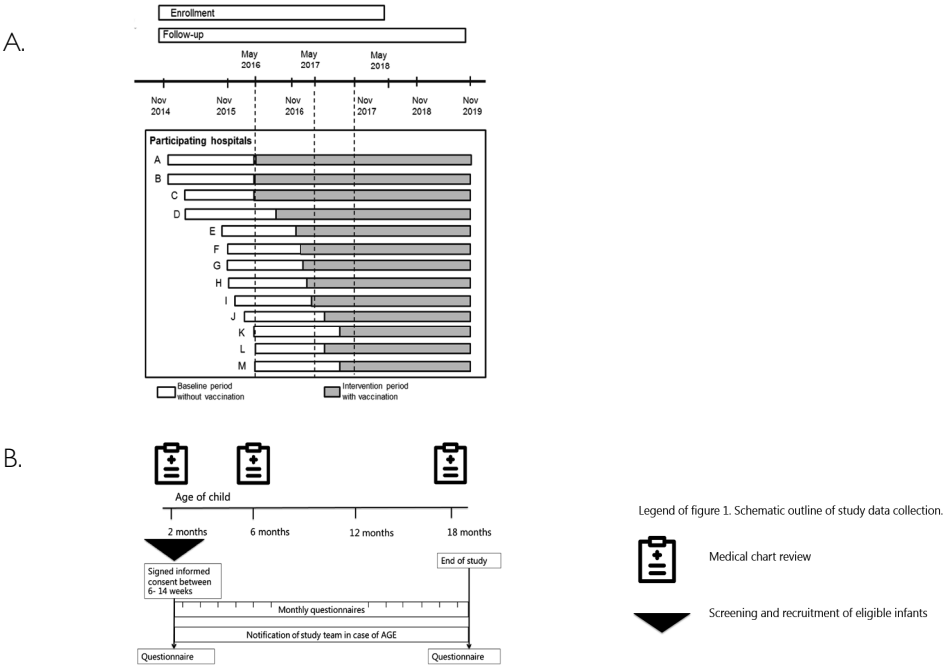


Figure 1. Schematic outline of study data collection and procedures. Abbreviations: AGE = acute gastroenteritis.

A. Implementation of a hospital-based selective rotavirus vaccination program: A screening log was recorded for infants with at least one of the qualifying MRC. Exclusion criteria were; known hypersensitivity to the vaccine components, history or predisposition of intussusception and/or diagnosis of severe combined immunodeficiency syndrome (SCID). During the pre-implementation period, eligible infants received standard of care only without rotavirus vaccination. Following implementation, eligible infants were offered rotavirus vaccination free of charge. Rotavirus vaccination status was documented in the screening log for each eligible infant. We also logged any serious adverse reaction as documented in the medical chart. Hospitals continued screening and vaccination until the end of the project in November 2019. The first dose human rotavirus vaccine (HRV) was administered by a healthcare professional at the study site between six and 14 weeks of age. The second dose was by default administered by parents at home, following detailed instructions, with a minimal interval of four weeks and no later than 23 weeks and 6 days of age. Alternatively, the second dose could be delivered at the site and administered by a healthcare professional.

B. Before-after cohort study: Eligible infants were not approached for participation in the cohort study if parents were not proficient in Dutch language, if the child was in custody or in an unstable home situation, if the infant had a poor medical prognosis, or if the infant was discharged from follow–up (including transfer to another non-participating hospital) before six weeks of age. Following informed consent, parents received a baseline questionnaire on household composition, socio-economic status and pregnancy, followed by short monthly questionnaires and a final questionnaire at 18 months of age. The monthly questionnaire consisted of seven items on respiratory and gastrointestinal symptoms during the past month, received vaccinations of the National Immunization Program (NIP) and rotavirus and solicited adverse events in the seven days following vaccination, type of feeding and daycare attendance. The final questionnaire at 18 months contained a modified quality of life questionnaire. Finally, trained research staff collected data from the participating child's hospital medical record at six weeks, five and 18 months of age, including rotavirus vaccination status and dates of vaccine administration, information on all hospitalizations, supportive therapy, medical treatment and complications

Sample size calculation was based on eight participating hospitals, an assumed VE of at least 60% against severe rotavirus AGE, at a cumulative incidence of four percent until 18 months of age and, a between hospital intra-class correlation of 0.002, as documented in study protocol.[11]

Microbiological analysis

Fecal samples were tested by multiplex realtime PCR for presence of rota-, noro-, adeno(type 40/41)- and, astrovirus. The laboratory analysis is described more elaborate in the supplement.

Definitions

AGE was defined as acute diarrhea or looser than normal stools more than three times per 24 hours, and/or forceful vomiting.[12] Reports of AGE were derived from three different sources; actively reported by parents, reported on monthly questionnaire and, retrieved form medical chart review (more elaborate in supplement). Severity was assessed by the Modified Vesikari score.[13,14]

The primary endpoints were defined as:

1. The protective effectiveness of at least one dose of HRV against severe rotavirus related AGE from 14 days post-dose one until 18 months of age.

2. The impact of the selective HRV vaccination program defined as the relative reduction in rotavirus related hospitalization (including symptomatic nosocomial infection) during follow-up comparing infants enrolled in the pre-implementation versus post-implementation periods.

Pre-specified secondary endpoints included 1) the effectiveness of a full series of HRV against severe rotavirus related AGE and, 2) the protective effectiveness of at least one dose of HRV against rotavirus related AGE of any severity.

Next, we performed subgroup analyses for infants born with 32-37 weeks, 30-32 weeks and < 30 weeks of gestation, term infants with congenital disorders and, infants with more than one risk condition.

As post-hoc analysis, we added all-cause (severe) AGE as outcome for all specified primary endpoints. This was decided because a stool sample was not obtained from a substantial proportion of AGE episodes (e.g. without a rotavirus test result) and previous studies have estimated up to 50 percent of severe AGE in infants caused by rotavirus.[15,16] In addition we quantified the probability of incorrectly estimating VE because of sparse confirmed rotavirus events.

Statistical analyses plan

For the primary analysis of VE, we used Cox regression modeling of the time to first episode of severe rotavirus AGE as a function of vaccination status with age (between two and 18 months) modeled as time-variable. Infants were censored at their first severe episode or when lost to follow-up. Rotavirus vaccination was modeled as a time-dependent covariate thereby accounting for weeks of observation in vaccinated infants pre dose one and the initial 14 days post dose one, when protection from vaccination is considered to be still minimal. VE was defined as 1 minus the Hazard Rate (HR) ×100%. The proportional hazard assumption was tested using Schoenfelds residuals. The primary analysis was adjusted for rotavirus seasonality (pre-specified). Weighted rotavirus epidemic intensity was calculated using the weekly data on rotavirus positive tests from the national virological surveillance. This surveillance includes aggregated test results from 20 sentinel laboratories in the Netherlands serving primary and secondary care.[17] Weight per week was derived by Rpackage timeseries accounting for each years' rotavirus season and amount of reporting labs. We considered the following additional variables as covariates: breastfeeding, young siblings (five years of age or less) in the household, daycare attendance, gestational age, household socio economic status (defined as the highest obtained parental education) and, parental origin.[18] We used likelihood ratio test to select the final model with covariates and present 95% confidence interval (CI) of the HR.

The impact of the HRV selective vaccination program was estimated from the proportion of infants with rotavirus related hospitalization in the post-implementation versus the pre-implementation period, expressed as 1 minus the risk ratio (RR). We used a mixed model with a binomial distribution and RR were obtained from odds ratio using the method described by Knol et al.[19] To account for potential cluster effects within hospitals, type of study site (academic versus general hospital) was added as a random intercept to the model.

For the secondary analyses of a complete HRV series and subgroup analyses we used the cox model as described above. For VE against rotavirus AGE episodes of any severity, accounting for multiple episodes within one individual, we used negative binomial regression with VE calculated as 1 minus the incidence rate ratios (IRR) ×100%. Person-time of observation was included as offset in the model.

All-cause AGE analyses were performed using the same methods as described above. To calculate posterior probability of VE in our study-population, we used Bayesian analysis, with uninformative priors, of the Cox model for the primary outcome of VE against severe rotavirus AGE.

All analyses were performed according to protocol (ATP), where all pre-implementation infants whose parents indicated willingness to receive HRV were compared to all post-implementation infants who received ≥ 1 dose of HRV. Only for the impact of HRV on hospitalization, we performed an intention to treat (ITT) analysis where all infants in the pre-implementation period were compared to all infants in the post-implementation period irrespective of HRV

vaccination status.

Data analysis were performed using the statistical software of RStudio version 3.6.1. Packages; *survminer, survival, lme4, rstanarm, timeseries.*

Ethical approval

The medical ethic board of the University Medical Center Utrecht declared that the RIVAR study was not covered by the Medical Research Involving Human Subjects Act. Rotavirus vaccine was implemented into routine care and study procedures were non-invasive.

Results

Between November 2014 and April 2016, a total of 13 hospitals with 15 locations started in the pre-implementation period of the RIVAR project and subsequently implemented rotavirus vaccination between May 2016 and November 2017. Throughout the project a total of 2,484 medical risk infants in the pre-implementation and 2,878 in the post-implementation period met the eligibility criteria (**figure 2**). Between November 2014 and April 2016, 631 of these high-risk infants were recruited in the 'before' cohort and contributed to 9,125 person-months of observation. An additional 851 high-risk infants were enrolled in the 'after' cohort, between May 2016 and July 2018, and contributed to 12,302 person-months. Follow-up of the last cohort participant was completed in December 2019.

Among 1,482 cohort participants 1,302 infants were born premature, 447 were small for gestational age and 251 had one or more congenital disorders. The median length of postnatal hospital stay was 28 days (interquartile range [IQR], 38 days) and total median number of hospitalization days (including initial admission) during follow-up was 34 (IQR 44 days).

The characteristics of participants in the before and after cohort were comparable (**table 1**). There was a small difference in the participation rate in the national immunization program (seven percent less participation in the HRV vaccinated group) and in completeness of follow-up (number of participants with complete follow-up is 14% lower in HRV vaccinated group). 719 infants in the after cohort were HRV immunized, for 599 infants information on receiving the second dose administration was available (83.3%).

A total of 1,223 AGE episodes were identified during follow-up, table 2. A fecal sample was collected from 564 (46.1%) episodes. Rotavirus was detected in 117 AGE samples (20.7%). Severe (≥11 Vesikari score) rotavirus positive AGE occurred in 18 infants in the before cohort and 20 infants in the after cohort. Hospitalization due to rotavirus AGE was reported in two versus two infants.

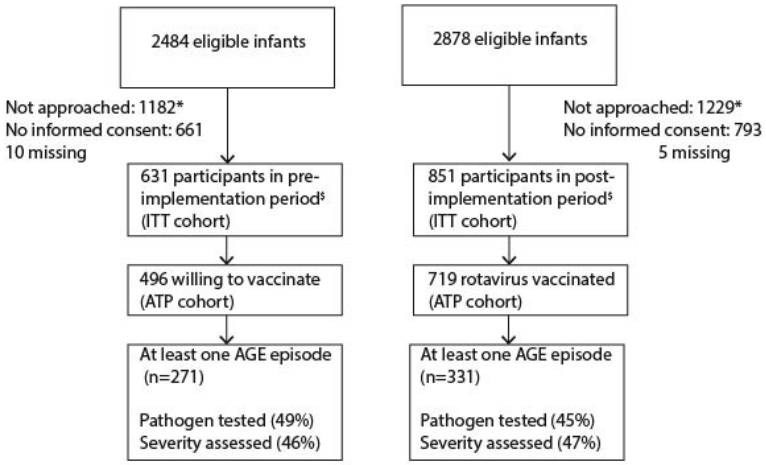


Figure 2. Flowchart of recruitment and cohort groups.

*Reasons for not approaching: 596 versus 663 discharged or referred (50.4% vs 53.9%), 201 versus 177 no Dutch speaking parent (17.0% vs 14.4%), 193 versus 96 unstable home situation (16.3% vs 7.8%), 82 versus 103 poor prognosis (6.9% vs 8.4%), 110 versus 190 other unspecified reason (9.3% vs 15.5%). Missing refers to missing information on whether infant was not approached or no consent was obtained. $82 missing information on willingness to vaccinate and 6 missing information on vaccination status. Abbreviations: ITT = intention to treat, ATP = according to protocol, AGE= acute gastroenteritis, n= number with characteristic.

Table 1. Comparison of characteristics between before-after cohort participants

	Intention to treat (ITT)			According to protocol (ATP)		
	Pre-implementation period: all infants N=631[$]	Post-implementation period: all infants N=851[$]	p-value	Pre-implementation: willing to vaccinate N=496	Post-implementation: vaccinated N=719	p-value
Male sex	361 (57.2%)	456 (53.8%)	0.19	286 (57.7%)	381 (53.0%)	0.11
Multiple births	158 (25.0%)	230 (27.1%)	0.37	115 (23.8%)	193 (26.8%)	0.15
Premature birth (gestation < 37 weeks)	549 (87.6%)	753 (88.8%)	0.47	432 (87.8%)	635 (88.3%)	0.79
Gestational age in weeks + days among those premature (SD)	31+4 (3+1)	31+6 (2+6)	0.03	31+3 (3+1)	32+1 (2+5)	**<0.001**

	Intention to treat (ITT)			According to protocol (ATP)		
	Pre-implementation period: all infants N=631[$]	Post-implementation period: all infants N=851[$]	p-value	Pre-implementation: willing to vaccinate N=496	Post-implementation: vaccinated N=719	p-value
Small for gestational age[£]	176 (27.9%)	271 (31.8%)	0.10	135 (27.2%)	238 (33.1%)	0.03
Presence of severe congenital disorder[*]	126 (20.0%)	125 (14.7%)	0.01	95 (19.2%)	106 (14.7%)	0.04
Length of postnatal hospital stay (IQR)	29 days (44)	27 days (38)	0.53	31 days (43)	27 days (35)	0.17
Total hospitalization days during follow-up (IQR)	35 days (48)	33 days (42)	0.35	37 days (48)	31 days (41)	0.13
Vaccinated within national immunization program	539 (85.4%)	753 (88.5%)	0.08	484 (97.6%)	652 (90.7%)	**<0.001**
Daycare ever	319 (56.5%)	464 (59.4%)	0.28	289 (58.6%)	398 (59.6%)	0.74
Average age at start in months (IQR)	6 (1-11)	5 (1-9)	0.06	6 (1-12)	5 (1-9)	**0.01**
Breastfed ever	355 (62.7%)	481 (61.4%)	0.61	312 (63.3%)	403 (602%)	0.29
Average duration of exclusive breastfeeding in weeks (SD)	16.8 (7.0)	16.3 (7.3)	0.40	16.6 (6.9)	16.4 (7.4)	0.69
Socieconomic status[^]			0.59			0.36
Higher	398 (71.3%)	568 (72.9%)		352 (71.5%)	492 (74.1%)	
Moderate	134 (24.0%)	183 (23.5%)		119 (24.2%)	153 (23.0%)	
Lower	26 (4.7%)	28 (3.6%)		21 (4.3%)	19 (2.9%)	

	Intention to treat (ITT)			According to protocol (ATP)		
	Pre-implementation period: all infants N=631[$]	Post-implementation period: all infants N=851[$]	p-value	Pre-implementation: willing to vaccinate N=496	Post-implementation: vaccinated N=719	p-value
Young sibling (≤ 5 yrs) in household	134 (24.4%)	167 (21.5%)	0.22	118 (24.2%)	148 (22.4%)	0.46
Young sibling attending daycare	87 (22.0%)	94 (17.3%)	0.07	77 (21.8%)	81 (17.5%)	0.13
Parental origin[#]			0.92			0.75
European parent(s)	471 (84.1%)	652 (83.3%)		417 (84.8%)	557 (83.4%)	
Non-European parent(s)	35 (6.3%)	31 (6.5%)		28 (5.7%)	38 (5.7%)	
Mixed	54 (9.6%)	80 (10.2%)		47 (9.6%)	73 (10.9%)	
Median age of parent(s) (IQR)	32.5 (27-38)	33 (27-39)	0.60	32.5 (27-38)	33 (27-39)	0.23
Mean number of months with completed folllow-up (SD)	14.5 (7.2)	14.5 (6.9)	0.84	16.4 (5.5)	14.9 (6.5)	**<0.001**
Number with complete follow-up until 18 months of age	421 (66.7%)	526 (61.8%)	0.05	380 (76.6%)	450 (62.6%)	**<0.001**

Percentages are derived excluding subjects with missing data on the variable. Statistical significance (p-value <0.05) is highlighted in bold. [$]82 missing information on willingness to vaccinate and 6 missing information on vaccination status. [£]Based on the 10th percentile growth curves (chapter 2). [*]Qualifying conditions in appendix figure S1. [^]Based on highest parental education. [#]Based on parental origin by World population by country[18]. Abbreviations: GA= gestational age, SD= standard deviation, IQR = interquartile range, yrs= years and, N = number in group.

Co-primary outcome

1. The adjusted HR for severe rotavirus AGE was 0.70 (95%CI 0.35;1.40) for rotavirus vaccinated versus unvaccinated infants in ATP analysis, resulting in a VE of 30% (95%CI -36%;65%) after at least one dose of HRV. Attending daycare and an increase in rotavirus epidemic intensity significantly increased the hazard of severe rotavirus AGE. Characteristics of these severe rotavirus AGE are presented in appendix table S2.

2. The impact of the selective HRV vaccination program defined as the relative reduction in rotavirus related hospitalization in the post-implementation versus pre-implementation period was 24%, RR 0.76 (95%CI 0.10;6.37).

Outcome estimates of primary, secondary and post-hoc analyses are presented in **table 3.** Secondary and pre-specified subgroup analyses are described more elaborate in the appendix.

Table 2. AGE events during follow-up in ITT and ATP before-after cohorts

	Intention to treat (ITT)		According to protocol (ATP)	
	Pre-implementation period: all infants N=631[$]	Post-implementation period: all infants N=851[$]	Pre-implementation: willing to vaccinate N=496	Post-implementation: vaccinated N=719
All-cause AGE				
Any AGE	549	674	499	597
Severe AGE	68/252 (27.0%)	79/227 (25.8%)	62/228 (27.2%)	71/279 (25.4%)
AGE hospitalization	43 (7.8%)	64 (9.5%)	42 (8.4%)	58 (9.7%)
Rotavirus AGE				
Any rotavirus AGE	49	68	47	67
Severe rotavirus AGE	18/42 (42.9%)	20/64 (31.3%)	17/39 (43.6%)	17/59 (28.8%)
Rotavirus hospitalization	2 (4.1%)	2 (2.9%)	2 (4.3%)	2 (3.0%)

Denominator changes for categories of severe all-cause and severe rotavirus AGE episodes, due to missing data on severity if AGE was unreported. Abbreviations: AGE = acute gastroenteritis.

Table 3. Primary, secondary and post-hoc outcomes

Outcome	Estimate	95% CI	Vaccine effectiveness
Effectiveness against severe rotavirus AGE ≥ 14 days after HRV administration*	HR 0.70	0.35;1.40	30%
Impact on rotavirus AGE hospitalization in post-implementation period	RR 0.76	0.10;6.37	24%
Effectiveness against rotavirus AGE of any severity among HRV vaccinated infants#	IRR 1.02	0.69;1.50	-2%
Effectiveness against severe rotavirus AGE ≥ 14 days after full course HRV*	HR 0.62	0.31;1.21	38%
Effectiveness against severe all-cause AGE ≥ 14 days after HRV administration*	HR 0.81	0.55;1.19	19%
Impact on all-cause AGE hospitalization in post-implementation period	RR 1.05	0.68;1.65	-5%
Effectiveness against all-cause AGE of any severity among HRV vaccinated infants#	IRR 0.87	0.76;1.01	13%

*Adjusted for daycare attendance and rotavirus epidemic intensity. #Adjusted for daycare attendance and parental educational level. Abbreviations: HR = hazard rate, RR = relative risk, IRR = incidence rate ratio and, CI = confidence interval.

All-cause AGE

The post-hoc analyses on severe all-cause AGE resulted in a VE estimate of 19% (95%CI -19;45%) for vaccinated versus unvaccinated infants in the ATP cohort. And HRV impact on all-cause AGE hospitalizations in the post- versus pre-implementation cohort of -5%, see **table 3.** The incidence rate of all-cause AGE of any severity in the pre- and post-implementation ATP cohorts was 733.9 (95%CI 670.7;800.7) and 660.3 (95%CI 608.7;715.4) per 1000 person-years, respectively. Results of subgroup analyses for all-cause AGE are presented in appendix.

The applied Bayesian analysis yielded a posterior probability of 0·049 for estimating a VE more than 60%, **figure 3**.

Discussion

In this prospective multicenter study, we evaluated VE and the impact of HRV among 1,482 infants with MRC and prolonged care using the quasi-experimental design of a step-wedge before-after cohort study. We found VE after at least one dose of the HRV to be substantially lower than previously estimated for healthy infants. We were unable to demonstrate statistically significant reductions in any of the pre-specified rotavirus confirmed outcomes. The point estimate for VE against severe rotavirus AGE was 30% in ATP analysis. The IRR for rotavirus AGE of any severity was 1.02 (95%CI 0.69;1.50), suggesting no effect. In subgroup analyses, we observed a trend towards lower VE with lower gestational age, although differences were non-significant.

If protection against rotavirus AGE is desired for these MRC infants, herd immunity (indirect protection via universal vaccination of healthy infants) might be the best alternative. Prevention by indirect effectiveness against rotavirus hospitalizations estimated by meta-analysis (48%, 95%CI 39;55%) was higher than our direct VE estimate.[20]

This low VE after at least one dose of HRV among infants with MRC is unexpected and deserves further discussion. We hypothesize that certain host and pathogen factors could be of influence. For instance prematurity, lower GA is known to be associated with poorer vaccine responses for some, but not all vaccines.[23] In a trial, HRV immune responses in premature infants were found to be of protective levels in 85 ·7% of 147 infants, although this proportion declined with younger GA.[22]

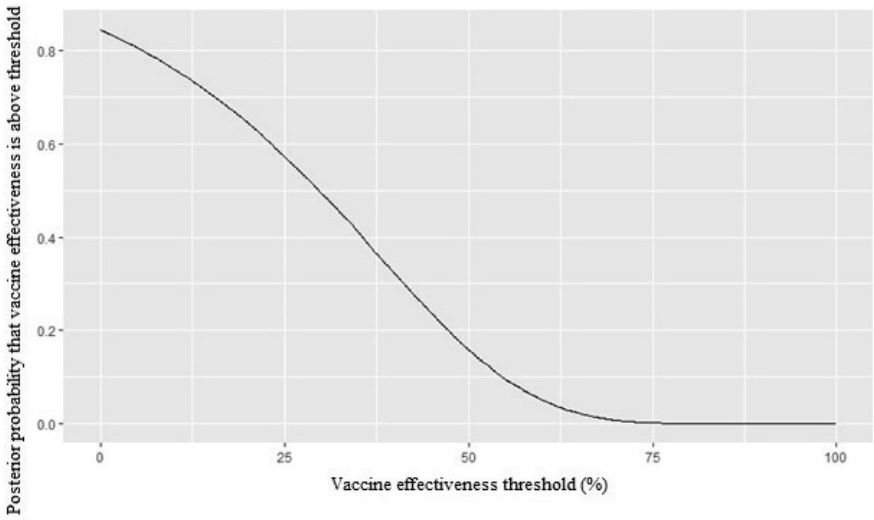


Figure 3. Posterior probability per vaccine effectiveness threshold

Premature infants in our study were generally of lower GA (33.8% 27-30 weeks compared to 20% in the immunogenicity study), therefore, immaturity of the gut and immune system and consequently a poorer rotavirus vaccine response may explain in part the lower VE in our study. In addition, the gut microbiome, is a known factor of influence on HRV immune response and is different between healthy term and premature infants. Some microbiota species are associated with lower rotavirus vaccine IgA responses,[23] and their presence in premature infants is different than in healthy term infants, depending on gestational maturity.[24] However, we also found low VE in term infants with congenital pathology suggesting that other mechanisms are involved as well. It is important to mention that based on the eligibility criteria, participants in our cohort represent a particularly vulnerable group of infants with prolonged care (between six and 14 weeks of age). For example the median length of post-natal hospital stay was 28 days. In addition, 83.3% of infants in our HRV vaccinated cohort received the recommended two doses and protection is lower after just one dose of HRV in healthy term infants (range 60-92%).[25,26]A pathogen related factor is genotype diversity, protection is primarily against the outer membrane proteins, defining the antigenetically distinct rotavirus G- and P- genotypes.[27] Although HRV elicits both homotypic and heterotypic immunity, the protective effectiveness may differ by rotavirus genotype. A meta-analysis of strain-specific VE found 94%, 87% and, 71% effectiveness against homotypic, fully – and, partially heterotypic rotavirus genotypes, respectively with overlapping confidence intervals.[28] In addition, during our study period (2015-2019) the most dominant circulating strains were all partially heterotypic (G3P8, G4P8 and, G9P8). The homotypic G1P8 rotavirus genotype did not exceed 14% in any of the study years,[29] as was noticed in more high-income countries.[30,31] VE in our study-population may have been influenced by this genotype distribution.

Some limitations need to be addressed. First, fewer than expected rotavirus positive AGE episodes (n=117) were detected, reducing the anticipated statistical power of the study. Cumulative severe rotavirus incidence was assumed at 4% during the 18 months of life for this population, we found only 2.7%. This was however the same for all infants in the Netherlands, the previous expected 3500 annual pediatric rotavirus hospitalizations was adjusted during the study period to 2024.[11,32] This resulted from reduced rotavirus epidemic intensity compared to pre-study years, coinciding with a shift towards a biennial pattern.[33] And furthermore, from incomplete sampling of AGE episodes during follow-up. In a post-hoc analysis we therefore analyzed all-cause AGE as outcome, which is a non-specific, but more sensitive measure of effect. The results were in line with our analysis of the primary outcome. Furthermore, the probability that our study had incorrectly estimated low VE, when true VE would be more than 60% (the estimate used in the sample size calculation) was small.

Second, our study suffered from lower than expected inclusions per hospital and incomplete follow-up. We therefore enrolled five more hospitals, adding to a total of 13 instead of eight, used for sample size calculation. Loss to follow-up occurred in 30% of participants (higher than

the anticipated ten percent), despite substantial efforts to keep parents of participants engaged in completing questionnaires and reporting AGE. The multiple and complex health issues that many parents of a MRC child encounter during infancy may be barriers to full engagement in an observational study like ours. Mean follow-up however, was at least one year after vaccination (14.5 months). A Cox model takes observation time into account and was adjusted for several covariates, thereby minimizing bias resulting from differential loss to follow-up.

Conclusion

In this population of infants with MRC and prolonged care, administration of at least one dose of HRV implied insignificant protection against severe rotavirus AGE. The findings are in contrast with the general rotavirus VE estimates for healthy infants and underline the importance of conducting separate studies on vaccine performance in specific populations.

Acknowledgements

Members of the RIVAR study team include: L.M. Zwart, C. Tims-Polderman, G. van Putten, C. Band and, M. van M Beurden, Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, the Netherlands. We would also like to thank all RIVAR participants and their parents or guardians, all research nurses of the different study sites for their contribution to this project. A special recognition to dr. van Werkhoven for assisting on the Bayesian analysis. We thank the Dutch Working Group on Clinical Virology from the Dutch Society for Clinical Microbiology (NVMM) and all participating laboratories for providing the virological data from the weekly Sentinel Surveillance system.

Funding sources were the Netherlands Organisation for Health Research and Development (grant number: 836021024), Healthcare Insurers Innovation Foundation, GlaxoSmithKline Biologicals SA (Study ID: 203108) and, UMC Utrecht.

Role of the funding source: None of the sponsors had a role in study design, data collection, data analysis, writing or submitting of the study. GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for final content and interpretation.

Declaration of Interests: The authors have no financial or personal relationships relevant to this study. None of the authors has any affiliation or received salary from any of the third party funders.

Trial registration: NTR5361 www.trialregister.nl

References

1. Kotloff KL. The Burden and Etiology of Diarrheal Illness in Developing Countries. ***Pediatr Clin North Am***. 2017;64(4):799-814. doi:10.1016/j.pcl.2017.03.006
2. Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality from Diarrhea. ***J Infect Dis***. 2017;215(11):1666-1672.
3. International Vaccine Access Center. Current Rotavirus Vaccine Intro status. ***Bloom Sch Public Heal.*** 2018;([cited 2019]). https://view-hub.org/map/?set=current-vaccine-intro-status&category=rv&group=vaccine-introduction
4. Burnett E, Parashar UD, Tate JE. Real-world effectiveness of rotavirus vaccines, 2006-19: a literature review and meta-analysis. ***Lancet Glob Heal.*** 2020;8(9):e1195-e1202. doi:10.1016/S2214-109X(20)30262-X
5. Soares-Weiser K, Maclehose H, Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review). ***Cochrane Rev***. Published online 2012. http://www.thecochranelibrary.com
6. Hungerford D, Smith K, Tucker A, et al. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. ***BMC Infect Dis***. 2017;17. doi:10.1186/s12879-017-2613-4
7. Chiappini E, Petrolini C, Sandini E, et al. Update on vaccination of preterm infants: a systematic review about safety and efficacy/effectiveness. Proposal for a position statement by Italian Society of Pediatric Allergology and Immunology jointly with the Italian Society of Neonatology. ***Expert Rev Vaccines***. 2019;18(5):523-545. doi:10.1080/14760584.2019.1604230
8. Rouers EDM, Bruijning-Verhagen PCJ, van Gageldonk PGM, van Dongen JAP, Sanders EAM, Berbers GAM. Association of Routine Infant Vaccinations With Antibody Levels Among Preterm Infants. ***Jama***. 2020;324(11):1068-1077. doi:10.1001/jama.2020.12316
9. Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. ***Arch Dis Child***. 2006;91(11):929-935. doi:10.1136/adc.2005.086306
10. Bruijning-Verhagen P, Mangen M-JJ, Felderhof M, et al. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med***. 2013;11(112). doi:10.1186/1741-7015-11-112
11. Bruijning-Verhagen PCJ. RIVAR study protocol. Published 2014. Accessed November 17, 2020. https://www.trialregister.nl/trial/5213
12. Ruuska T, Vesikari T. Rotavirus Disease in Finnish Children: Use of Numerical Scores for Clinical Severity of Diarrhoeal Episodes. ***Scand J Infect Dis***. 1990;22(3):259-267. doi:10.3109/00365549009027046
13. Schnadower D, Tarr PI, Gorelick MH, et al. Validation of the modified vesikari score in children with gastroenteritis in 5 US emergency departments. ***J Pediatr Gastroenterol Nutr***. 2013;57(4):514-519. doi:10.1097/MPG.0b013e31829ae5a3
14. Freedman SB, Eltorky M, Gorelick M. Evaluation of a Gastroenteritis Severity Score for Use in Outpatient Settings. ***Pediatrics***. 2010;125(6):e1278-e1285. doi:10.1542/peds.2009-3270
15. Wilhelmi I, Roman E, Sánchez-Fauquier A. Viruses causing gastroenteritis. ***Clin Microbiol Infect***. 2003;9(4):247-262. doi:10.1046/j.1469-0691.2003.00560.x
16. Xie J, Nettel-Aguirre A, Lee BE, et al. Relationship between enteric pathogens and acute gastroenteritis disease severity: a prospective cohort study. ***Clin Microbiol Infect.*** 2019;25(4):454-461. doi:10.1016/j.cmi.2018.06.016
17. Nederlandse Werkgroep voor Klinische Virologie. Virologische weekstaten. Accessed in Feb 2020. https://www.rivm.nl/virologische-weekstaten/recente-virologie-uitslagen
18. World population by Country 2020. Accessed September 11, 2020. https://worldpopulationreview.com/continents/capitals/europe
19. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. ***CMAJ***. Published online 2012. doi:10.1503/cmaj.101715
20. Rosettie KL, Vos T, Mokdad AH, et al. Indirect Rotavirus Vaccine Effectiveness for the Prevention of Rotavirus Hospitalization: A Systematic Review and Meta-Analysis. ***Am J Trop***

Med Hyg. Published online 2017. doi:10.4269/ajtmh.17-0705
21. Baxter D. Impaired functioning of immune defences to infection in premature and term infants and their implications for vaccination. ***Hum Vaccin***. Published online 2010. doi:10.4161/hv.6.6.12008
22. Omenaca F, Sarlangue J, Szenborn L, et al. Safety, Reactogenicity and Immunogenicity of the Human Rotavirus Vaccine in Preterm European Infants: A Randomized Phase IIIb Study. ***Pediatr Infect Dis J.*** 2012;31(5). doi:10.1097/INF.0b013e3182490a2c
23. Ciabattini A, Olivieri R, Lazzeri E, Medaglini D. Role of the microbiota in the modulation of vaccine immune responses. ***Front Microbiol***. 2019;10(JUL). doi:10.3389/fmicb.2019.01305
24. Chernikova DA, Madan JC, Housman ML, et al. The premature infant gut microbiome during the first 6 weeks of life differs based on gestational maturity at birth. ***Pediatr Res.*** 2018;84(1):71-79. doi:10.1038/s41390-018-0022-z
25. Lopez-Guerrero DV, Arias N, Gutierrez-Xicotencatl L, et al. Enhancement of VP6 immunogenicity and protective efficacy against rotavirus by VP2 in a genetic immunization. ***Vaccine***. 2018;36(22):3072-3078. doi:10.1016/J.VACCINE.2017.03.104
26. Yeung KHT, Tate JE, Chan CC, et al. Rotavirus vaccine effectiveness in Hong Kong children. ***Vaccine.*** 2016;34(41):4935-4942. doi:10.1016/j.vaccine.2016.08.047
27. Grilli G, Levy-Bruhl D, Limia A, Mckeown P, Wiese-Posselt M. ECDC Expert opinion on rotavirus vaccination in infancy. ***Eur Cent Dis Prev Control.*** Published online 2016.
28. Leshem E, Lopman B, Glass R, et al. Distribution of rotavirus strains and strain-specific effectiveness of the rotavirus vaccine after its introduction: A systematic review and meta-analysis. ***Lancet Infect Dis***. 2014;14(9):847-856. doi:10.1016/S1473-3099(14)70832-1
29. Schurink-van t Klooster TM, de Melker HE. The National Immmunisation Programme in the Netherlands: Surveillance and developments. ***Natl Inst Public Heal Environ***. Published online 2019:102-125. doi:10.1007/978-94-6265-282-8_2
30. Middleton BF, Danchin M, Quinn H, Ralph AP. Rotavirus Epidemic in Rural and Remote Australia. ***Pathogens***. 2020;9(790):1-12.
31. Pietsch C, Liebert UG. Rotavirus vaccine effectiveness in preventing hospitalisations due to gastroenteritis. A descriptive epidemiological study from Germany. ***Clin Microbiol Infect***. Published online April 2018. doi:10.1016/j.cmi.2018.03.046
32. Bruijning-Verhagen P, van Dongen JAP, Verberk JDM, et al. Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting. ***BMC Med***. 2018;16(168). doi:10.1186/s12916-018-1134-3
33. Verberk JDM, Pijnacker R, Bruijning-Verhagen P, et al. Biennial Pattern of Rotavirus Gastroenteritis in The Netherlands and a Shifting Age Distribution Following a Low Rotavirus Season, 2010-2016. ***Pediatr Infect Dis J.*** 2018;37:248-250. doi:10.1097/INF.0000000000001880

Supplementary Material

Methods

Laboratory analyses

Fecal samples were placed in biosecurity envelopes and mailed to the study laboratory for PCR testing. RNA and DNA were isolated from the samples using the MagnaPura96® (Roche Diagnostics, Pleasanton, CA USA) and amplified by ABI75000 realtime PCR system® (Thermofisher Scientific, Foster City, CA, USA). Prior to extraction, a non-human internal control was spiked into the lysis buffer of the samples to monitor for sample inhibition. Positive and negative controls for each pathogen were tested in every run. Fecal samples collected within fourteen days of symptom onset were defined as AGE samples.

Three sources of AGE reporting

- Episodes actively reported by parents with or without a fecal sample collected and including a daily symptom severity score and healthcare attendance. For these episodes we calculated the modified Vesikari Score (MVS). A score of less than eight was defined mild, nine to ten moderate and a score of eleven and more as severe.[1,2]
- Episodes reported on the monthly questionnaire for which the study team was not notified. For these episodes information was available on duration of symptoms and healthcare attendance.
- Episodes retrieved from medical chart review. These included hospitalized episodes only, with or without diagnostic fecal testing performed. Nosocomial AGE was defined as AGE occurring ≥48 hours of admission.

We reported this cohort study according to the STROBE checklist.[3]

Results

Secondary outcomes

Analyses for complete series HRV resulted in an univariate HR of 0.68 (95%CI 0.35;1.34) for rotavirus vaccinated versus unvaccinated infants in ATP cohorts, adjusted for attending daycare and season the HR was 0.62 (95%CI 0.31;1.21). Translating this into a VE of 38% (95%CI -21;69%) after completing the two doses HRV series against severe rotavirus AGE.

The incidence rate (IR) of rotavirus AGE of any severity in the at least one dose HRV vaccinated (ATP) cohort was 67.1 per 1000 person-years (95%CI 51.3;86.1). In the willing to vaccinate (ATP) cohort, the incidence rate was 61·5 per 1000 person-years (95%CI 44.3;83.1). There was no statistical significant difference, incidence rate ratio (IRR) 1.05 (95%CI 0.72;1.55). The negative binomial model resulted in an adjusted IRR of 1.02 (95%CI 0.69;1.50), corresponding with a VE of -2% (95%CI -50;31%).

Overall, there was little difference in results per pre-specified subgroup compared to the full cohorts, but confidence intervals were wider because of smaller numbers. The estimated VE after at least one dose against severe rotavirus AGE varied between 3.3% for the subgroup of infants with a gestational age 30-32 weeks and 49.0% for subgroup of term infants with congenital disorders. See **table S1**.

Table S1. Coefficients and hazard rates for subgroups

Subgroup	Coefficient*	95% CI	Multivariate Hazard ratio*
Gestational age 32-37 weeks	-0.12	-2.08;0.37	0.89
Gestational age 30-32 weeks	-0.03	-1.45;2.80	0.97
Gestational age below 30 weeks	-0.26	-1.74;1.53	0.77
Term and congenital disorder	-0.67	-3.30;5.50	0.51
Multiple risk conditions	0.25	-1.41;4.79	1.28

Rotavirus severe AGE as outcome comparing vaccinated versus unvaccinated infants in ATP cohorts using the main analysis Cox model with an interaction term for subgroup. *Adjusted for daycare attendance and rotavirus epidemic intensity. Abbreviations: CI = confidence interval.

All-cause AGE subgroup analyses

With all-cause severe AGE as outcome in subgroup analyses, premature infants (GA 32-37 weeks) and term infants with a congenital disorder had a higher estimated VE (44.6% and 68.0% respectively). And preterm infants of lowest gestational age (<30 weeks) or infants with multiple conditions seemed to benefit less from HRV vaccination (VE -3.6% and 4.4% respectively).

CONGENITAL DISORDERS ACCORDING TO ICD-10	Qualifies as eligible		
	Yes	No	Sometimes
Congenital malformation central nervous system and senses			
Anencephaly	■		
Microcephaly		■	
Spina bifida and meningo(myeleo)cele	■		
Encephalocele			■
Neuromuscular disease	■		
Hydrocephalus/holoprosencephaly without neural tube defect			■
Other congenital CNS malformation			■
Congenital defect in senses		■	
Microphthalmia		■	
Other congenital eye disorders		■	
Inborn errors of the ears		■	
Other innate sense abnormalities		■	
Congenital anomaly cardiovascular			
Lack of umbilical cord artery		■	
Transposition of the large vessels	■		
Tetralogy of Fallot	■		
Ventricle septum defect			■
Hypoplastic left heart syndrome	■		
Coarctation of the aorta	■		
Tricuspidis atresia / stenosis	■		
Complicated heart defect	■		
Other birth defects of heart and blood vessels			■
Congenital anomaly digestive system			
Cleft lip with or without cleft palate		■	
Split palate without cleft lip	■		
Esophagus atresia/stenosis/fistula	■		
Intestinal/anal atresia	■		
Hirschsprungs' disease	■		
Malrotation/volvulus	■		
Other congenital disorder of digestive tract			■
Congenital respiratory abnormality			
Choanal atresia	■		
Tracheal disorder	■		
Lung hypoplasia	■		
Lobar emphysema	■		
Hydro/chylo thorax	■		
Diaphragmatic hernia			■
Relaxation of diaphragm	■		
Other congenital respiratory disorders			■
Congenital malformation urogenital system			
Hypospadias and/or epispadias		■	

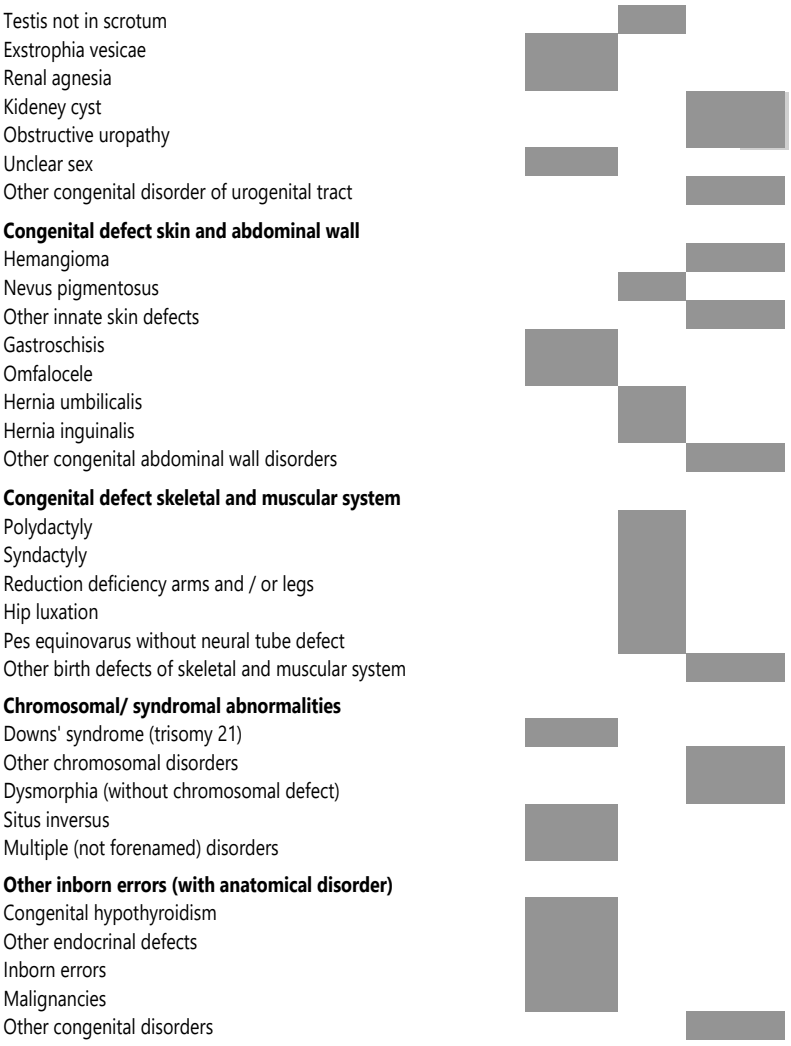


Figure S1. List of eligible congenital disorders[4]. Abbreviations: ICD-10 = international code of diseases 10th edition. *Qualifying conditions are those that last longer than 12 months, involve multiple organ systems and/or are expected to require pediatric specialty care. Defined into categories: A. Cardiovascular, B. Pulmonary, C. Neurodevelopmental, D. Chromosomal, E. Perinatal and F. Other.

Table S2. Characteristics of infants with severe rotavirus AGE among HRV vaccinated and unvaccinated infants

Case	Sex	Gestation in week + days	Birthweight in grams	Congenital disorder	SGA	HRV	Age* severe rotavirus AGE	Age* HRV1	Age* HRV2
1	M	34+6	1800	no	yes	yes	10	2	
2	M	37+0	2100	no	yes	yes	14	1	3
3	M	25+2	900	no	no	no	7		
4	M	36+1	2500	yes	no	yes	11	1	
5	M	37+2	3500	yes	no	yes	3	2	4
6	F	41+0	3500	yes	no	yes	15	2	3
7	M	29+4	1300	no	no	no	8		
8	F	35+6	2500	no	no	no	16		
9	F	29+0	1200	no	no	yes	10	1	3
10	F	33+2	2000	no	no	no	4		
11	F	32+2	2200	no	no	yes	2	1	
12	F	32+0	1800	no	no	yes	14	1	4
13	M	35+0	3000	no	no	yes	5	1	4
14	M	32+4	1800	no	no	no	12		
15	F	30+6	1600	no	no	no	9		
16	M	31+4	1300	no	yes	yes	13	1	
17	M	31+6	1800	no	no	yes	12	1	4
18	M	30+1	1600	no	no	no	12		
19	F	27+5	1000	no	no	yes	17	1	3
20	M	31+2	1700	no	no	no	9		
21	F	29+2	1300	no	no	no	15		
22	M	35+6	1900	no	yes	no	13		
23	M	36+0	2200	no	yes	yes	10	2	3
24	M	31+0	2000	no	no	yes	9	1	4
25	F	30+3	1600	no	no	yes	13	1	2
26	M	35+0	2100	no	yes	no	9		
27	M	36+0	2200	no	yes	no	15		
28	F	25+6	800	yes	no	no	15		
29	F	25+6	700	yes	yes	no	15		
30	M	35+1	3700	no	no	no	10		
31	F	38+5	3200	yes	no	no	5		
32	M	35+6	3100	no	no	no	13		

Case	Sex	Gestation in week + days	Birthweight in grams	Congenital disorder	SGA	HRV	Age* severe rotavirus AGE	Age* HRV1	Age* HRV2
33	F	41+3	3000	yes	yes	yes	5	3	4
34	F	34+0	1700	yes	yes	yes	15	2	

* Age in months. Abbreviations: SGA = small for gestational age, AGE = acute gastroenteritis, HRV = human rotavirus vaccination, HRV1 = first dose of human rotavirus vaccination, HRV2 = second dose of human rotavirus vaccination.

References

1. Schnadower D, Tarr PI, Gorelick MH, et al. Validation of the modified vesikari score in children with gastroenteritis in 5 US emergency departments. ***J Pediatr Gastroenterol Nutr.*** 2013;57(4):514-519. doi:10.1097/MPG.0b013e31829ae5a3

2. Freedman SB, Eltorky M, Gorelick M. Evaluation of a Gastroenteritis Severity Score for Use in Outpatient Settings. ***Pediatrics***. 2010;125(6):e1278-e1285. doi:10.1542/peds.2009-3270

3. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. ***Epidemiology.*** 2007;18(6):800-804. doi:10.1097/EDE.0b013e3181577654

4. Hindori-Mohangoo AD, Schonbeck Y, Pal-de Bruin KM van der. Aangeboren Afwijkingen in Nederland 2001-2012: Gebaseerd Op Landelijke Perinatale Registraties.; 2014. https://www.tno.nl/media/4521/2014-r-11308-rapportage-aangeboren-afwijkingen-2001-2012-def.pdf

Chapter 5

Safety and Tolerability of Human Rotavirus Vaccination in Medical Risk Infants in the Netherlands

Josephine A.P. van Dongen, Shannon M. Watkins, Elsbeth D.M. Rouers, Rob Schuurman, Caterina Band, Louis J. Bont, Obbe F. Norbruis, Marieke A.C. Hemels, Gijs T.J. van Well, Arine M. Vlieger, Jacqueline van der Sluijs, Helene G. Stas, Gerdien Tramper-Stranders, Elly A. Kleinlugtenbeld, Anne A.M.W. van Kempen, Margreet Wessels, Maaike C. van Rossem, A.C.M. (Carin) Dassel, Marlies A. van Houten, Dasja Pajkrt, Marc J.M. Bonten and, Patricia C.J. Bruijning-Verhagen. On behalf of the RIVAR study team.

Under review, revisions submitted

Abstract

Objective: Rotavirus vaccination is recommended for prevention of severe rotavirus disease. While the vaccine is well tolerated in healthy term infants, there are limited data on premature infants. We aim to assess the safety and tolerability among infants born between 27-37 weeks of gestation in need of prolonged postnatal medical care.

Methods: The Netherlands has no national rotavirus immunization program, but selective human rotavirus vaccination (HRV) for high-risk premature infants was implemented in participating hospitals. HRV vaccination and occurrence of any vaccine related serious adverse event (SAE) was systematically documented. As secondary endpoints solicited adverse events (AE) following administration of national immunization program (NIP) vaccines with or without HRV were prospectively collected.

Results: Among 2077 rotavirus vaccinated infants, ten vaccine related SAE were documented, resulting in hospital admission or prolonged hospitalization. There were no deaths and all infants recovered. The adjusted risk ratio (RR) for any AE following concomitant NIP+HRV administration was 1.07 (95%CI 1.04-1,10) and, for HRV administration alone RR was 0.90 (95% CI 0,80-0.98), compared to NIP administration. Gastrointestinal AE were statistically significant reported more often after receiving HRV (p-value <0,001).

Conclusion: Among vulnerable premature infants, vaccine related SAE were reported in 0.25 per 100 HRV vaccine doses. HRV is generally well tolerated when co-administered with NIP vaccines, but associated with approximately ten percent higher risk of gastrointestinal AE.

Introduction

Premature infants are at increased risk of severe rotavirus acute gastroenteritis.[1–4] Therefore prevention of rotavirus disease is particularly important for premature infants. Since 2006 two rotavirus vaccines have been licensed; RotaTeq© (Merck and Co, USA) and, Rotarix© (GSK, Belgium). Both vaccines were previously studied in premature infants and demonstrated efficacy and immunogenicity.[5,6] Findings on rotavirus vaccine safety and tolerability from these studies indicate that rates of adverse events (AE) are similar to those observed among term infants.[6,7] However the trials included a limited number of infants with gestational ages (GA) less than 30 weeks, and for Rotarix (GSK), no infants with GA < 27 weeks were included. Moreover, inclusion criteria required premature infants were healthy and medically stable at time of enrollment. This relatively healthy study population may not be representative, as a complicated postnatal course, is common in (very) premature infants, and may influence AE rates.[6,7]

Very premature infants (GA <30 weeks) can experience more and different vaccine AE following routine vaccines other than rotavirus vaccination. A recent review found that cardiorespiratory events (apnea, bradycardia and desaturation) occurred in 13-30% of very premature infants following DTaP-IPV-Hib-HepB vaccine.[8] In addition vomiting and hypotonia occurred more frequently in premature infants, while rates of local and other general symptoms were comparable.[8]

More real-world data on safety and tolerability of rotavirus vaccination in these infants, with or without concurrent administration of other routine immunizations, is needed to guide clinicians in the individual assessment of risks and benefits and to counsel parents on anticipated AE.

In the Netherlands, a national rotavirus vaccination policy has not been introduced yet, but a pilot was conducted in 13 Dutch hospitals implementing rotavirus vaccination in routine neonatal care for medical risk infants, including premature infants (Risk-group Infant Vaccination Against Rotavirus [RIVAR] project). This selective vaccine strategy was supposed to prevent those infants most at risk of severe disease.[2] Within this setting we evaluated the safety and tolerability of rotavirus vaccination among medical risk infants. Here we focus on premature infants with gestational ages between 27-37 weeks. Because infants with GA below 27 weeks are vaccinated off-label, and the decision to offer HRV was based on local policy, the group was analysed and described separately. Data on infants with other medical risk conditions are described in supplementary material.

Patients and methods

Study setting and subjects

For a full description of the RIVAR project we refer to **chapter 4** and the Dutch trial registry.[9] In brief, an implementation project for selective rotavirus vaccination was conducted in

participating secondary pediatric hospitals. Eligible infants included those with prematurity, low birth weight and/or, presence of a severe congenital disorder (list added in **chapter 4**). Eligibility further required an inpatient hospital stay or a planned outpatient visit between six and 14 weeks postnatal age, allowing for first dose rotavirus vaccine administration on site within the appropriate age-window. The target population therefore represented infants with medical risk conditions who required prolonged pediatric care after birth. Within participating hospitals, a prospective cohort study was set-up starting enrollment from one year before rotavirus vaccination implementation (rotavirus unvaccinated infants), until 12-18 months post-implementation (rotavirus vaccinated infants). Participating infants were followed from approximately six weeks until 18 months of age for occurrence of acute gastroenteritis to evaluate vaccine effectiveness as primary outcome. In addition, all vaccinations received and solicited AE were prospectively documented for tolerability assessment as secondary outcome. To guide recommendations of rotavirus vaccination, tolerability was analyzed for subgroups of infants with medical risk conditions separately.

Data collection

Safety assessment was a secondary outcome of the RIVAR project. The research staff reviewed medical records for each rotavirus vaccination eligible infant at approximately five months of age to check rotavirus vaccination dates and documentation of any vaccine related serious vaccine adverse reaction (SAE) following administration. Vaccine related SAE was defined as any reaction that was fatal, life threatening, disabling or incapacitating, required in-patient treatment or prolonged existing hospitalization, or which required intervention to prevent the previously stated outcomes and, considered related to rotavirus vaccination as judged by the treating physician and documented in the patient medical record (**Figure 1**). All eligible infants with at least one HRV administration were included in the analysis. In addition, we described "vaccine failure" when rotavirus acute gastroenteritis led to hospitalization and occurred at least 14 days after second HRV dose.

For tolerability assessment, we used data from participants of the before-after cohort study. Monthly parental questionnaires contained date and type of the NIP primary series and/or HRV immunizations received, the occurrence of solicited AE and, whether they sought healthcare, in the seven days following administration. Solicited AE were fever, rash, irritability, loss of appetite, vomiting, looser and/or, bloody stools. We defined vaccine administration concomitant when vaccination dates were identical for at least one NIP and HRV (NIP+HRV) vaccination or if they were with a maximum of three days apart, such that the seven-day post-vaccination period for reporting solicited AE covered both vaccinations. All monthly data from cohort participants that included information on type and date of vaccination and AE reporting were included in the analysis. The standard vaccination schedule is shown in **Figure 1**.

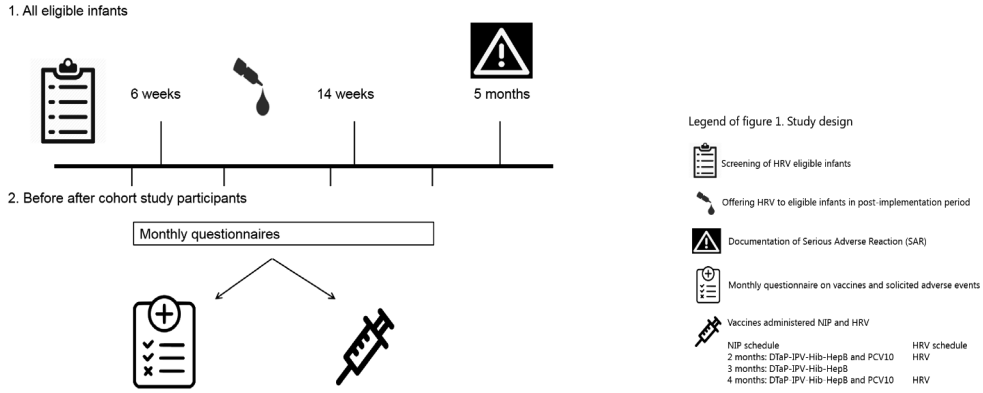


Figure 1. Study design and primary series NIP schedule. Abbreviations: HRV = human rotavirus vaccine, NIP = national immunization program, DTaP-IPV-Hib-HepB = hexavalent diphtheria-tetanus toxoids-accelular pertussis-inactivated polio-Haemophilus influenzae type B-hepatitis B vaccine, PCV10 = 10-valent pneumococcal vaccine.

Outcomes

1) The outcome for safety was defined as the number of vaccine related SAE per 100 vaccine doses in high-risk premature infants.

2) For tolerability, we compared the occurrence of at least one solicited AE in the seven days following receipt of either NIP vaccines (DTaP-IPV-Hib-HepB and/or PCV10), concomitant NIP+HRV or, HRV only. We estimated the relative risk of AE per vaccine administration with NIP only as reference. The number of solicited AE per vaccine administration was compared using incidence rate ratio (IRR). Comparisons were performed for the subgroup of fever and gastrointestinal AE (vomiting, bloody and/or, looser stools) and, for AE related healthcare attendance.

In secondary analysis of tolerability we reported the cumulative incidence of solicited AE that infants experienced during completion of the primary series of either NIP or NIP+HRV. In addition, occurrence of fever, gastrointestinal solicited AE and, AE related healthcare attendance were described.

Analysis

1) Each vaccine related SAE was described in terms of diagnosis, infant characteristics, timing in relation to HRV vaccination and, where applicable, results of faecal testing. Rotavirus positive faecal samples were additionally genotyped, RNA was extracted from faecal samples using the MagnaPure96 nucleic acid extraction system. The purified RNA was subsequently subjected to PCR amplification and sequencing of the VP4 and VP7 genes according to Simmonds

et al. and Zeller et al., respectively.[10,11] The obtained sequences were used for rotavirus type determination in the web-based typing tool RotaC.[12]

2) Comparison of baseline characteristics between the groups was done using Chi-square, student-T or non-parametric tests depending on the distribution. For the primary tolerability outcome of at least one AE we used a mixed model with binomial distribution and a random intercept per infant. We estimated odds ratios for type of vaccine administration (NIP, HRV or NIP+HRV), adjusting for age at vaccination. Odds ratio was transformed into risk ratio (RR) using the method described by Knol et al.[13] Predefined covariates in multivariate analysis included: GA, small for gestational age, presence of congenital disorders, older siblings, parental age, parental background and, socio-economic status. To assess whether the effect of co-administration of HRV on solicited AE was dependent on GA, we added an interaction term to the model. The final model was selected based on the Akaike Information Criterion. For the number of solicited AE experienced after vaccine administration, we estimated adjusted incidence rate ratio (IRR) using negative binomial regression. We performed complete case analysis, potentially induced bias was explored by comparing complete cases to those with missing information. As statistical software SPSS version 25.0.0.2 and RStudio version 3.6.1 were used, with packages *lme4, MASS*.

Results

1) Safety

A total of 5730 high-risk premature infants ≥ 27 weeks of GA fulfilled the eligibility criteria, figure 2. The median GA was 33 weeks and 1 days, 1962 (34.2%) were small for gestational age and, 549 (9.6%) had one or more congenital pathologies. Among 2077 HRV vaccinated infants ten vaccine related SAE were documented, 0.25 per 100 vaccine doses. These included two cases of intussusception (one ultrasound confirmed), two cases of necrotizing enterocolitis and, one clinical sepsis (no pathogen detected). One infant developed acute gastroenteritis that required hospital admission (shortly after vaccination, no stool sample available) and one infant lactose intolerance (occurrence of diarrhea and severe abdominal cramps after both vaccine doses, which resolved after lactose free formula milk was introduced). Three infants developed sudden cardiorespiratory events. For detailed information see Appendix A **table S1.** All infants recovered and there were no deaths. Two infants with hospitalized rotavirus acute gastroenteritis were classified as vaccine failures, partially heterotypic genotypes were detected in sampled feces. In particular regarding the VP4 genotype, which in both cases did not match the genotype of the vaccine strain.

Five out of 13 hospitals had a policy to vaccinate infants with GA < 27 weeks, 82 out of 92 (85.9%) eligible infants were vaccinated with at least one dose of HRV. No vaccine related SAE were documented. For safety data concerning term infants with congenital disorders, see **appendix B**, among 118 vaccinated infants two vaccine related SAE were documented.

2) Tolerability

The group of high-risk participating premature infants ≥ 27 weeks of GA consisted of 1206 infants. Data on at least one vaccine administration and AE were available for 1041 (86.3%) infants, including 471 in the NIP only and 570 in the NIP+HRV group (**figure 2**). Patient characteristics of NIP versus NIP +HRV vaccinated infants were largely comparable (**table 1**). Age at first vaccination was slightly younger among HRV vaccinated infants (59 days versus 61 days of postnatal age, p=0.0). In the seven days following 1350 vaccinations any AE was reported out of 3031 reported vaccine administrations (44.5%). The total number of reported AE was 2057, resulting in an incidence rate of 0.68 (95%CI 0.65;0.71) per vaccine administration. A total of 134 vaccine administrations were followed by an AE related healthcare contact (4.4%).

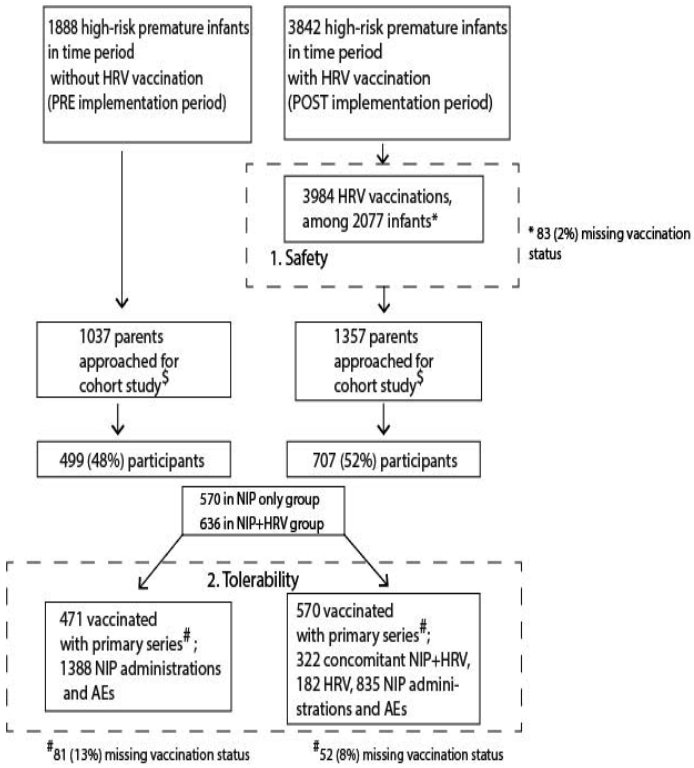


Figure 2. Flowchart of high-risk premature infants and cohort study-participants with gestational age between 27 and 37 weeks. $Reasons for not approaching eligible infants: 446 versus 484 discharged or referred, 154 versus 124 language barrier, 147 versus 80 unstable social environment, 38 versus 41 poor prognosis, 96 versus 130 other unspecified reason, 14 missing and 1626 eligible during follow-up, when recruitment for cohort study was ended. Abbreviations: HRV = human rotavirus vaccine, NIP = national immunization program, AE = solicited adverse event.

Table 1. Baseline table of vaccinated infants with gestational age ≥ 27 weeks

Characteristic	NIP vaccinated (N=471)	NIP + HRV vaccinated (N=570)	p-value
Gestational age in weeks+days (mean, SD)	32+1 (2+4)	32+3 (2+4)	0.07
Gestation subgroups			0.16
27-30 weeks	113 (24.0)	116 (20.4)	
30-37 weeks	358 (76.0)	454 (79.6)	
Birthweight in grams (median, IQR)	1770 (840-2700)	1780 (990-2570)	0.80
Small for gestational age (yes,%)[£]	135 (28.7)	180 (31.6)	0.31
Sex (male, %)	269 (57.1)	301 (52.8)	0.17
Multiple birth (yes, %)	122 (25.9)	157 (27.2)	0.64
Congenital pathology (yes, %)	38 (8.1)	48 (8.4)	0.84
Number of disorders			0.49
1 (%)	30 (78.9)	42 (87.5)	
2 (%)	5 (13.1)	6 (12.5)	
>2	3 (7.9)	-	
Age at first vaccination in days (median, IQR)	61 (48-74)	59 (40-78)	**<0.001**[*]
Sibling (yes, %)	99 (21.5)	120 (21.4)	0.97
Parental education[#]			0.44
High	342 (73.5)	422 (75.4)	
Medium	104 (22.4)	123 (22.0)	
Lower	19 (4.1)	15 (2.7)	
Parental background[^]			0.85
European	399 (85.6)	477 (85.0)	
Non-European	25 (5.4)	28 (5.0)	
Mixed	42 (9.0)	56 (10.0)	
Average parental age in years (median, IQR)	32.5 (27.0-38.0)	33.0 (27.0-39.0)	0.41

Percentages are derived excluding subjects with missing data on the variable. Statistical significance (p-value <0.05) is highlighted in bold. [*]Rank-sum test. [£] Based on 10th percentile perinatal growth curves.[14] [#]Based on highest parental educational level. [^]Based on parental background and categorized according to world population by country.[15] Abbreviations: HRV = human rotavirus vaccine, N = number in group, SD = standard deviation, IQR = interquartile range.

Overall, there was a 10% difference in occurrence of any solicited AE following NIP (45.5%) versus NIP+HRV (55.7%) vaccine administration, **table 2**. AE were reported less frequently for HRV only administration (36.4%), largely due to a reduced frequency of fever (5.2%). Gastrointestinal AE were more frequent after HRV only administration (16.4%) and after concomitant NIP+HRV administration (17.0%) compared to NIP vaccination (6.0%). No

differences were observed in the frequency of related healthcare attendance between NIP only, concomitant NIP+HRV or, HRV only administrations.

The adjusted RR for at least one solicited AE in the seven-day post-vaccination period was 1.07 (95%CI 1.04-1.10) for concomitant NIP+HRV versus NIP only and 0.90 (95%CI 0.80-0.98) for HRV only vaccination (**table 3**). The final model included GA, presence of a sibling in the household and, age at vaccination as covariates. The interaction term for GA was not statistically significant. Analysis of the number of AE per vaccine administration yielded comparable results with an adjusted IRR of 1.07 (95% CI 0.96-1.19) for NIP+HRV versus NIP only (**table 3**). GA, sibling and, age at vaccination were included in the model.

Table 2. Solicited AE following receipt of NIP vaccines, concomitant NIP+HRV or HRV only vaccination as part of the primary series in high-risk premature infants (≥ 27 weeks of gestational age)

Reported adverse events	NIP only vaccination N=1233	Concomitant NIP +HRV vaccination N=305	HRV only vaccination N=176	p-value
At least one solicited adverse event	558 (45.5%)	170 (55.7%)	63 (36.4%)	**<0.00**
Fever	213 (17.3%)	60 (19.7%)	9 (5.2%)	**<0.00**
Gastrointestinal	74 (6.0%)	50 (16.4%)	30 (17.0%)	**<0.00**
Mean number of solicited adverse events	1.49 (SD 0.81)	1.55 (SD 0.76)	1.79 (SD 0.97)	**<0.00***
Number of solicited AE				0.08
1	363 (29.6%)	101 (33.1%)	31 (17.9%)	
2	139 (11.3%)	47 (15.4%)	20 (11.6%)	
>2	56 (4.6%)	22 (7.2%)	12 (7.0%)	
Any AE related healthcare attendance	59 (4.8%)	15 (4.9%)	7 (4.0%)	0.78#
Type of healthcare				0.18#
General practitioner	18 (1.5%)	2 (0.7%)	4 (2.3%)	
Outpatient clinic	7 (0.6%)	2 (0.7%)	1 (0.6%)	
Emergency room	12 (1.0%)	-	1 (0.6%)	
Hospitalization	32 (2.6%)	12 (3.9%)	3 (1.7%)	

Statistical significance (p-value <0.05) is highlighted in bold. *ANOVA test. # Fisher Exact test. Abbreviations: HRV = human rotavirus vaccine, N = number in group, NIP = national immunization program.

Table 3. Outcome estimates

	Unadjusted estimate	95% CI	Adjusted estimate*	95% CI
NIP only vaccination	Ref	-	Ref	-
At least one solicited AE after concomitant NIP+HRV vaccination	RR 1.07	1.03-1.10	RR 1.07	1.04-1.10
At least one solicited AE after HRV only vaccination	RR 0.90	0.79-0.98	RR 0.90	0.80-0.98
Number of solicited AE after NIP+HRV vaccination	IRR 1.06	0.96-1.18	IRR 1.07	0.96-1.19

*Adjusted for age at vaccination (in months), older sibling in household, gestational age in weeks. Abbreviations: RR = relative risk, IRR = incidence rate ratio CI = confidence interval, NIP = national immunization program, HRV = human rotavirus vaccine.

Results of secondary outcomes are presented in appendix A, **table S2**. A total of 736 infants (70.7%) reported any solicited AE in the seven-day post-vaccination period during completion of the primary series with or without HRV and 99 (9.5%) infants had any AE related healthcare contact.

Characteristics for infants with GA <27 weeks were relatively similar with the exception of older age at vaccination for HRV vaccinated infants (72 versus 63 days), shown in **table S3** of Appendix A. Tolerability for infants with a GA below 27 weeks is different than for those born past 27 weeks of gestation, fewer AE were reported, however numbers are small (see appendix A **table S3 and S4**).

The tolerability among 134 term infants with congenital disorders was similar as among high-risk premature infants of ≥ 27 weeks GA and is described in **appendix B**. Exploration of potential bias induced by complete case analyses are shown in appendix A, **table S5**. There were statistical significant less infants born as twins among those with missing information, and average parental age was lower as was family educational level.

Discussion

Our findings indicate that about one in 200 high-risk premature infants experienced a vaccine related SAE following a two-dose HRV course that was associated with hospitalization, increased length of hospital stay or life support intervention, but all resolved without long-term sequelae. Administration of HRV with or without concomitant administration of NIP vaccines was

generally well tolerated, although risk of AE increased by seven percent when HRV was added. Gastrointestinal AE were reported in one in four infants who received HRV. Reassuringly, this increased rate of (gastrointestinal) AE did not result in more frequent healthcare attendance for AE among NIP versus NIP+HRV vaccinated infants, ten versus nine percent, respectively. For HRV only vaccine administration fever as AE is less commonly reported (5.2%) compared to NIP vaccines (17.3%).

Rotavirus vaccines have been available worldwide since 2006, and over 100 countries have implemented a globally licensed vaccine in their infant immunization program.[16] In Cochrane systematic reviews on safety of these vaccines, SAE were reported in 2.3-7.6% of healthy term infants following vaccination, no increased risk compared to placebo.[17,18] Gastrointestinal SAE occur in 0.1-0.6% of HRV vaccinated term infants, but this is without mention of possible relatedness to vaccination.[19–21] A prior study, among infants generally healthy and on average of older gestational age, identified two vaccine related SAE among 670 HRV vaccinated premature infants,[6] which is lower than in our study. Given the clinical vulnerability of the infants in our study receiving rotavirus vaccination, an active approach and systematic screening of all medical records was chosen to guarantee complete case finding. However, it makes it difficult to interpret our finding of 0.25 vaccine related SAE per 100 vaccine doses in the context of existing evidence. It is well known that rates of (vaccine related) SAE following vaccination are generally higher in premature infants,[8] but to what extend this also applies to HRV is uncertain. Our findings indicate that clinicians should be vigilant about the possibility of vaccine related SAE when vaccinating against rotavirus in infants with prematurity and clinical vulnerability.

In line with results of prior HRV tolerability studies in premature and term infants,[6,19–21] HRV seemed well tolerated among high-risk premature infants and was associated with only a small increase in AE when combined with NIP vaccines. The observed frequency of AEs in 45-55% of our study population is even slightly lower than the 60% reported in a Dutch study of healthy term infants receiving NIP vaccines.[22] Gastrointestinal AE appear a class effect of oral rotavirus vaccines and occur in up to 25% of premature infants in our and other studies, but they rarely require medical attention.[6,7,23] Although symptoms may be mild, it is important to counsel parents about this possible side effect prior to vaccination.

Because infants with GA < 27 weeks were excluded from the pre-licensure trials of HRV, administration of HRV to these infants is off-label. In our study, fewer solicited AE among infants of GA < 27 weeks were reported to those among premature infants ≥ 27 weeks. No vaccine related SAE was documented. Although the numbers are small, these findings are reassuring.

The Netherlands currently has no national rotavirus vaccine policy and uptake in private market is very low.[24,25] We recently showed that vaccine effectiveness of at least one dose HRV among our study population of medical risk infants was substantially lower than expected at 30%

(**chapter 4**). This raises the question whether the benefits of rotavirus vaccination outweigh the possible risks of vaccine related SAE in this particular population, especially in a setting with low rotavirus incidence as currently seen in the Netherlands.[26,27] Alternatively, protecting these infants through herd immunity by implementing universal infant vaccination against rotavirus may be a strategy worth considering. It has been shown that herd immunity effects can reduce the risk of severe rotavirus acute gastroenteritis by 48% among unvaccinated infants.[28]

Important limitations should be mentioned. First, for the observed vaccine related SAE we cannot confirm or exclude causality between the event and administration of HRV. In our evaluation, we relied on clinical judgement by the treating physician, considering timing of the event in relation to vaccine administration and/or type of SAE and patient comorbidities. At most, we can therefore conclude that a causal link is plausible. For some vaccine related SAE, other vaccines co-administered with HRV may also have triggered the event.

Second, our results on tolerability assessment are based on parent reported solicited AE, which may be subject to variability in perception between parents. Although fever, vomiting and loose stools can be assessed quite objectively, we cannot rule out that reporting may have been influenced by whether infants received the newly introduced HRV, which could increase parent's attentiveness to AE. This effect is likely small as percentages of parent reported AE between the two groups were similar. Differences were only observed for gastrointestinal adverse events, which is in line with previous results on tolerability of HRV.

Third, data were missing on some covariates and vaccinations in approximately 10% of infants. Our analyses are based on complete cases only, by comparison of infants with missing versus complete data, we explored the potential of bias this induced. Although family educational level was lower among infants with missing data, educational level was not associated with AE in univariate analysis and therefore complete case analysis is justified and results are generalizable to the broader population of vulnerable premature infants.

Conclusion

In conclusion, we observed higher incidence of vaccine related SAE following HRV among vulnerable premature infants than reported in literature. Clinicians should be aware and must outweigh the risks and benefits of HRV for this particular group. HRV administration is generally well tolerated, also in infants < 27 weeks of GA, but associated with approximately ten percent higher risk of gastrointestinal AE when co-administered with NIP vaccines.

Acknowledgements

We would like to thank the RIVAR study team, investigators and research nurses of participating hospitals, participants and their parents or guardians for contribution to this study.

Funding: The Netherlands Organization for Health Research and Development (836021024), Healthcare Insurers Innovation Foundation, UMC Utrecht and, GlaxoSmithKline Biologicals SA (203108).

Role of funding sources: GlaxoSmithKline reviewed a version of the manuscript prior to submission in order to confirm factual accuracy. The authors are solely responsible for final content and interpretation, and share final responsibility for the decision to submit for publication.

Declaration of interests: There are no personal or financial relationships relevant to this manuscript, as confirmed by all authors.

Trial registration: in Dutch trial registry as NTR5361 www.trialregister.nl

References

1. Briggs-Steinberg C, Shah S, Perinatol AJ. Rationale for In-Neonatal Intensive Care Unit Administration of Live, Attenuated Rotavirus Vaccination Rotavirus Vaccines. ***Am J Perinatol.*** Published online 2018. doi:10.1055/s-0038-1660463

2. Bruijning-Verhagen P, Mangen M-JJ, Felderhof M, et al. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med.*** 2013;11. doi:10.1186/1741-7015-11-112

3. Kilich E, Sadarangani M. Use of rotavirus vaccines in preterm babies on the neonatal unit. ***Expert Rev Vaccines.*** 2016;15(12):1463-1465. doi:10.1080/14760584.2016.1216318

4. Dahl RM, Curns AT, Tate JE, Parashar UD. Effect of rotavirus vaccination on acute diarrheal hospitalizations among low and very low birth weight US infants, 2001-2015. ***Pediatr Infect Dis J***. 2018;37(8):817-822. doi:10.1097/INF.0000000000001930

5. Vesikari T, Matson DO, Dennehy P, et al. Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine. ***N Engl J Med***. 2006;354(1):23-33. doi:10.1056/NEJMoa052664

6. Omenaca F, Sarlangue J, Szenborn L, et al. Safety, Reactogenicity and Immunogenicity of the Human Rotavirus Vaccine in Preterm European Infants: A Randomized Phase IIIb Study. ***Pediatr Infect Dis J.*** 2012;31(5). doi:10.1097/INF.0b013e3182490a2c

7. Goveia MG, Rodriguez ZM, Dallas MJ, et al. Safety and Efficacy of the Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine in Healthy Premature Infants. ***Pediatr Infect Dis J.*** 2007;26(12):1099-1104. doi:10.1097/INF.0b013e31814521cb

8. Omeñaca F, Vázquez L, Garcia-Corbeira P, et al. Immunization of preterm infants with GSK's hexavalent combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine: A review of safety and immunogenicity. ***Vaccine***. Published online 2018. doi:10.1016/j.vaccine.2018.01.005

9. Bruijning-Verhagen PCJ. RIVAR study protocol. Published 2014. Accessed November 17, 2020. https://www.trialregister.nl/trial/5213

10. Simmonds MK, Armah G, Asmah R, et al. New oligonucleotide primers for P-typing of rotavirus strains: Strategies for typing previously untypeable strains. ***J Clin Virol.*** 2008;42(4):368-373. doi:10.1016/j.jcv.2008.02.011

11. Zeller M, Rahman M, Heylen E, et al. Rotavirus incidence and genotype distribution before and after national rotavirus vaccine introduction in Belgium. ***Vaccine***. 2010;28(47):7507-7513. doi:10.1016/J.VACCINE.2010.09.004

12. Maes P, Matthijnssens J, Rahman M, Van Ranst M. RotaC: A web-based tool for the complete genome classification of group A rotaviruses. ***BMC Microbiol.*** 2009;9:2-5. doi:10.1186/1471-2180-9-238

13. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. ***CMAJ.*** Published online 2012. doi:10.1503/cmaj.101715

14. Hoftiezer L, Dijs-Elsinga J, van Dillen J, et al. Perined population curves. Published 2018. Accessed May 28, 2019. https://www.perined.nl/publicaties1/geboortegewichtcurven

15. World population by Country 2020. Accessed September 11, 2020. https://worldpopulationreview.com/continents/capitals/europe

16. International Vaccine Access Center. Current Rotavirus Vaccine Intro status. ***Bloom Sch Public Heal.*** 2018;([cited 2019]). https://view-hub.org/map/?set=current-vaccine-intro-status&category=rv&group=vaccine-introduction

17. Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: Vaccines in use. ***Cochrane Database Syst Rev***. 2019;2019(3).

doi:10.1002/14651858.CD008521.pub4

18. Soares-Weiser K, Maclehose H, Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review). ***Cochrane Rev.*** Published online 2012. http://www.thecochranelibrary.com

19. Zaman K, Anh DD, Victor JC, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: A randomised, double-blind, placebo-controlled trial. ***Lancet.*** 2010;376(9741):615-623. doi:10.1016/S0140-6736(10)60755-6

20. Rivera L, Peña LM, Stainier I, et al. Horizontal transmission of a human rotavirus vaccine strain-A randomized, placebo-controlled study in twins. ***Vaccine.*** Published online 2011. doi:10.1016/j.vaccine.2011.10.015

21. Anh DD, Carlos CC, Thiem D V., et al. Immunogenicity, reactogenicity and safety of the human rotavirus vaccine RIX4414 (RotarixTM) oral suspension (liquid formulation) when co-administered with expanded program on immunization (EPI) vaccines in Vietnam and the Philippines in 2006-2007. ***Vaccine.*** 2011;29(11):2029-2036. doi:10.1016/j.vaccine.2011.01.018

22. Kemmeren JM, van der Maas NA, de Melker HE. Comparison of the tolerability of newly introduced childhood vaccines in the Netherlands. ***Eur J Pediatr.*** 2017;176(6):757-768. doi:10.1007/s00431-017-2901-4

23. Briggs-steinberg C, Aboudi D, Hodson G, Pharm D, Shah S. Clinical Tolerance of In-Neonatal Intensive Care Unit Administration of Rotavirus ***Vaccine***. 2019;1(212).

24. Bruijning-Verhagen P, van Dongen JAP, Verberk JDM, et al. Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting. ***BMC Med***. Published online 2018. doi:10.1186/s12916-018-1134-3

25. Blokhuis P. Changes in neonatal screening and vaccination. Lett to Parliam. Published online 2020.

26. Hahné S, Hooiveld M, Vennema H, et al. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. ***Euro Surveill***. 2014;19.

27. Verberk JDM, Pijnacker R, Bruijning-Verhagen P, et al. Biennial Pattern of Rotavirus Gastroenteritis in The Netherlands and a Shifting Age Distribution Following a Low Rotavirus Season, 2010-2016. ***Pediatr Infect Dis J.*** 2018;37:248-250. doi:10.1097/INF.0000000000001880

28. Rosettie KL, Vos T, Mokdad AH, et al. Indirect Rotavirus Vaccine Effectiveness for the Prevention of Rotavirus Hospitalization: A Systematic Review and Meta-Analysis. ***Am J Trop Med Hyg.*** Published online 2017.

Supplementary Material

Appendix A

Table S1. Detailed information on vaccine related SAE and hospitalized vaccine failure after first and second HRV administration

Nr	Event	Sex	Gestational age in weeks + days	Birth weight in grams	Congenital disorder	Age at HRV1*	Age at HRV2*	Age at SAE*	Rotavirus positive feces sample
2	Severe AGE	M	32+3	2000	no	52		55	
3	Intussusception	F	33+5	1500	no	49	120	124	
4	Cardio-resp incidents	F	30+3	1300	no	50	80	51	
5	Sepsis	F	28+4	800	no	56	91	92	
6	NEC	M	27+4	1000	no	58		62	no
7	Lactose intolerance	M	32+0	1600	no	68	120	120	
8	NEC	M	33+1	2000	yes	68		68	yes
10	Intussusception	F	33+0	1500	no	95	126	127	
11	Cardio-resp incidents	F	28+3	700	no	58	108	109	
13	Cardio-resp incidents	M	27+3	2900	yes	99		99	
16	Vaccine Failure	M	27+2	800	no	109	144	344	yes (Genotype G3P8)
17	Vaccine Failure	M	31+6	1800	no	51	125	384	yes (Genotype G9P8)

* Age in days. Abbreviations: M=male, F=female, SAE = serious adverse event, HRV = human rotavirus vaccine, AGE = acute gastroenteritis, Cardio-resp = cardiorespiratory events, NEC=necrotizing enterocolitis, HRV1 = first dose, HRV2 = second dose.

Secondary outcomes

Results of the secondary endpoints are presented in **table S2**. The mean cumulative number of solicited AE during the primary series of NIP was 1.77 compared to 1.97 for NIP+HRV vaccinated infants.

Table S2. Solicited AE for receipt of the primary series with or without HRV per infant (≥ 27 weeks of gestational age)

Reported adverse events associated with receipt of primary series	NIP vaccinated infants (N=471)	NIP+HRV vaccinated infants (N=570)	p-value
Any solicited adverse event	332 (70.5%)	404 (70.9%)	0.89
Fever	152 (32.3%)	191 (33.5%)	0.67
Gastrointestinal adverse event	66 (14.0%)	144 (25.3%)	**<0.001**
Any AE related healthcare attendance	48 (10.2%)	51 (8.9%)	0.47

Statistical significance (p-value <0.05) is highlighted in bold. Abbreviations: HRV = human rotavirus vaccine, N = number in group, NIP = national immunization program.

Table S3. Baseline characteristics and solicited AE for receipt of primary series with or without HRV per infant, for off-label subgroup of high-risk premature infants (gestational age < 27 weeks)

Characteristic	NIP vaccinated (N=5)	NIP + HRV vaccinated (N=22)
Gestational age in weeks+days (mean, SD)	26+1 (0+4)	26+0 (0+5)
Birthweight in grams (median, IQR)	925 (805-1045)	820 (523-1199)
Small for gestational age (yes,%)[£]	0	3 (13.6)
Sex (male, %)	2 (40.0)	12 (54.5)
Multiple birth (yes, %)	0	6 (27.3)
Congenital pathology (yes, %)	0	0
Age at first vaccination in days (median, IQR)	63 (54-72)	72 (45-99)
Concomitant NIP+HRV administration	NA	10 (45.5)
Sibling (yes, %)	1 (20.0)	4 (18.2)

Characteristic	NIP vaccinated (N=5)	NIP + HRV vaccinated (N=22)
Parental education#		
High	3 (60.0)	15 (62.8)
Medium	2 (40.0)	6 (27.3)
Lower	0	1 (4.5)
Parental background ^		
European	3 (60.0)	14 (63.6)
Non-European		4 (18.2)
Mixed	2 (40.0)	4 (18.2)
Average parental age in years (median, IQR)	30.5 (17.7-43.3)	34.5 (27.5-41.5)
Parent reported solicited adverse event		
Any solicited adverse event	4 (80%)	15 (68%)
Fever	3 (60%)	8 (36%)
Gastrointestinal adverse event	2 (40%)	4 (18%)
Any AE related healthcare attendance	3 (60%)	8 (36%)

For the subgroup of infants with GA before 27 weeks, we only took those receiving care in a hospital with a policy to vaccinate off-label, as our study population. Percentages are derived excluding subjects with missing data on the variable. ᶻ Based on 10th percentile perinatal growth curves. # Based on highest parental educational level. ^Based on parental background and categorized according to world population by country. Abbreviations: N = number in group, SD = standard deviation, IQR = interquartile range, NIP = national immunization program, HRV = human rotavirus vaccine.

Table S4. Solicited AE following receipt of NIP vaccines or concomitant NIP+HRV vaccination as part of the primary series in off-label subgroup of high-risk premature infants (gestational age < 27 weeks)

Reported adverse events after primary series vaccine administrations	Any NIP vaccination (N=14)	Concomitant NIP+HRV vaccination (N=17)
At least one solicited adverse event	9 (64.3%)	7 (41.2%)
Fever	4 (28.6%)	4 (23.5%)
Gastrointestinal adverse event	2 (14.3%)	2 (11.8%)
Any healthcare attended	3 (21.4%)	3 (17.6%)
Hospitalization	3 (21.4%)	2 (11.8%)

For the subgroup of infants with GA before 27 weeks, we only took those receiving care in a hospital with a policy to vaccinate off-label, as our study population. #1 missing information on solicited adverse events. Abbreviation: NIP = national immunization program, HRV = human rotavirus vaccine, N = number in group

Exploration of potential bias induced by complete case analyses

Comparing infants for whom complete data were available on vaccination status to those with missing information, we only observed differences in variables that were not associated with occurrence of solicited AEs in univariate analysis (proportion of infants from multiple birth, median parental age and family educational level, **table S5**); we therefore conclude missing information is independent of the outcome of solicited AE and complete case analysis induced little bias in our study results.

Table S5. Infants with missing data versus complete cases

Characteristic	Missing (N=59)	Complete (N=960)	p-value
Gestational age in weeks+days (mean, SD)	32+1 (2+3)	32+2 (2+4)	0.59
Birthweight in grams (median, IQR)	1640 (825-2465)	1780 (930-2630)	0.42
Small for gestational age (yes,%)[£]	25 (42.2)	288 (30.0)	0.05
Sex (male, %)	28 (47.5)	532 (55.4)	0.23
Multiple birth (yes, %)	36 (61.0)	714 (74.4)	**0.02**
Congenital pathology (yes, %)	3 (5.1)	82 (8.5)	0.35
Age at first vaccination in days (median, IQR)	60 (41-79)	61 (45-77)	0.77
Sibling (yes, %)	6 (13.6)	210 (21.9)	0.20
Parental education[#]			0.03
High	30 (62.5)	728 (75.8)	
Medium	14 (29.2)	206 (21.5)	
Lower	4 (8.3)	26 (2.7)	
Parental background [^]			0.57
European	42 (84.0)	823 (85.7)	
Non-European	4 (8.0)	46 (4.8)	
Mixed	4 (8.0)	91 (9.5)	
Average parental age in years (median, IQR)	30.5 (25.0-36.0)	33.0 (27.5-38.5)	**0.03**

Percentages are derived excluding subjects with missing data on the variable. Statistical significance (p-value <0.05) is highlighted in bold. [£] Based on 10th percentile perinatal growth curves. [#] Based on highest parental educational level. [^]Based on parental background and categorized according to world population by country. Abbreviations: HRV = human rotavirus vaccine, N = number in group, SD = standard deviation, IQR = interquartile range.

Appendix B

Term infants with congenital disorders

A total of 763 infants were born with a GA >37 weeks and with at least one congenital disorder, flowchart **figure S2**. Among the 118 HRV vaccinated infants, two vaccine related SAE were reported. Both concerned hospitalization 12 and 19 days after first dose of HRV, respectively, no information on second HRV dose was available. The first case was classified as (potentially) vaccine induced. The second as vaccine failure, sequencing was performed revealing a G3P8 genotype. Among 134 infants participating in the before-after cohort study, 79 infants were immunized with the NIP primary series vaccines and 55 infants with NIP and HRV vaccines, characteristics are shown in **table S6**. Out of all vaccine moments, 49.1% (79/161) experienced a solicited AE versus 59.1% (13/22), respectively (**table S7**).

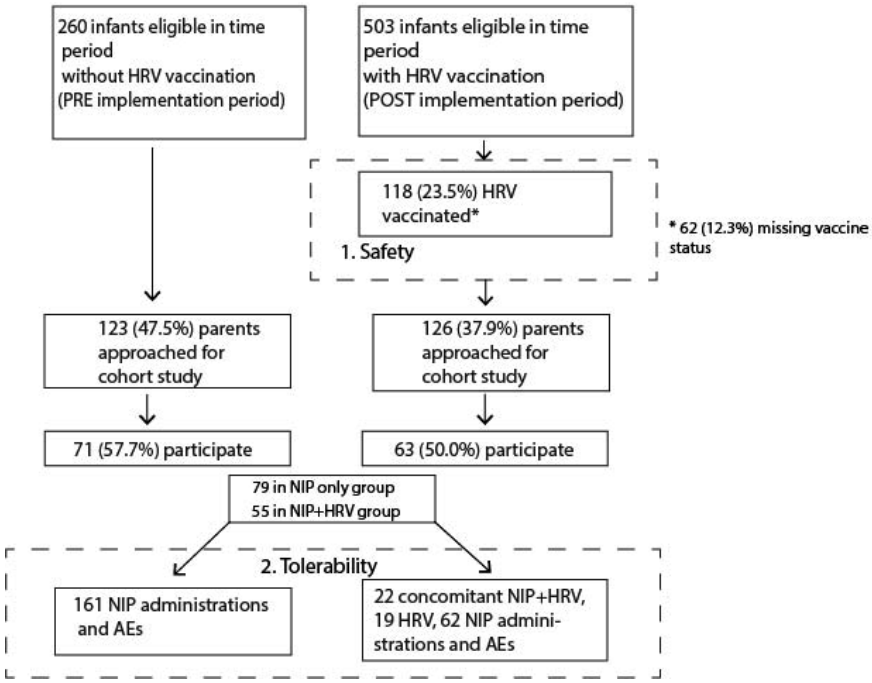


Figure S2. Flowchart of term infants with congenital disorders and cohort study-participants

Table S6. Characteristics of term infants with congenital disorders and solicited AE for receipt of the primary series with or without HRV per infant

Characteristic	NIP vaccinated (N=79)	NIP+HRV vaccinated (N=55)	p-value
Mean gestational age in week + days (SD)	39+2 (1+2)	39+0 (1+3)	0.22
Median birthweight in grams (IQR)	3340 (2685-3995)	3330 (2525-4135)	1.0
Sex (male, %)	44 (55.7)	32 (58.2)	0.76
Number of congenital disorder, n (%)			0.25
1	55 (69.6)	7 (67.3)	
2	21 (26.6)	11 (20.0)	
> 2	3 (3.8)	7 (12.7)	
Type of congenital disorder, n (%)			
Neurodevelopmental	4 (5.1)	2 (3.6)	1.0
Cardiovascular	31 (3.2)	28 (50.9)	0.18
Pulmonary	2 (2.5)	5 (9.1)	0.12
Chromosomal	14 (17.7)	90 (18.2)	0.95
Perinatal	1 (1.3)	1 (1.8)	1.0
Other*	36 (45.6)	23 (41.8)	0.67
Age at first vaccination (median, IQR)	62 (40-84)	61 (34-88)	0.86
Concomitant NIP+HRV administration	NA	10	NA
Sibling (yes, %)	34 (49.3)	18 (34.6)	0.11
Parental education#			0.13
High	46 (65.7)	9 (75·0)	
Medium	16 (22.9)	12 (23.1)	
Lower	8 (11.4)	1 (1.9)	
Parental background^			0.90
European	60 (85.7)	45 (86.5)	
Non-European	10 (14.3)	7 (13.5)	
Average parental age in years (median, IQR)	33.5 (27.5-39.5)	34·3 (27.7-40.9)	0.49

Characteristic	NIP vaccinated (N=79)	NIP+HRV vaccinated (N=55)	p-value
Parent reported solicited AE			
Any solicited AE	57 (72.2)	46 (83.6)	0.12
Fever	41 (51.9)	34 (61.8)	0.26
Gastrointestinal AE	20 (30.8)	22 (41.5)	0.23
Any AE related healthcare attendance	8 (10.1)	4 (7.2)	0.40

Percentages are derived excluding subjects with missing data on the variable. Statistical significance (p-value <0.05) is highlighted in bold. *Infants can have multiple congenital disorders, in category Other there are duplicates. #Based on highest parental educational level. ^Based on parental background and categorized according to world population by country. Abbreviations: N = number in group, IQR = interquartile range, SD = standard deviation.

Table S7. Solicited AE following receipt of NIP vaccines or concomitant NIP+HRV vaccination as part of the primary series in term infants with congenital disorders

Reported AE after primary series vaccine administrations	Any NIP vaccination (N=161)	Concomitant NIP+HRV vaccination (N=22)
At least one solicited AE	79 (49.1%)	13 (59.1%)
Fever	47 (29.2%)	4 (18.2%)
Gastrointestinal AE	11 (6.8%)	5 (22.7%)
Any healthcare attended for AE	8 (5.0%)	1 (4.5%)
Hospitalization	3 (1.9%)	0

Abbreviations: NIP = national immunization program, HRV = human rotavirus vaccine, N = number in group

Chapter 6

Non-specific effects of human rotavirus vaccination in medical risk infants in the Netherlands

Josephine AP van Dongen, Elsbeth DM Rouers, Marc JM Bonten,
Patricia CJ Bruijning-Verhagen.
On behalf of the RIVAR study group.

Under review, revisions submitted

Abstract

Background: The WHO recommends research into non-specific effects of vaccination. For rotavirus vaccines, these have not yet been well established. We studied non-specific effects using data from a quasi-experimental before-after study comparing cohorts of rotavirus vaccinated and unvaccinated infants with medical risk conditions up to 18 months of age.

Methods: Infants were enrolled at six weeks of age before and after a stepped-wedge implementation of a risk-group based rotavirus vaccination program. Other infant vaccinations were administered according to the Dutch National Immunization Program and similar in both periods. Non-specific effect outcomes were prospectively collected using monthly questionnaires and included acute hospitalization (excluding for acute gastro-enteritis), monthly incidence of acute respiratory illness and eczema. We used time-to-event analysis and negative binomial regression to assess the effect of at least one dose of rotavirus vaccination for each of these outcomes.

Findings: The analysis included 496 rotavirus unvaccinated and 719 vaccinated high-risk infants. In total, 1067 (88%) were premature, 373 (31%) small for gestational age and 201 (17%) had a congenital pathology. The adjusted hazard ratio for first acute hospitalization was 0.91 (95%CI 0.76;1.16) for rotavirus vaccinated versus unvaccinated infants. Adjusted incidence rate ratio for acute respiratory illness was 1.05 (95%CI 0.96;1.15) and for eczema 0.89 (95%CI 0.69;1.15).

Interpretation: The results suggest no, or minimal non-specific effects from rotavirus vaccination on non-target diseases in high-risk infants.

Introduction

Beneficial non-specific effects have been attributed to (live attenuated) vaccines in both adults and children.[1] Non-specific effects are defined as effects of vaccines on morbidity and mortality that are not explained by the prevention of the target diseases,[2] or as resistance towards unrelated pathogens in vaccine recipients.[3] For instance, since the introduction of the first human vaccine, Vaccinia, reductions in measles and scarlet fever were observed besides the effect on smallpox.[3] The proposed mechanism for non-specific effects on non-target infections and hospitalizations is trained immunity.[1] Trained immunity is induced by epigenetic reprogramming that results in enhanced innate immune responses to reinfection and to non-target pathogens.4 Immunological studies in infants and adults established that vaccines can induce activation of innate immune cells against other than target diseases.[5–8] The duration of these beneficial non-specific effects is thought to last between three months and one year or until the next (non-live) vaccine is given.[1,9]

Epidemiologic studies suggest that bacillus Calmette-Guérin (BCG) vaccination can offer protection against respiratory infections and (recurrent) bladder cancer.[10] A recent randomized controlled trial showed that neonatal BCG vaccination prevented non-tuberculosis infectious diseases in the first six weeks of life.[11] For the Measles Mumps Rubella (MMR) vaccine, a reduction in childhood mortality was observed mediated by prevention of respiratory infections.[12] For Oral Polio vaccine (OPV) research indicated lower hospitalization rates and protection against otitis media.1 However, conflicting reports on reduction in all-cause case fatality after OPV have been published.[13–15]

Another observation from epidemiological studies is a non-specific effect on atopy. There are two reports of reduced atopy after BCG vaccination,[16,17] however a randomized controlled trial found no effect but a potential trend towards less (severe) eczema.[18] The mechanism resulting in atopy prevention is less well studied, the Th1 stimulating property of live-vaccines may prevent allergic sensitization and reduce atopy (which is Th2 mediated).[17,19]

Yet, two systematic reviews on routine childhood vaccinations and non-specific effects concluded that low quality studies and heterogeneity of the available evidence should raise caution in interpretation.[20,21] The World Health Organization recommends more research towards non-specific effects of vaccines.[22,23]

Rotavirus vaccines are live-attenuated and orally administered, like OPV. It is hypothesized that rotavirus vaccination can therefore induce beneficial non-specific effects through similar mechanisms, but this has been little studied thus far. One study reported a decrease of 31% in non-rotavirus hospitalization rates in the 60 days following rotavirus vaccination, but misclassification of rotavirus infections could not be completely ruled out.[24] To our knowledge, no literature is available on non-specific effects of rotavirus vaccination on respiratory infections or atopy.

We explored potential non-specific effects in a prospective cohort of medical risk infants in the

Netherlands who did or did not receive rotavirus vaccination in a quasi-experimental setting.

Methods

For a detailed description of the study we refer to a previous publication (**chapter 4**). In short, thirteen Dutch hospitals with a neonatal intensive or high care ward participated in the project that combined the implementation of rotavirus vaccination program for medical risk infants with a prospective before-after cohort study. During both periods with and without rotavirus vaccination, infants were recruited at six weeks of age if they had at least one medical risk condition; 1) prematurity (gestational age < 36 weeks), 2) low birthweight (< 2500 grams) and/or 3) congenital pathology (list in **chapter 4**), and received prolonged pediatric care between six and 14 weeks of postnatal age at the participating site. Hospitals entered the study in a stepped-wedge approach and each site implemented rotavirus vaccination in routine care for medical risk infants between months 12-18 of the project. The schedule for other routine childhood immunizations according to the National Immunization Program (NIP) was left unchanged (**Figure 1**). Post-implementation, the human rotavirus vaccine (HRV, Rotarix, GSK, Belgium) was used at all sites. HRV was given in a two-dose schedule, with first dose preferably between six and nine weeks of age and the second dose with a minimum interval of four weeks and no later than 24 weeks of age. The first dose was administered by a physician in participating hospitals, the second dose was given by parents at home after detailed instruction.

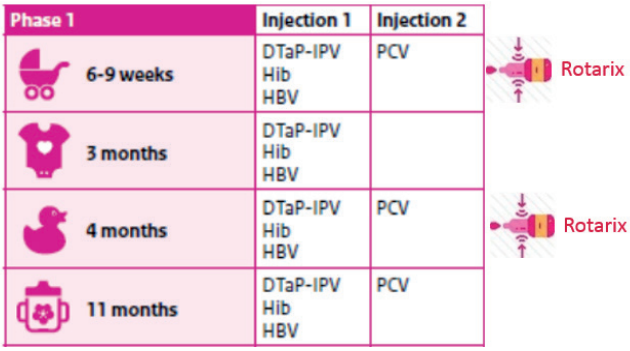


Figure 1. Vaccination schedule RIVM@2021.

Legend: Rotarix = human rotavirus vaccination

Abbreviations: DTaP-IPV = Diphteria Tetanus accelular Pertussis-Inactivated Polio vaccine, Hib = Haemophilus influenza type B, HBV = Hepatitis B vaccine, and PCV = Pneumococcal conjugate vaccine.

Data collection

Data collection for cohort participants included monthly parental questionnaires until 18 months of age. Parents answered yes/no questions concerning acute respiratory illness (ARI) symptoms, presence of eczema symptoms and hospital admission in the past month. ARI symptoms included fever with or without nasal congestion/runny nose, cough and earache. In addition the number of days with ARI symptoms in each month was recorded. For hospitalization, the reason and number of hospital days was also collected.

Non-specific effect outcomes

We defined non-specific effect outcomes of rotavirus vaccination as the relative change in incidence of parent-reported acute hospitalization, ARI or eczema between rotavirus vaccinated and unvaccinated infants.

Acute hospitalization was defined as any hospital admission following initial post-natal discharge, excluding hospital admissions for acute gastroenteritis. Hospital admissions for scheduled medical or surgical interventions were also excluded.

Analyses

Descriptive statistics were used to compare patient characteristics and outcomes between vaccinated and unvaccinated infants. We calculated the cumulative incidence and incidence rate for each non-specific effect outcome by group status. As secondary outcomes, we calculated the cumulative acute hospitalization days and days with ARI symptoms for rotavirus vaccinated and unvaccinated infants.

Next, we used Cox regression to model the effect of at least one dose of rotavirus vaccination on time to first hospital admission, with age (between two and 18 months) as time axis. Infants were censored when lost to follow up, dropped-out, deceased or hospitalized, whichever came first. The proportional hazard assumption was visualized graphically and tested with Schoenfelds residuals. The final model with covariates was derived using log-likelihood ratio test, hazard ratios (HR) and their 95% confidence intervals (CI) were provided. Infants were categorized as rotavirus vaccinated from 28 days post-dose one onwards.

For ARI, we used a negative binomial model with offset for persontime of observation to compare the number of months with ARI between rotavirus vaccinated and unvaccinated groups. Incidence rate ratios (IRR) were obtained with their 95% CIs. We used Akaike Information Criterion to select the final model. The analysis was repeated for the outcome months with eczema.

For the secondary outcome of cumulative days hospitalized or days with ARI complaints we used a Poisson model. Because of overdispersion for hospitalization days we used a negative binomial model.

In sensitivity analyses, we separately analysed effects up to six months of age, covering the

initial three months post-rotavirus vaccination, and up to eleven months of age, covering the period up to the booster vaccinations of the NIP. We also analysed hospitalizations for infectious diseases separately, using Cox modelling as described above.

For all models, we considered the following covariates: sex, type of medical risk condition, gestational age, breastfeeding, daycare attendance, type of hospital care (i.e. academic versus general), family educational level, parental origin, NIP vaccination status, presence of siblings in the household and season with high rates of respiratory infections (from October until April).

All analyses were performed on according to protocol cohorts, where all high-risk infants whose parents indicated willingness to vaccinate their child against rotavirus in the pre-implementation cohort are compared to infants that received at least one HRV dose in the post-implementation cohort. This information was based on a parental questionnaire at start of the study, see **chapter 4**.

We performed complete case analyses, missing information is documented. As statistical software SPSS version 25 and RStudio version 5.0 were used, with packages *MASS, fmsb, survival* and *survminer*.

Results

A total of 1482 high-risk infants with one or more medical risk conditions were enrolled in the study. The population for analysis included 719 rotavirus vaccinated infants and 496 infants whose parents indicated willing to vaccinate against rotavirus, but who were enrolled before rotavirus vaccination was implemented. In total, 1067 infants (87.8%) were born premature, 373 infants (30.7%) were small for gestational age and 201 infants (16.5%) had at least one congenital condition. Baseline characteristics were comparable between the rotavirus vaccinated and unvaccinated group (**table 1**), with the exception of follow up, which was complete for 450 vaccinated infants (62.6%) and 380 (76.6%) of unvaccinated infants. The proportion of observation months during seasons with or without high rates of respiratory infections was not significantly different between the groups, ARIs occurring in-season was also not different.

Table 1 Baseline table with characteristics of vaccinated and unvaccinated infants

	According to protocol groups protocol (ATP)		
	Pre-implementation: willing to vaccinate	Post-implementation: vaccinated	p-value
	N=496	N=719	
Male sex	286 (57.7%)	381 (53.0%)	0.11
Multiple births	115 (23.8%)	193 (26.8%)	0.15
Premature birth (gestation < 37 weeks)	432 (87.8%)	635 (88.3%)	0.79
Small for gestational age[£]	135 (27.2%)	238 (33.1%)	**0.03**
Presence of severe congenital disorder[*]	95 (19.2%)	106 (14.7%)	**0.04**
Vaccinated according to NIP	484 (97.6%)	652 (90.7%)	**<0.001**
Daycare attendance	289 (58.6%)	398 (59.6%)	0.74
Socioeconomic status[^]			0.36
Higher	352 (71.5%)	492 (74.1%)	
Moderate	119 (24.2%)	153 (23.0%)	
Lower	21 (4.3%)	19 (2.9%)	
Parental origin[#]			0.75
European parent(s)	417 (84.8%)	557 (83.4%)	
Non-European parent(s)	28 (5.7%)	38 (5.7%)	
Mixed	47 (9.6%)	73 (10.9%)	
Mean number of months with completed follow-up (SD)	16.4 (5.5)	14.9 (6.5)	**<0.001**
Number with complete follow-up until 18 months of age	380 (76.6%)	450 (62.6%)	**<0.001**
Mean proportion of months during ARI season (SD)[$]	0.50 (0.18)	0.50 (0.18)	0.75

Percentages are computed excluding subjects with missing data on the variable. Statistical significance (p-value <0.05) is highlighted in bold. [£] Based on the 10th percentile perinatal growth curves. [*]For a list of qualifying congenital disorders, see chapter 4. [^]Based on highest parental education level. [#]Based on parental origin by World population by country[25] [$] ARI season in the Netherlands is defined from October until April.[26] Abbreviations: GA= gestational age, SD= standard deviation, IQR = interquartile range, yrs= years, NIP = National Immunization Program and, N = number in group.

Non-specific effect outcomes by vaccination status are described in **table 2**. Twenty-one hospitalizations for acute gastroenteritis were excluded from the acute hospitalizations (eleven among unvaccinated and ten among vaccinated infants, respectively). Thirty-nine percent of infants were hospitalized at least once or reported one month with eczema. For 82% of infants at least one ARI episode was reported. Incidence of any of the non-specific effect outcomes or the mean cumulative number of days hospitalized or with ARI symptoms show no significant differences (**table 2**).

Table 2 Non-specific effect outcomes for vaccinated and unvaccinated infants

	Pre-implementation: willing to vaccinate N=496	Post-implementation: vaccinated N=719
At least one acute hospitalization	212 (43.0%)	262 (39.2%)
Cumulative number of hospitalizations	367	433
Incidence of hospitalization* (95%CI)	0.54 (0.48;0.59)	0.48 (0.43;0.52)
Mean cumulative number of hospitalization days	8.3	8.2
At least one ARI	411 (83.4%)	584 (87.3%)
Cumulative number of months with ARI	1888	2660
Incidence of months with ARI (95%CI)	2.77 (2.64;2.89)	2.92 (2.81;3.04)
Mean cumulative number of days with ARI	23.2	24.5
At least one month with eczema	204 (41.4%)	270 (40.4%)
Cumulative number of reported eczema	995	1215
Incidence of months with eczema (95%CI)	1.46 (1.37;1.55)	1.33 (1.26;1.41)

Percentages are derived excluding cases with missing information (n=53). *Incidence per person year of observation. Abbreviations: N=number in group, CI = confidence interval and, ARI = acute respiratory illness.

Based on the adjusted Cox model at least one dose of HRV was not significantly protective against first acute hospitalization (HR for time to first acute hospitalization 0.91; 95%CI 0.71;1.18, **table 3**). The final model included gestational age, presence of a congenital disorder, type of hospital care and seasonality as covariates.

In addition, no effect was observed on the occurrence of ARI (adjusted incidence rate ratio (IRR) 1.05; 95%CI 0.96;1.15), or eczema (adjusted IRR: 0.89; 95%CI 0.69;1.15, **table 3**). Comparing the secondary outcomes of cumulative or hospitalization days showed no statistically significant difference. The cumulative number of days with ARI was increased for vaccinated infants (**table 3**).

Table 3 Effect estimates of non-specific effects

	Univariate	95% CI	Multivariate estimate	Lower 95% CI	Upper 95% CI
HR for acute hospitalization*	0.85	0.66-1.09	0.91	0.71	1.18
IRR for ARI#	1.07	0.99-1.17	1.05	0.96	1.15
IRR for eczema#	0.94	0.74-1.18	0.89	0.69	1.15
Secondary					
RR Cumulative number of days hospitalized	0.91	0.66-1.25	0.83	0.59	1.16
RR Cumulative number of days with ARI	1.06	1.04-1.09	1.06	1.03	1.09
Sensitivity					
HR for infectious diseases hospitalization*	0.93	0.56-1.60	0.96	0.58	1.62
HR for acute hospitalization until 6 months*	1.08	0.76-1.53	1.20	0.85	1.71
HR for acute hospitalization until 11 months*	0.87	0.65-1.16	0.95	0.71	1.27
IRR for ARI until 6 months#	1.05	0.89-1.24	0.94	0.78	1.14

	Univariate	95% CI	Multivariate estimate	Lower 95% CI	Upper 95% CI
IRR for ARI until 11 months#	1.10	0.99-1.22	1.03	0.92	1.15
IRR for eczema until 6 months#	0.99	0.71-1.41	0.91	0.62	1.33
IRR for eczema until 11 months#	0.96	0.73-1.24	0.89	0.66	1.19

* Adjusted for: gestational age, presence of congenital disorder, type of hospital care and seasonality. #Adjusted for: gestational age, daycare attendance, parental educational level, presence of sibling in the household, vaccinated according to NIP program and seasonality. Abbreviations: HR = hazard ratio, IRR = incidence rate ratio, RR = relative risk, CI = confidence interval

In sensitivity analyses we observed that the non-specific effects estimates were closer to one and non-significant when restricting to the six or eleven months of age for all non-specific effect outcomes, **table 3**. Restricting to acute hospitalizations for infectious diseases resulted in an adjusted HR of 0.96 (95%CI 0.58;1.62).

Discussion

This quasi-experimental prospective study assessed the potential non-specific effects of rotavirus vaccination among 1215 infants with medical risk conditions. Our results suggest that HRV does not offer significant protection against non-target diseases leading to acute hospitalization, or result in reduced incidence of ARI or atopy up to 18 months of age.

Non-specific effects of (live-attenuated) vaccines are increasingly being studied. Currently, 22 trials are being performed or completed on the potential protective effect of BCG vaccination against COVID-19 disease.[22] For rotavirus vaccines however, there has been very little research into non-specific effects despite their availability and widespread use for more than a decade. While some promising results of beneficial non-specific effects, in particular for BCG vaccine are available,[1,4,9,19] other studies report contradictory and less convincing results.[12–14,27] The results of our study add to the growing body of evidence hinting towards absence of non-specific effects, at least for rotavirus vaccines.

Opposite to our result, a reduction in acute hospitalization due to non-target diseases after rotavirus vaccination was reported in a previous study from the United States.[24] As a secondary analysis, this study compared hospitalization rates in the 60-day post-vaccination window for rotavirus vaccinated and unvaccinated infants, excluding hospitalizations coded as rotavirus gastro-enteritis. A reduction of 31% (95%CI 27-35%) was reported. However, coding for rotavirus hospitalizations is known to be incomplete.[28] By including hospitalizations for gastro-

enteritis without the rotavirus specific code, misclassification may have occurred and could explain the observation mediated by direct, rather than indirect vaccine effects.

Most likely, a reduction in acute hospitalizations resulting from non-specific effects would be mediated by lowering infection incidence. This is however not supported by our findings that show a similar rate of ARI in vaccinated and unvaccinated infants. Furthermore, when restricting the analysis to hospitalizations for infectious diseases only, an even smaller effect was estimated. Alternatively, one could argue that non-specific effects following rotavirus vaccination reduce severity of ARI, rather than ARI incidence, thereby reducing the risk of hospitalization. However, no reduction was observed in days with ARI symptoms, which could be considered a proxy for severity. Another hypothesis mentions that inactivated childhood vaccinations abrogate the beneficial non-specific effects of earlier administered live vaccines. To investigate this, we conducted a sensitivity analysis in which we restricted the analysis to the time-period up to the next routine childhood vaccination at 11 months, but the effect estimate was unchanged. Jointly, our results do not support the existence of non-specific effects for rotavirus vaccines lowering overall hospitalization rates, infection incidence or severity.

For eczema, we did not find a significant effect of rotavirus vaccination either. Evidence on preventing atopy by vaccination so far is based on one underpowered randomized clinical trial and several heterogeneous low-quality observational studies.[29] Unfortunately, our study was also underpowered to draw any firm conclusion on the effect of rotavirus vaccination on eczema incidence. Our point estimate of 0.89 suggests some benefit may exist, but this warrants confirmation in other controlled studies.

In this study the majority of infants was born prematurely. While non-specific effects have also been investigated among low birthweight infants in multiple randomized trials,[6,30,31] premature infants have a higher risk of respiratory morbidity and hospitalization.[32] Therefore any non-specific effect on ARI incidence should become apparent in this specific study population. However, direct vaccine effectiveness in our study population was lower than previously anticipated (**chapter 4**). If the direct vaccine response in this population is reduced, this may also apply to non-specific vaccine effects. Overall, there is an additional need for research into non-specific effects of rotavirus vaccination in a healthy term infant population.

A few limitations of this study need to be addressed. First, we used complete cases only, missing information is documented and comparing participants with complete versus missing data did not reveal significant differences (data not shown). Loss to follow up occurred in approximately 30% of participants. By using time-to-event analysis and including an offset for observation time this was taken into account in our analyses and we therefore expect this has minimal effect on our results.

We were unable to assess severity of ARI, a discrimination in episodes by severity might further explain why the difference in acute hospitalizations was not reflected in occurrence of ARI. Instead, we assessed number of days with ARI complaints and observed no relevant difference

between vaccinated and unvaccinated infants. Duration of disease could function as a proxy for severity.

In conclusion, rotavirus vaccination in medical risk infants was not associated with beneficial non-specific effects on (acute hospitalization due to) non-target diseases. The study results suggest that beneficial non-specific effects, as observed for some other live-attenuated vaccines, may not apply to oral rotavirus vaccines, but studies in healthy term infants are needed to further establish this.

Acknowledgements

We would like to thank all participating infants and their parents or guardians, all principal investigators and research nurses at the hospitals and the RIVAR study team for their contribution to this project. Dr. Cristian Spitoni is gratefully acknowledged for his contribution to the analysis. RIVAR study group: Zwart L.M., Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Tims-Polderman C., Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Beurden, van M., Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Bont, L.J., Department of Pediatrics, University Medical Center Utrecht, Utrecht, the Netherlands; Norbruis O.F., Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands; Hemels, M.A.C., Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands; Well, van G.T.J., Department of Pediatrics, Maastricht University Medical Center, Maastricht, the Netherlands; Vlieger, A.M., Department of Pediatrics, St. Antonius Hospital, Nieuwegein, the Netherlands; Sluijs, van der J., Department of Pediatrics, Maxima Medical Centre, Veldhoven, the Netherlands; Stas, H.G., Department of Pediatrics, Maasstad Hospital, Rotterdam, the Netherlands; Tramper-Stranders, G., Department of Pediatrics, St. Franciscus Hospital, Rotterdam, the Netherlands; Kleinlugtenbeld, E.A., Department of Pediatrics, Albert Schweitzer Hospital, Rotterdam, the Netherlands; Kempen, van A.A.M.W., Department of Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; Wessels, M., Department of Pediatrics, Rijnstate Hospital, Arnhem, the Netherlands; Rossem, van M.C., Department of Pediatrics, Rijnstate Hospital, Arnhem, the Netherlands; Dassel, A.C.M., Department of Pediatrics, Deventer Hospital, Deventer, the Netherlands; Houten, van M.A., Department of Pediatrics, Spaarne Gasthuis, Hoofddorp and Haarlem, the Netherlands; Pajkrt, D. , Department of Pediatrics, Amsterdam University Medical Center, Amsterdam, the Netherlands.

Trial registration: as NTR5361 in www.trialregister.nl

Funding: UMC Utrecht, GSK Biologicals SA (studyID 203108), the Netherlands Organisation for Health Research and Development (grantnumber 836021024), Healthcare Insurers Innovation Foundation

Role of funding source: GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for final content and interpretation. Sponsors had no role in study design, data collection, analysis, writing or submitting of the study.

References

1. de Bree LCJ, Koeken VACM, Joosten LAB, et al. Non-specific effects of vaccines: Current evidence and potential implications. ***Semin Immunol.*** 2018;39(April):35-43. doi:10.1016/j.smim.2018.06.002

2. Aaby P, Kollmann TR, Benn CS. Nonspecific effects of neonatal and infant vaccination: Public-health, immunological and conceptual challenges. ***Nat Immunol***. 2014;15(10):895-899. doi:10.1038/ni.2961

3. Benn CS, Netea MG, Selin LK, Aaby P. A Small Jab - A Big Effect: Nonspecific Immunomodulation By Vaccines. ***Trends Immunol.*** 2013;34(9):431-439. doi:10.1016/j.it.2013.04.004

4. Pollard AJ, Finn A, Curtis N. Non-specific effects of vaccines: Plausible and potentially important, but implications uncertain. ***Arch Dis Child.*** 2017;102(11):1077-1081. doi:10.1136/archdischild-2015-310282

5. Freyne B, Donath S, Germano S, et al. Neonatal BCG vaccination influences cytokine responses to toll-like receptor ligands and heterologous antigens. ***J Infect Dis***. 2018;217(11):1798-1808. doi:10.1093/infdis/jiy069

6. Jensen KJ, Larsen N, Sørensen SB, et al. Heterologous immunological effects of early BCG vaccination in low-birth-weight infants in guinea-bissau: A randomized-controlled trial. ***J Infect Dis***. 2015;211(6):956-967. doi:10.1093/infdis/jiu508

7. Kleinnijenhuis J, Quintin J, Preijers F, et al. BCG-induced trained immunity in NK cells: Role for non-specific protection to infection. ***Clin Immunol***. 2014;155(2):213-219. doi:10.1016/j.clim.2014.10.005

8. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. ***Proc Natl Acad Sci U S A***. 2012;109(43):17537-17542. doi:10.1073/pnas.1202870109

9. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. ***Nat Rev Immunol.*** 2020;20(6):375-388. doi:10.1038/s41577-020-0285-6

10. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. ***Clin Microbiol Infect***. 2019;25(12):1473-1478. doi:10.1016/j.cmi.2019.04.020

11. Prentice S, Nassanga B, Webb EL, et al. BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial. ***Lancet Infect Dis***. 2021;0(0):1-11. doi:10.1016/S1473-3099(20)30653-8

12. Aaby P, Martins CL, Garly ML, et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: Randomised controlled trial. ***BMJ.*** 2010;341(7785):1262. doi:10.1136/bmj.c6495

13. Lund N, Andersen A, Hansen ASK, et al. The Effect of Oral Polio Vaccine at Birth on Infant Mortality: A Randomized Trial. ***Clin Infect Dis***. 2015;61(10):1504-1511. doi:10.1093/cid/civ617

14. Lund N, Andersen A, Monteiro I, Aaby P, Benn CS. No effect of oral polio vaccine administered at birth on mortality and immune response to BCG: A natural experiment. ***Vaccine***. 2012;30(47):6694-6699. doi:10.1016/j.vaccine.2012.08.055

15. Aaby P, Rodrigues A, Biai S, et al. Oral polio vaccination and low case fatality at the paediatric ward in Bissau, Guinea-Bissau. ***Vaccine***. 2004;22(23-24):3014-3017. doi:10.1016/j.vaccine.2004.02.009

16. Marks GB, Ng K, Zhou J, et al. The effect of neonatal BCG vaccination on atopy and asthma at age 7 to 14 years: An historical cohort study in a community with a very low

prevalence of tuberculosis infection and a high prevalence of atopic disease. ***J Allergy Clin Immunol***. 2003;111(3):541-549. doi:10.1067/mai.2003.171

17. Aaby P, Shaheen SO, Heyes CB, et al. Early BCG vaccination and reduction in atopy in Guinea-Bissau. **Clin Exp Allergy**. 2000;30(5):644-650. doi:10.1046/j.1365-2222.2000.00803.x

18. Steenhuis TJ, Van Aalderen WMC, Bloksma N, et al. Bacille-Calmette-Guerin vaccination and the development of allergic disease in children: A randomized, prospective, single-blind study. ***Clin Exp Allergy***. 2008;38(1):79-85. doi:10.1111/j.1365-2222.2007.02859.x

19. Hopkin JM, Enomoto T, Shimazu S, Shirakawa T. Inverse association between tuberculin responses and atopic disorder. ***Thorax***. 1996;51(SUPPL. 3):1995-1998. doi:10.1136/thx.51.suppl_3.a1

20. Kandasamy R, Voysey M, McQuaid F, et al. Non-specific immunological effects of selected routine childhood immunisations: Systematic review. ***BMJ***. 2016;355. doi:10.1136/bmj.i5225

21. Higgins JPT, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: Systematic review. ***BMJ***. 2016;355. doi:10.1136/bmj.i5170

22. Clinicaltrials.gov. BCG and COVID trials. Published 2021. Accessed February 26, 2021. https://clinicaltrials.gov/ct2/results/map?cond=BCG+vaccine+AND+covid&map=

23. WHO Meeting of the Strategic Advisory Group of Experts on immunization, October 2017 – conclusions and recommendations. ***Wkly Epidemiol Rec***. 2017;92(22):301-320. https://www.who.int/wer/2017/wer9222/en/

24. Rogers MAM, Basu T, Kim C. Lower Incidence Rate of Type 1 Diabetes after Receipt of the Rotavirus Vaccine in the United States, 2001–2017. ***Sci Rep***. 2019;9(1):7727. doi:10.1038/s41598-019-44193-4

25. World population by Country 2020. Accessed September 11, 2020. https://worldpopulationreview.com/continents/capitals/europe

26. Reukers DFM, Asten L van, Brandsem PS, et al. Annual Report Surveillance of Influenza and Other Respiratory Infections in the Netherlands: Winter 2018/2019.; 2019. doi:DOI 10.21945/RIVM-2019-0079

27. Stensballe LG, Ravn H, Birk NM, et al. BCG vaccination at birth and rate of hospitalization for infection until 15 months of age in Danish children: A randomized clinical multicenter trial. ***J Pediatric Infect Dis Soc***. 2019;8(3):213-220. doi:10.1093/jpids/piy029

28. Wilson SE, Deeks SL, Rosella LC. Importance of ICD-10 coding directive change for acute gastroenteritis (unspecified) for rotavirus vaccine impact studies: Illustration from a population-based cohort study from Ontario, Canada. ***BMC Res Notes***. 2015;8(1):4-9. doi:10.1186/s13104-015-1412-5

29. Freyne B, Curtis N. Does neonatal BCG vaccination prevent allergic disease in later life? ***Arch Dis Child***. 2014;99(2):182-184. doi:10.1136/archdischild-2013-305655

30. Biering-Sørensen S, Jensen KJ, Monterio I, Ravn H, Aaby P, Benn CS. Rapid protective effects of early BCG on neonatal mortality among low birth weight boys: Observations from randomized trials. ***J Infect Dis***. 2018;217(5):759-766. doi:10.1093/infdis/jix612

31. Biering-Sørensen S, Aaby P, Lund N, et al. Early BCG-Denmark and Neonatal Mortality among Infants Weighing <2500 g: A Randomized Controlled Trial. ***Clin Infect Dis.*** 2017;65(7):1183-1190. doi:10.1093/cid/cix525

32. Steiner L, Diesner SC, Voitl P. Risk of infection in the first year of life in preterm children: An Austrian observational study. ***PLoS One***. 2019;14(12):1-11. doi:10.1371/journal.pone.0224766

Supplementary Material

Table S1. Reasons for acute hospitalization, excluding acute gastroenteritis, planned treatment, surgery or examination.

Reason for hospitalization	Hospitalizations in pre-implementation: willing to vaccinate (N=367)	Hospitalizations in post-implementation: vaccinated (N=433)
Infectious (n,%)	45 (12.3)	56 (12.9)
IR per person year	0.06	0.06
Growth problems (n,%)	20 (5.4)	9 (2.1)
IR per person year	0.03	0.01
Feeding problems (n,%)	27 (7.4)	36 (8.3)
IR per person year	0.04	0.04
Non-infectious intestinal (n,%)	13 (3.5)	12 (2.8)
IR per person year	0.02	0.01
Breathing difficulties (n,%)	124 (33.8)	119 (27.5)
IR per person year	0.18	0.13
Excessive crying (n,%)	6 (1.6)	11 (2.5)
IR per person year	0.01	0.01
Other reason (n,%)	132 (36.0)	190 (43.9)
IR per person year	0.19	0.21

Abbreviatons: IR = incidence rate, n = number with characteristic, N = number in group.

Chapter 7

Evaluation of implementing a rotavirus vaccine program targeting high-risk infants in The Netherlands

Josephine A.P. van Dongen, Caterina Band, Margit J. Heslinga, Sandra J. Fokkert,
Elsbeth D.M. Rouers, Marc J.M. Bonten and, Patricia C.J. Bruijning-Verhagen.
On behalf of the RIVAR study team.

Submitted

Abstract

Background: Prior to introduction of a rotavirus vaccination program in the Netherlands, a pilot was conducted in 13 hospitals to trial the implementation process, assess feasibility and vaccine coverage. A targeted rotavirus vaccination program for high-risk infants was scheduled to be introduced in 2020.

Methods: Between May 2016 and October 2017 pediatric and neonatal departments in 13 hospitals implemented targeted rotavirus vaccination for medical risk infants, including those with prematurity, low birth weight and/or a congenital disorder. Rotavirus vaccination was available as standard care without charge. Vaccination status of all eligible infants was documented and feasibility was evaluated based on surveys and in-depth interviews.

Results: Overall mean vaccine coverage among eligible medical risk infants was 52.3% (95%CI 50.8;53.7%) and ranged between 24.4% (95%CI 21.3;27.5%) and 83.4% (95%CI 79.9;87.0%) per site and between 22.9% (95%CI 18.7;27.1%) and 58.3% (95%CI 56.3;60.4%) per type of medical risk condition. Only 34.1-38.5% of surveyed parents were informed of the vaccine as part of standard care. In-depth interviews revealed infant, healthcare and vaccine related barriers and facilitators of this implementation program.

Conclusion: Implementation of a hospital-based targeted rotavirus vaccination program, resulted in suboptimal vaccine coverage among high-risk infants and was not introduced in 2020. Involvement of the national immunization program existing structure would be preferable in order to reach a substantial larger proportion of the risk-groups.

Background

Immunization in childhood has been found a highly (cost-)effective preventive measure[1]. However successful introduction of new vaccines is dependent upon multiple factors[2]. Requirements for successful implementation of new vaccines are structured organization of the immunization program, raising awareness and providing adequate information to parents, favorable vaccine characteristics, and a feasible implementation strategy. Specifically for childhood immunization, parental conceptions influence the willingness to receive vaccination and therefore vaccination coverage[3–5]. In addition, the attitude and perceptions of health care providers (HCP) towards vaccination have been identified as important determinants for implementation success[6–8]. Vaccination coverage is a key performance indicator to evaluate vaccine strategy and implementation policy.

As of 2020, at least 98 countries have implemented rotavirus vaccination in their National Immunization Program (NIP)[9]. Globally licensed rotavirus vaccines are Rotarix (GSK, Belgium) and RotaTeq (Merck and Co, USA). They both have a high efficacy against severe rotavirus gastroenteritis ranging from 80 to 100% in high-income countries[10–14]. The two vaccines are generally well-tolerated. In the Netherlands, the health council advised, in 2007, against universal rotavirus vaccination, due to insufficient evidence on a specific risk group for vaccination and rotavirus genotype distribution[15]. Because it was demonstrated that infants with medical risk conditions (MRC) had increased disease burden[16], a targeted vaccination strategy was piloted for infants with MRC only. This Risk-group Infant Vaccination Against Rotavirus (RIVAR) project started in 2014. For program execution, pediatric secondary and tertiary care facilities were made responsible, instead of well-baby clinics that offer all routine childhood vaccines of the NIP. The main objectives of the RIVAR project were: 1) to determine vaccine effectiveness of rotavirus vaccination among infants with MRC and 2) to assess the feasibility of implementing a targeted rotavirus vaccine program in secondary and tertiary hospitals in the Netherlands. The second aim of the RIVAR project is described in this implementation study.

Methods

RIVAR project and intervention

A full description of the project is published at www.trialregister.nl (NTR5361)[17] and vaccine effectiveness is described elsewhere (**chapter 4**). In brief, rotavirus vaccination was implemented in thirteen Dutch hospitals with a Neonatal Intensive Care Unit (NICU) or post-Intensive Care (IC) ward. This intervention was added to standard care for premature infants (gestational age (GA) below 36 weeks), infants with a low birthweight (LBW) less than 2500 grams and/or infants with severe congenital pathology (for a list of conditions, see **chapter 4**). In order to be eligible for rotavirus vaccination, infants should receive in- or out-patient care in the participating hospitals between six and fourteen weeks of age, corresponding with the time window for the first dose of rotavirus vaccine administration. Rotarix, the human rotavirus vaccine (HRV) was

used within the RIVAR project. Exclusion criteria were: known hypersensitivity to the vaccine, severe diarrhea, previous intussusception or severe immunodeficiency. All hospitalized infants in a participating hospital were screened and basic patient characteristics were entered into a digital Case Report Form (CRF). At the age of five months, the HRV immunization status was retrieved from medical records for all eligible infants and recorded in the CRF.

A subset of eligible infants participated in the before-after cohort-study and was followed until 18 months of age for the occurrence of acute gastroenteritis.

Implementation of a targeted rotavirus vaccination program

Hospitals implemented the rotavirus vaccination program at different time points and entered the project one year prior to implementation of HRV (step wedged design). During a preparatory pre-implementation year the organizational and logistical infrastructure for patient selection and vaccine administration was set up in each hospital. Various educational activities targeting physicians and nurses were organized, such as group-presentations, e-learnings, and workshops. Nurses received practical tutorials for administration. We distributed pocket cards among medical doctors with eligibility criteria, (contra-) indications, the vaccination schedule and possible side effects of HRV. Posters and hand-outs were distributed to clinical wards and out-patient clinics highlighting key elements of the program. Shortly before implementation, email newsletters were distributed to all HCP involved in the upcoming HRV implementation. The implementation of HRV was supported by research personnel and -nurses. Administration of HRV first dose was scheduled during hospital stay or combined with a planned out-patient visit. The second dose of HRV was administered by parents at home, after they received instructions. Cold chain was guaranteed by a cooling device upon collection from the hospital. According to the product information, HRV can be administered in premature infants of at least 27 weeks gestation. However, national guidelines vary in their advice for HRV in these infants. Decisions about allowing administration of HRV on the in-patient-ward and to infants born before a gestational age of 27 weeks were left to the discretion of local policy in participating hospitals. Regular audits were performed to guide the implementation throughout the project. Every two months the interim vaccination coverage was communicated to all hospitals. The program execution was discussed in order to identify improvements and caveats.

Evaluation survey

Among a sample of HCP and parents involved with rotavirus vaccination in the participating hospitals we performed a survey to evaluate the implementation of the HRV program. The survey focused on study-specific and program specific themes. The themes were divided into: 1) rotavirus vaccination information provision, 2) program execution and 3) preference of rotavirus vaccination strategy. Information provision and execution were assessed using

statements that could be scored on a five-point Likert-scale (from completely disagree to fully agree). Statements like "The information provided to me about rotavirus vaccination was easy to understand" were proposed for information provision and "I received timely information; I had sufficient time to decide whether I wanted to vaccinate my child" for the execution. The survey contained multiple choice questions on preference of rotavirus vaccination strategy, for instance preferred setting for patient selection, indication and vaccine delivery. The survey questionnaires are attached as supplementary material. A sample of five to ten HCP and parents per participating hospital were invited to complete the questionnaires. Both parents of vaccinated and non-vaccinated infants were invited to participate.

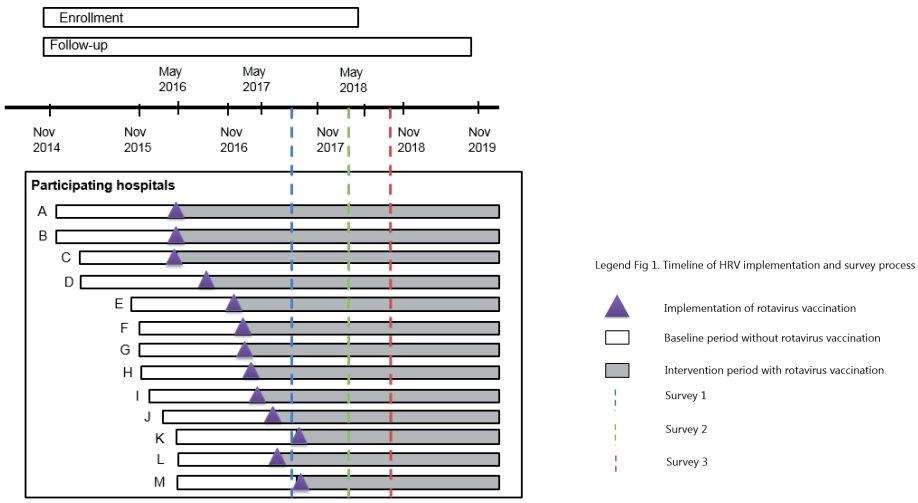


Figure 1. Timeline of HRV implementation and survey process

Invitations were sent via newsletters, RIVAR Facebook page and personal email. Questionnaires were developed and distributed via SurveyMonkey©. There were three surveys at different time points (**Figure 1**). Hospitals participated in the different surveys at least three months after implementation of HRV.

In addition, the first two themes (1. information provision and 2. program execution) were further explored by the in-depth interviews. We conducted semi-structured interviews with HCP and research personnel on barriers and facilitators encountered during the implementation process. We approached different type of HCP and research personnel from a selection of participating hospitals. The interviews were performed by JvD, documented and verified with each interviewee.

Outcome definitions

The primary feasibility outcome was the overall vaccination coverage and timeliness of vaccination among eligible infants. Vaccination coverage was calculated as the proportion of eligible infants that received at least one of the two doses of HRV. Timeliness of vaccination was defined as administration of the first dose of HRV between six and fourteen weeks of postnatal age, preferably between six and nine weeks of age. Timeliness for administration of the second dose was determined as an interval of at least four weeks post-dose one and no later than 24 weeks of postnatal age. We assessed differences in vaccination coverage and timeliness between infants with different types of MRC and between participating hospitals (i.e. academic versus general hospital). In addition, vaccination coverage relative to time since implementation is reported. Because only five hospitals had a policy of vaccinating infants with GA < 27 weeks, we reported that group separately (see supplement).

From the survey results, we defined several indicators of implementation success. These included: 1) the proportion of HCP and parents that agreed with clear information provision, 2) the proportion of HCP and parents that agreed with timely and effective execution of the program and 3) the vaccination strategy chosen by the highest proportion of HCP and parents as best approach. Any differences between type of HCP (i.e. medical doctor versus non-medical doctor) and parents of vaccinated or unvaccinated infants was also presented. In this paper we focused on program specific themes as described above, study-specific outcomes are described in the supplementary material. Theme related quantitative survey results were integrated with qualitative interview outcomes.

Analyses

We used Pearsons Chi-square, Fisher Exact, Students'T or non-parametric tests for comparison of vaccinated and unvaccinated infants, depending on the measured variable and its distribution.

Survey statements scored on the five-point Likert-score were dichotomized in agree and neutral/disagree.

Theoretical thematic analysis of semi-structured interviews was done by JvD and PB. The barriers, facilitators and themes were identified and discussed in group meetings 18. After consensus was achieved, within each theme the different barriers and facilitators were distinguished.

SPSS version 25.0 and RStudio version 5.0 were used as statistical software.

This paper used the StaRI recommendations for reporting implementation studies, and the COREQ checklist for qualitative research[19,20].

Results

Evaluation of the intervention

Among 4958 screened infants in 13 hospitals post-implementation of the rotavirus vaccination program, 4621 had a GA of ≥27 weeks and were eligible for HRV vaccination. In total, 2370 infants were vaccinated with at least one HRV dose, resulting in overall mean vaccination coverage of 52.3% (95%CI 50.8-53.7%). The differences in coverage among types of MRC and hospitals (academic versus general) are presented in **table 1**. Over time the vaccine coverage slightly improved, with a maximum between 6 and 12 months since implementation. The subset of infants participating in the cohort-study had a significant higher vaccination coverage compared to those not participating (**table 1**). Vaccination coverage per site ranged between 24.4% (95%CI 21.3;27.5%) and 83.4% (95%CI 79.9;87.0%). Timeliness of first dose HRV administration between six and nine weeks of age was 51.8% (1213/2340 infants), 2164 infants (92.5%, 95%CI 91.4;93.5%) were vaccinated within 14 weeks of age. For the second HRV dose limited information was available due to at home self-administration, 665 out of 772 infants (86.1%, 95%CI 83.7;88.6%) were vaccinated on time. There were no statistical significant differences in timeliness by type of medical risk group or type of hospital.

Table 1. Comparison of characteristics among HRV vaccinated and unvaccinated infants (GA ≥ 27 weeks) with medical risk conditions

	Vaccinated N=2370	Unvaccinated N=2162	p-value
Type of MRC			
Premature	1317 (58.3%)	941 (41.7%)	**0.00**
SGA	144 (54.8%)	119 (45.2%)	
Premature and SGA	662 (57.5%)	490 (42.5%)	
Congenital pathology	89 (22.9%)	299 (77.1%)	
Premature and congenital pathology	78 (36.4%)	136 (63.6%)	
SGA and congenital pathology	31 (28.7%)	7 (71.3%)	
Premature, SGA and congenital pathology	46 (33.1%)	93 (66.9%)	
Birthweight <2500 grams	2 (66.7%)	1 (33.3%)	
Hospital type			
Academic	438 (28.2%)	1116 (71.8%)	**0.00**
General	1932 (64.9%)	1046 (35.1%)	
Time since implementation			

	Vaccinated N=2370	Unvaccinated N=2162	p-value
0-6 months	429 (47.7%)	470 (52.3%)	**0.001**
6-12 months	486 (56.5%)	374 (43.5%)	
> 12 months	1455 (52.5%)	1318 (47.5%)	
Participant in cohort study			
Yes	695 (87.3%)	101 (12.7%)	**0.00**
No	1675 (44.8%)	2061 (55.2%)	

Percentages are derived excluding missing information. Statistical significance (p-value <0.05) is highlighted in bold. Abbreviation: SGA = small for gestational age, MRC = medical risk condition

Evaluation of the implementation strategy

A total of 136 HCP completed the survey (**table 2**). Of these, 42 were actively approached and 94 responded on invitations for the survey in the newsletter; 123 were female (89.8%), and 51 (38.1%) were medical doctor versus 56 (40.9%) nurses. In total, 194 parents of vaccinated infants and 19 parents of unvaccinated infants completed the SurveyMonkey; 44 parent pairs were actively approached and 169 parent pairs responded to the survey invitation in the newsletters or on Facebook. For a flowchart of total approached and responded, see supplement **figure S2**. The total number of survey respondents and their characteristics are presented in **table 2.** Among parents of vaccinated infants, 168 (87.0%) were female, median age 33.0 years (IQR 5.0) and 131 had a high educational level (68.6%). Among parents of unvaccinated infants that completed the questionnaire, 17 (89.5%) were female, median age 32.0 years (IQR 6.0) and 15 (78.9%) highly educated. For the interviews, five HCP were approached and three responded.

Table 2. Characteristics of participants of evaluation survey

Characteristic	HCP (N=136)	Parents of vaccinated infants (N=194)	Parents of unvaccinated infants (N=19)
Sex (female, %)*	123 (89.8)	168 (87.0)	17 (89.5)
Age (median years, IQR)*	42.0 (20.0-62.0)	33.0 (28.0-38.0)	32.0 (26.0-38.0)
Educational level (n,%)*			
Higher/medical doctor	51 (38.1)	131 (68.6)	15 (78.9)
Medium/other HCP	83 (61.9)	48 (25.1)	4 (21.1)
Lower		12 (6.3)	

* One missing for sex, three missing for age and education among parents of HRV vaccinated infants. Abbreviations: HCP = healthcare providers, N = number in group, IQR = interquartile range, n = number with characteristic.

Theme 1. Information provision

Among HCP, 93 (72.1%) stated that the information provision was clear and 70/115 (60.9%) felt sufficiently informed about rotavirus vaccination. Among parents of vaccinated infants, 149 (85.6%) were positive about the amount of information they received and, 159 parents (91.4%) thought the provided information was clear. Five parents of unvaccinated infants (29.4%) stated they did not receive enough information to base their decision on and three found the information was unclear (17.6%). A pediatric research nurse in a secondary care facility mentioned during the interview on information provision:

"*The age period for the first dose is actually no real limitation, when parents of eligible infants are properly informed at eight weeks of age there is ample opportunity to vaccinate them in time.*" (Int. HCP2).

The other two interviewees mentioned parents of eligible infants were overwhelmed and wondered how much of the information provided shortly after birth on this new vaccine would linger.

"*In the two years the project has run in both hospitals I have spoken to many parents of eligible children. Most parents were overwhelmed by the situation they were in." (Int. HCP1) "How much information lingers shortly after delivery?*" (Int. HCP3).

Explicitly focusing on the favorable characteristics of HRV administration in the information provision; being non-invasive (oral), quick, the possibility for concomitant administration with other NIP vaccines, was mentioned as facilitating factor.

"… *parents of young premature infants are benevolent to vaccination. Because of oral administration, they are more inclined to choose rotavirus vaccination for their child.*" (Int. HCP2).

Theme 2. Program execution

Among HCP, 96 (76.2%) agreed to the statement "In my hospital all eligible infants are routinely informed about rotavirus vaccination" and 66 HCP (52.8%) agreed that the vaccine was routinely offered to eligible infants. Among parents of vaccinated infants, 139 (80.3%) agreed to the statement "I received timely information about rotavirus vaccination; I had sufficient time to decide whether I wanted to vaccinate my child." whereas among parents of unvaccinated infants, eight (50.0%) agreed to this statement. Among parents of vaccinated infants, 59 parents (34.1%) agreed to the statement "I was first informed about rotavirus vaccination by a pediatric doctor/nurse as part of standard care", and among parents of unvaccinated infants five (38.5%) agreed.

An infant related barrier was the health status of the infant during the age-window for first rotavirus vaccination, as was expressed by an on-site research nurse:

"*In general the infants admitted to the tertiary center, especially in the case of severe congenital*

anomaly, need more complex care, often involving a multitude of pediatric specialists. Vaccination as a rule is only appropriate when the infant is stable which is often not the case during admission in tertiary care." (Int. HCP1).

The implementation of rotavirus vaccination protocol was adapted to local policy by each participating hospital. Sometimes, additional restrictions on administration were adopted, limiting opportunities for vaccination for the most vulnerable infants. One of the interviewees remarked:

"*This center has an in-hospital vaccination policy which stipulates not to offer vaccination to infants born under 27 weeks of gestation; not to administer vaccination in the NICU setting; to offer vaccination only at time of discharge on the infant/surgical ward or during outpatient visits*." (Int. HCP1). In addition, the variation in out-patient follow-up for these infants made it difficult to implement a vaccination program in an uniform and standardized way. As was clarified by a neonatologist:

"*There is no national follow-up program for eligible infants, in-hospital administration of first dose HRV is the best way for infants born before 32 weeks of gestation... Almost all eligible infants are born in a hospital, we do see these infants. The vast majority in our hospital is however born at term. The eligible infants represent approximately 20%, prematurity is the main group, smaller group of dysmature and infants with a congenital disorder even smaller. It is complex and individual care… Rotavirus vaccination is not part of the standard thought processes, not routine*." (Int. HCP3).

Awareness, belief and attitude towards rotavirus vaccination as new standard of care for infants with MRC was mentioned both as a barrier and as facilitator. An on-site research nurse said:

"*The institution is proud to be a participating hospital, feels it can offer it's patients additional care and even issued a press release once the rotavirus vaccination became available… However, the quick turnover of pediatric residents – most of the time unfamiliar with the RIVAR project – does not help the implementation process*." (Int. HCP1).

For the execution of the program hospital nurses might be the best option, suggested by a HCP: "*Nurses provide stable care for these infants. In a training hospital there is a high turnover of residents and it takes time to create awareness among new physicians... Well-baby clinic physicians can function as safety net*…." (Int. HCP3).

On the other hand, endorsement by a medical doctor can improve willingness to vaccinate: "*In the tertiary center it was often just the research nurse discussing and explaining the need for rotavirus vaccination while it was never mentioned by the pediatrician (or resident). The implicit message to parents might be that it is of inferior importance since it is not discussed as part of current practice.*" (Int. HCP1).

Theme 3. Preference of rotavirus vaccination strategy

A majority of HCP 74/122 (60.7%) were in favor of providing HRV for infants with MRC, free of charge; 47 HCP (38.5%) thought HRV should be provided for all infants in the Netherlands, as part of the NIP. The preferred setting for targeted vaccine indication was the second and third line of care according to 64/75 (85.3%) of overall HCP, these were mainly other (non-medical doctor) HCP. Differences between medical doctors and other HCP in their experience with the HRV program are shown in **table 3**, all are statistically significant. Among parents of vaccinated infants, 94 (55.0%) were in favor of a universal vaccination program as opposed to nine parents of unvaccinated infants (69.2%). Of vaccinated infants, 72 parents (42.1%) choose for well-baby clinics as preferred setting for vaccine delivery. Differences between parents of vaccinated and unvaccinated infants in their experience with targeted rotavirus vaccination are presented in **table 4**, perceived timely information differed significantly. Reasons for refusing vaccination were; administration not possible within age limits (n=4), not being offered the vaccine (n=2), off-label (n=1), and perceived risks did not outweigh potential benefits (n=6).

Table 3. Health care providers' experience with the targeted rotavirus vaccination program

Statement	Medical doctors (N=51)	Other HCP (N=84)	p-value
Information provision about implementation of rotavirus vaccination in my hospital was clear (n agree with statement, %)	29/48 (60.4)	64/80 (80.0)	**0.02**
Rotavirus vaccination should be available for high risk children (n, %)	34/44 (77.3)	40/78 (51.3)	**0.005**
Second and third line care centers should be responsible for providing rotavirus vaccination (n, %)	10/34 (29.4)	21/42 (50.0)	**0.01**

Percentages are derived excluding respondents with missing information. Statistical significance (p-value <0.05) is highlighted in bold.

Table 4. Parental experience with the targeted rotavirus vaccination program

Statement	Vaccinated infants (N=194)	Unvaccinated infants (N=19)	p-value
The information provided to me about rotavirus vaccination was clear (n agree with statement, %)	159/174 (91.4)	14/17 (82.4)	0.22
I was first informed about rotavirus vaccination by a pediatric doctor/ nurse (n agree with statement, %)	59/173 (34.1)	5/13 (38.5)	0.83
I received timely information; I had sufficient time to decide whether I wanted to vaccinate my child (n agree with statement, %)	139/173 (80.3)	8/16 (50.0)	**0.01**
Rotavirus vaccination should be available for all children (n, %)	94/171 (55.0)	9/13 (69.2)	0.32

Percentages are derived excluding respondents with missing information. Statistical significance (p-value <0.05) is highlighted in bold.

Discussion

This study evaluated the implementation of a targeted rotavirus vaccination program for infants with MRC in secondary and tertiary care. This strategy resulted in 52.3% of eligible infants receiving at least one dose of HRV (with a wide variety in coverage among sites and infants from different risk-groups). Less than 40% of parents were informed about the vaccine as part of standard care and reaching these vulnerable infants proved difficult. If vaccinated, however, timely vaccination was feasible for over 90% of these medical risk infants.

A targeted vaccine strategy is rare, only Croatia implemented a risk-group rotavirus vaccination program in 2011[21] and Spain introduced rotavirus vaccination for premature babies between 25 and 32 weeks of GA.[22] Arguments for a targeted vaccine strategy are to protect those at highest risk of severe disease, mortality and complications[16]. Vaccination coverage is known to be lower among premature infants <33 weeks of GA and LBW infants[23], as was also observed for rotavirus vaccination[24]. Yet, this was studied in a setting with universal rotavirus vaccination. Whether a targeted vaccination program was feasible in practice with sufficient coverage among these risk-group infants was not systematically assessed.

This implementation study indicates that a targeted rotavirus vaccination strategy for infants

with MRC in secondary and tertiary care seems not satisfactory for several reasons. Even though information provision was perceived as clear by most of the survey respondents and the majority of HCP believed all eligible infants were routinely informed about rotavirus vaccination, less than 40% of parents stated that they received information on rotavirus vaccination as part of standard care. This was clarified by the interviews, suggesting that awareness among involved HCP was difficult to achieve. An on-site dedicated physician, as was available for the cohort-study participants, can offer individual parent counseling, facilitate the information provision and, assist in vaccine planning. This yielded a 87.3% vaccination coverage among the subset of infants participating in the cohort-study. Furthermore, recommendation by a HCP is known to be the main driver for choosing vaccination and 80% of parents would visit a HCP to gather information on rotavirus vaccination[25,26]. In addition, significantly fewer parents of unvaccinated infants felt they received information timely. Feeling overwhelmed by information, shortly before or at the time vaccination decisions have to be made, can lead to refusal[27,28]. In this survey parents and HCP of eligible infants were approached, perspectives of parents or HCP of ineligible infants on HRV vaccination we did not assess. A targeted vaccine program was chosen as preferred vaccination strategy by most survey respondents. However, for delivery of vaccines medical doctors in particular favored counseling and vaccine delivery by youth healthcare professionals at well-baby clinics, rather than at the hospital. Endorsement by medical doctors was brought forward as a facilitator during the interviews and suggests a need for collaboration with hospital care. As observed throughout the project by the interviewees, the varying out-patient follow-up policies resulted in individual based vaccine indications, making structured and uniform embedding into standard of care difficult. Only for infants with a GA < 30 weeks or birthweight below 1000 grams a national follow-up policy is available[29,30]. In addition, uniform recommendations about on-ward rotavirus vaccine administration and off-label use in those <27 weeks GA are needed for consistency in policy and across sites.

If a hospital-based targeted vaccination program for medical risk infants is the preferred strategy, we recommend an elaborate educational program for involved HCP as well as integration with the existing NIP structure, which – in the Netherlands - is executed by youth healthcare professionals.

In the small group of infants with GA <27 weeks treated in an off-label policy hospital we observed timely vaccination is possible in 86% and with an acceptable safety profile (**chapter 5**).

There were some limitations. First, although offering HRV as part of standard care to infants with MRC was suggested by the RIVAR protocol, it was not mandatory or structured in a single format. We therefore relied on each participating hospital how they incorporated this new standard of care and supervised execution of the program. As mentioned, we saw a broad variety in on-site protocols which possibly reflected in the achieved vaccination coverage. However in the absence of a national guideline, rotavirus vaccination should be adopted to local policy. Thus, our results reflect real life practice for targeted rotavirus vaccination.

Secondly, within the study protocol the upper limit for vaccination with first dose was 14 weeks (which is earlier than according to the product information) and not all hospitals in the Netherlands participated. The window of opportunity for rotavirus vaccination was thereby narrow and limited to care in participating hospitals. The Dutch healthcare infrastructure has limited NICU and neonatal post-IC/HC beds, creating a relatively fast referral policy for medical risk infants to general pediatric wards. This might have reduced the amount of vaccinated infants. This limitation would be obsolete if rotavirus vaccination was not offered in a study specific setting.

Conclusions

To conclude, implementation of a targeted rotavirus vaccination strategy in secondary and tertiary care facilities in the Netherlands, yielded a suboptimal vaccination coverage among infants with MRC. Alternatively, implementation strategies including involvement of the existing NIP structure should be considered.

Acknowledgements: All RIVAR study team members*, survey and interview respondents and (parents of) participants are gratefully acknowledged for their contribution to this study.

*RIVAR study team, rivar@umcutrecht.nl: Zwart L.M., Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Tims-Polderman C., Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Beurden, van M., Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Bont, L.J., Department of Pediatrics, University Medical Center Utrecht, Utrecht, the Netherlands; Norbruis O.F., Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands; Hemels, M.A.C., Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands; Well, van G.T.J., Department of Pediatrics, Maastricht University Medical Center, Maastricht, the Netherlands; Vlieger, A.M., Department of Pediatrics, St. Antonius Hospital, Nieuwegein, the Netherlands; Sluijs, van der J., Department of Pediatrics, Maxima Medical Centre, Veldhoven, the Netherlands; Stas, H.G., Department of Pediatrics, Maasstad Hospital, Rotterdam, the Netherlands; Tramper-Stranders, G., Department of Pediatrics, St. Franciscus Hospital, Rotterdam, the Netherlands; Kleinlugtenbeld, E.A., Department of Pediatrics, Albert Schweitzer Hospital, Rotterdam, the Netherlands; Kempen, van A.A.M.W., Department of Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; Wessels, M., Department of Pediatrics, Rijnstate Hospital, Arnhem, the Netherlands; Rossem, van M.C., Department of Pediatrics, Rijnstate Hospital, Arnhem, the Netherlands; Dassel, A.C.M., Department of Pediatrics, Deventer Hospital, Deventer, the Netherlands; Houten, van M.A., Department of Pediatrics, Spaarne Gasthuis, Hoofddorp and Haarlem, the Netherlands; Pajkrt, D. , Department of Pediatrics, Amsterdam University Medical Center, Amsterdam, the Netherlands.

Ethical Approval and Consent to participate: The RIVAR study protocol was approved by the Institutional Review Board of University Medical Center Utrecht, which declared it does not involve the Human Subject Act.

Funding: This work was supported by the Netherlands Organization for Health Research and Development (grant number 836021024), Healthcare Insurers Innovation Foundation, GlaxoSmithKline Biologicals SA (study ID 203108) and UMC Utrecht. GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for final content and interpretation. No sponsor had a role in design, collection, analysis, writing or decision to submit the article.

This study is registered as NTR5361 in the Dutch trial registry (www.trialregister.nl).

References

1. Narváez J, Osorio MB, Castañeda-Orjuela C, et al. Is Colombia reaching the goals on infant immunization coverage? A quantitative survey from 80 municipalities. ***Vaccine***. Published online 2017. doi:10.1016/j.vaccine.2017.01.073

2. Levine et al., Osinusi K. The future of immunisation policy, implementation, and fi nancing. ***Lancet.*** 2011;(378):439-448. doi:10.1016/S0140

3. Sjö Gren E, Ask LS, Rtqvist K, Asp M. Parental conceptions of the rotavirus vaccine during implementation in Stockholm: A phenomenographic study. ***J Child Heal Care***. 2017;21(4):476-487. doi:10.1177/1367493517734390

4. Veldwijk J, Lambooij MS, Bruijning-Verhagen PCJ, Smit HA, Wit GA de. Parental preferences for rotavirus vaccination in young children: A discrete choice experiment. ***Vaccine***. 2014;32(47):6277-6283. doi:10.1016/J.VACCINE.2014.09.004

5. Glanz JM, Newcomer SR, Narwaney KJ, et al. A population-based cohort study of undervaccination in 8 managed care organizations across the United States. ***JAMA Pediatr.*** 2013;167(3):274-281. doi:10.1001/jamapediatrics.2013.502

6. Çataklı T, Duyan-Çamurdan A, Aksakal-Baran FN, Güven AE, Beyazova U. Attitudes of physicians concerning vaccines not included in the national immunization schedule. ***Turk J Pediatr***. Published online 2018. doi:10.24953/turkjped.2018.03.009

7. Mita V, Arigliani M, Zaratti L, Arigliani R, Franco E. Italian Physicians' Opinions on Rotavirus Vaccine Implementation. ***Pathogens***. 2017;6(56). doi:10.3390/pathogens6040056

8. Dubé E, Gilca V, Sauvageau C, et al. Clinicians' opinions on new vaccination programs implementation. ***Vaccine.*** 2012;30(31):4632-4637. doi:10.1016/j.vaccine.2012.04.100

9. Global Introduction status - Rotavirus. Accessed June 21, 2019. http://rotacouncil.org/vaccine-introduction/global-introduction-status/

10. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis. ***N Engl J Med***. 2006;354(1):11-22. doi:10.1056/NEJMoa052434

11. Itzler R, Koch G, Matson DO, et al. Robustness of the healthcare utilization results from the Rotavirus Efficacy and Safety Trial (REST) evaluating the human-bovine (WC3) reassortant pentavalent rotavirus vaccine (RV5). ***BMC Pediatr***. 2010;10. http://www.biomedcentral.com/1471-2431/10/42

12. Vesikari T, Matson DO, Dennehy P, et al. Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine. ***N Engl J Med***. 2006;354(1):23-33. doi:10.1056/NEJMoa052664

13. Vesikari T, Karvonen A, Korhonen T, et al. Safety and immunogenicity of RIX4414 live attenuated human rotavirus vaccine in adults, toddlers and previously uninfected infants. ***Vaccine***. 2004;22(21):2836-2842. doi:10.1016/j.vaccine.2004.01.044

14. Vesikari T, Itzler R, Karvonen A, et al. RotaTeq??, a pentavalent rotavirus vaccine: Efficacy and safety among infants in Europe. ***Vaccine***. Published online 2009. doi:10.1016/j.vaccine.2009.10.041

15. Toenders WGM. CFH-Rapport Beoordeling Rotavirus RIX4414 (Rotarix). Vol 3.; 2007.

16. Bruijning-Verhagen P, Mangen M-JJ, Felderhof M, et al. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med***. 2013;11(112). doi:10.1186/1741-7015-11-112

17. Bruijning-Verhagen PCJ. RIVAR study protocol. Published 2014. Accessed November 17, 2020. https://www.trialregister.nl/trial/5213

18. Braun V, Clarke V. Using thematic analysis in psychology. ***Qual Res Psychol.*** 2006;3(2):77-

101.

19. Pinnock H, Barwick M, Carpenter CR, et al. Standards for Reporting Implementation Studies (StaRI) Statement. ***BMJ***. 2017;356(March):1-9. doi:10.1136/bmj.i6795

20. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. ***Int J Qual Heal Care.*** 2007;19(6):349-357. doi:10.1093/intqhc/mzm042

21. Tešović G. Childhood vaccinations in Croatia. ***Period Biol***. 2012;114(2):149-166.

22. ECDC. Rotavirus infection: Recommended vaccination schedule. ***ECDC.*** Published 2021. Accessed February 24, 2021. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=32&SelectedCountryIdByDisease=-1

23. Navar-Boggan AM, Halsey NA, Escobar GJ, Golden WC, Klein NP. Underimmunization at discharge from the neonatal intensive care unit. ***J Perinatol.*** 2012;32(5):363-367. doi:10.1038/jp.2011.111

24. Fathima P, Gidding HF, Snelling TL, et al. Timeliness and factors associated with rotavirus vaccine uptake among Australian Aboriginal and non-Aboriginal children: A record linkage cohort study. ***Vaccine***. 2019;(xxxx). doi:10.1016/j.vaccine.2019.08.013

25. Benninghoff B, Pereira P, Vetter V. Role of Healthcare Practitioners in Rotavirus disease awareness and vaccination – Insights from a survey among caregivers. ***Hum Vaccin Immunother.*** Published online June 18, 2019:21645515.2019.1632685. doi:10.1080/21645515.2019.1632685

26. Morin A, Lemaître T, Farrands A, Carrier N, Gagneur A. Maternal knowledge, attitudes and beliefs regarding gastroenteritis and rotavirus vaccine before implementing vaccination program: Which key messages in light of a new immunization program? ***Vaccine.*** 2012;30(41):5921-5927. doi:10.1016/j.vaccine.2012.07.050

27. Ames H, Glenton C, Lewin S. Parents'and informal caregivers'views and experiences of communication about routine childhood vaccination: a synthesis of qualitative evidence (Review). ***Cochrane Database Syst Rev***. 2017;(2):1-121. doi:10.1002/14651858.CD011787.pub2.www.cochranelibrary.com

28. Dubé E, Vivion M, Sauvageau C, Gagneur A, Gagnon R, Guay M. "Nature Does Things Well, Why Should We Interfere?" ***Qual Health Res***. 2016;26(3):411-425. doi:10.1177/1049732315573207

29. Pediatrics AA of. Follow-up care of high-risk infants. ***Pediatrics.*** 2004;114(5 SUPPL. 2):1377-1397. doi:10.1542/peds.2004-0866

30. Rijken M, Landelijke Neonatale Follow-up. Aanbeveling Landelijke Neonatale Follow-up - NICU follow-up Doelgroep. Published online 2015:4-6. https://www.nvk.nl/Portals/0/richtlijnen/Neonatale Follow up NICU/Richtlijn LNF januari 2015.pdf

31. Hindori-Mohangoo AD, Schonbeck Y, Pal-de Bruin KM van der. Aangeboren Afwijkingen in Nederland 2001-2012: Gebaseerd Op Landelijke Perinatale Registraties.; 2014. https://www.tno.nl/media/4521/2014-r-11308-rapportage-aangeboren-afwijkingen-2001-2012-def.pdf

Supplementary Material

Vaccination coverage for premature infants with gestational age (GA) < 27 weeks

Of 319 eligible infants with a gestation below 27 weeks, 81 received care in a participating hospital with a policy to vaccinate off-label. In total, 44 infants were male (54.3%), 13 (16.0%) were small for gestational age and one had a congenital pathology (1.2%). HRV was administered to 71 infants for at least one dose of HRV (87.7% 95%CI 80.3-95.0%). And 12 infants were vaccinated within six and nine weeks of postnatal age (16.9%), 61 before 14 weeks (85.9%).

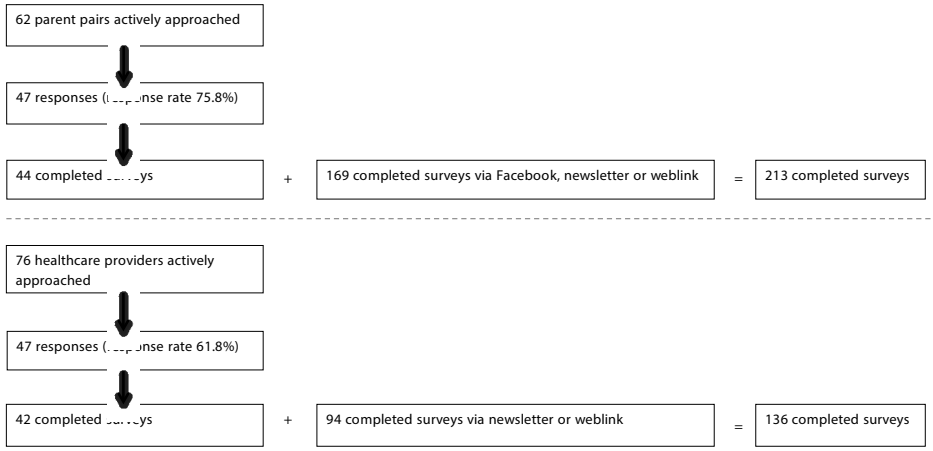


Figure S2 Flowchart of those approached for- and responded to the evaluation survey.

Study-specific outcomes of evaluation survey and in-depth interviews

For most HCP (53.1%), the RIVAR research personnel was the main source of information on rotavirus vaccination and the vaccination strategy in their hospital. As opposed to 46.9% that stated to be informed via colleagues, websites or other sources. Differences between medical doctors and other HCP are presented in **table S1**.

Table S1. Experience of the RIVAR study program among physicians

Statement	Medical doctors (N=51)	Other HCP (N=84)	p-value
I am aware of the rotavirus vaccination protocol within the RIVAR project (n agree with statement, %)	37/48 (77.1)	53/78 (67.9)	0.27

Statement	Medical doctors (N=51)	Other HCP (N=84)	p-value
I know how to prescribe rotavirus vaccination for my patient within the RIVAR project (n agree with statement, %)	33/46 (71.7)	31/73 (42.5)	0.002
I know which agreements apply in my hospital about administration of rotavirus vaccination and how to arrange this (n agree with statement, %)	32/47 (68.1)	61/77 (79.2)	0.17

Percentages are derived excluding respondents with missing information. Statistical significance (p-value <0.05) is highlighted in bold.

The instructions for at home administration of the second dose were clear for 130 parents (74.7%) of vaccinated infants. Among the remaining 43 parents, 35 (81.4%) experienced some level of difficulty in administration of the second dose.

In-depth interviews: A study-specific infant related barrier is the eligibility criteria of care between six and 14 weeks of age in a participating facility. A pediatric nurse raised this during the interview: "*Half of this population is already at home before six weeks of age. Well baby clinics include follow-up for these children.*". A study specific healthcare related issue was the sole responsibility of pediatricians for implementation, two interviewees addressed this: "*Is it wise or useful to lay responsibility with the pediatrician? Shouldn't the well-baby clinic physicians function as a safety net? What is the benefit of making the pediatrician solely accountable? The only group that is missed by well-baby clinic physician are the infants with congenital disorders." and "The pediatrician is responsible for indication setting. But all practical aspects, administration and logistics of vaccination are not handled by them.*".

Another study-specific healthcare related barrier was confusion about RIVAR cohort-study and RIVAR project. A research nurse highlighted this during the interview: "*From the start of the project confusion existed with regards to cohort-study versus project. Most health care professionals in both hospitals initially perceived the rotavirus vaccine to be a study vaccine and as such only available to cohort-study participants. Since most eligible infants did not participate in the cohort-study it was thought that there was no need for involvement of the treating pediatrician.*".

A study specific issue that functioned both as barrier and facilitator was the use of a research nurse/employee to facilitate implementation: "*…Throughout the study period the research nurse was responsible, but therefore it was no standard care." and "The initial set-up was supported by sufficient time and money within the study budget. Then I found three medium care nurses who now administer the vaccination.* ".

Implementation Evaluation Questionnaire for Parents

General

What is your gender?

a.Male

b.Female

How old are you?

How many children do you have?

What ethnic background do you have?

a.Dutch/Northern European

b.Surinamese

c.Antillean

d.Moroccan

e.Turkish

f.Other, i.e.

What is your highest level of completed education?

a.None completed education

b.Primary school

c.Lower vocational education

d.Secondary school

e.Secondary vocational education

f.High school

g.Higher professional education

h.Academic education (university/college)

Information provision about rotavirus vaccination and organization of administration

Rate the following six statements on a scale from 1 to 5.

1: totally disagree

2: disagree

3: neutral

4: agree

5: totally agree

I.I received enough information from the hospital about rotavirus vaccination.

II.The information provided to me about rotavirus vaccine, was easy to understand.

III.If I had questions about rotavirus vaccination, I knew who to address/I could contact.

IV.I received timely information about rotavirus vaccination; I had sufficient time to decide whether I wanted to vaccinate my child.

V.The instructions about vaccinating my child at home were clear to me.

VI.Giving my child the second dose of rotavirus vaccine at home was no problem for me.

VII.I was first informed about rotavirus vaccination by a pediatrician/pediatric resident or nurse.

VIII.I searched for information about rotavirus vaccination on:

(Multiple answers possible)

a.RIVAR website

b.Website RIVM

c.Different websites, i.e.

d.RIVAR facebook group

e.Different facebook pages, i.e.

f.Other, i.e

g.I did not search for information

IX.Note, below, any suggestions to improve the provision of information about rotavirus vaccination.

X.For parents of unvaccinated infants; I choose not to vaccinate my child against rotavirus because…

The hospital where your child is (or was) receiving care joins the RIVAR project. Therefore your child belongs to the first group of children in the Netherlands who is offered rotavirus vaccination, without payment by parents/guardians. We are interested in your opinion about rotavirus vaccination for children in the Netherlands.

XI.Rotavirus vaccination should be available for

a.Children whose parents are willing to pay €135 for rotavirus vaccination, free market price.

b.Children with increased risk of rotavirus infection, such as children born premature, with low birth weight or congenital diseases.

c.All children (also without increased risk).

d.None of the above.

XII.My child could best be vaccinated against rotavirus by:

a.My childs general practioner

b.My childs pediatrician

c.The Public Health Service (GGD)/well baby clinic

d.Self-administration at home

Questions in grey are not asked to parents of unvaccinated infants.

Implementation Evaluation Questionnaire for Healthcare providers

General

What is your gender?

a.Male

b.Female

How old are you?

What is your function?

a.Pediatrician/neonatologist

b.Pediatric resident

c.Pediatric or neontology nurse

d.Physician assistent

e.Other, i.e.

In your hospital rotavirus vaccination is implemented via the RIVAR project. This is a pilot where high risk infants (born premature and/or dysmature, and/or with a congenital disorder) are offered rotavirus vaccination, without costs involved.

Information provision about rotavirus vaccination and execution of the implementation program

Rate the following three statements on a scale from 1 to 5.

1: totally disagree

2: disagree

3: neutral

4: agree

5: totally agree

I.Information provision with regard to implementation of rotavirus vaccination in my hospital was clear.

II.I am aware of the rotavirus vaccination protocol within the RIVAR project.

III.In my hospital all eligible infants are routinely informed about rotavirus vaccination.

IV.I know how to prescribe rotavirus vaccination for my patient within the RIVAR project.

V.I know which agreements apply in my hospital about administration of rotavirus vaccination and how to arrange this.

VI.I am aware of the age restrictions for administration of rotavirus vaccination.

VII.In my hospital vaccination against rotavirus is sufficiently imbedded, all eligible infants routinely receive vaccination within the age restrictions according to the RIVAR project.

VIII.I have sufficient knowledge about the working mechanism of rotavirus vaccination.

IX.I have sufficient knowledge about the adverse events of rotavirus vaccination.

X.In my hospital parents are first informed about rotavirus vaccination by a pediatrician/pediatric resident or nurse.

XI.I received information about rotavirus vaccination via:

(Multiple answers possible)

a.RIVAR implementation group-presentations

b.RIVAR website/e-learning

c.Website of RIVM

d.Other website, i.e.

e.RIVAR research dedicated physician

f.Colleagues

g.Other, i.e.

XII.Which hurdles do you encounter in the execution of the RIVAR implementation program to prevent eligible infants to receive rotavirus vaccination in your hospital?

(Multiple answers possible)

a.A child is already discharged and doesn't receive care within the age-restrictions for vaccination.

b.A child is too ill or instable to receive vaccination with the age-restrictions.

c.In my hospital children are not vaccinated on the ward, it regularly occurs that a child is hospitalized past 14 weeks of postnatal age.

d.It regularly happens that parents refuse rotavirus vaccination for their child.

e.Difficulties in prescribing rotavirus vaccination.

f.Other, i.e.

XIII.Note, below, any suggestions to improve the provision of information about or the execution of rotavirus vaccination implementation program.

The following questions concern your opinion about rotavirus vaccination for children in the Netherlands.

XIII.Rotavirus vaccination should be available for

a.All children, invested with the National Immunization Program.

b.Children with increased risk of rotavirus infection, such as children born premature, with low birth weight or congenital diseases, free of charge.

c.Children whose parents are willing to pay the free market price for vaccination.

XIV.If a, I am in favor of universal rotavirus vaccination because:

(Multiple answers possible)

a.Rotavirus infections causes high disease burden in children, even when they are otherwise "healthy".

b.The typical seasonality of rotavirus infections lead to capacity problems in pediatric hospital care.

c.The costs of vaccination are outweighed by the benefits in the form of disease reduction (cost effective).

d.It is complicated to implement a targeted vaccination program for high risk infants only, universal vaccination is more efficient.

e.Other, i.e.

XV.If b, Rotavirus vaccination should be free of charge and part of standard care for high risk infants; born premature or dysmature or with congenital disorders. But not for "healthy" infants, because:

(Multiple answers possible)

a.In "healthy" infants the costs of vaccination dont outweigh the benefits, the money could be better spent.

b.In "healthy" infants, the severity and frequency of rotavirus infections is insufficient to justify vaccination.

c.Adding an extra vaccination to the National Immunization Program affects compliance.

d.Other, i.e.

XVI.If b, The responsibility for indicating eligible infants should lay with:

a.The preventative care system, the municipal health physicians set the indication.

b.The first line care system, the general practitioner sets the indication.

c.The second- and third line care system, the pediatrician sets the indication.

XVII.If b, Which healthcare system should deliver rotavirus vaccination to eligible infants:

a.Rotavirus vaccination administered via second and third line pediatric care (conform RIVAR project).

b.Rotavirus vaccination administered via second and third line pediatric care in cooperation with well-baby clinics.

c.Rotavirus vaccination administered via first line care, general practitioner.

d.Rotavirus vaccination administered via well-baby clinics, second and third line pediatric care not involved.

e.Other, i.e.

XVIII.If c, Rotavirus vaccination should not be implemented as standard of care in the Netherlands, because:

(Multiple answers possible)

a.The risk of adverse events (such as intussusception).

b.The rotavirus disease burden doesn't justify implementation.

c.The high costs related, the money could be better spent.

d.Other, i.e.

Chapter 8

Summary and general discussion

Introduction

Rotavirus is a dominant cause of acute gastroenteritis (AGE) in children.[1,2] Rotavirus AGE is characterized by acute onset of diarrhea, fever and/or vomiting. Morbidity and mortality due to rotavirus disease in a developed country, like the Netherlands, primarily affects infants with prematurity, low birth weight or presence of a severe congenital disorder.[3] Providing rotavirus vaccination to this specific population was thought to prevent at least those infants most at risk of severe disease.[4]

This thesis described the Risk-group Infant Vaccination Against Rotavirus (RIVAR) project, in which rotavirus vaccination was provided to a specific medical risk population with the aim to study vaccine effectiveness, safety and program feasibility. The group of infants studied in the RIVAR project was defined as infants with 1) one or more medical risk conditions (MRC): premature birth (before 36 weeks of gestation), a low birthweight (below 2500 grams) and/or, a severe congenital pathology. And 2) receiving prolonged in- or out-patient care (between six and 14 weeks of postnatal age) in a participating hospital. This chapter includes a summary of most important findings, a discussion of these findings and recommendations for clinical practice and future research on infant rotavirus vaccination.

Summary of this thesis

As a baseline measurement and to guide prioritization for prevention strategies we assessed the community burden of all-cause AGE, and pathogen specific disease in this population, using data from the unvaccinated RIVAR cohort (**chapter 2**). Community disease burden due to rotavirus was not systematically studied previously, and prior information on rotavirus infections in this medical risk population was obtained from studies conducted in hospital settings. We found that the incidence of all-cause AGE in medical risk infants was comparable to that among healthy infants, however severity in terms of symptoms, healthcare attendance and hospitalization was two to three times higher. Rotavirus and norovirus were most frequently detected as pathogen, and rotavirus resulted in a more severe disease course. In addition, the all-cause AGE in this population led to important societal impact as reflected by 30% daycare absenteeism and parental work loss. We concluded that, compared to studies in healthy infants, the community AGE disease burden among medical risk infants was considerably increased.

Next, we updated a previous cost-effectiveness analysis[4] of rotavirus vaccination to take into account the change in rotavirus epidemiology, lower hospitalization rates and updated estimates on community disease burden (**chapter 3**). We estimated that universal rotavirus vaccination would generate the highest reduction in population disease burden due to rotavirus. However, targeted vaccination (of medical risk infants) was cost-saving in the main and sensitivity analysis,

and had the most favorable risk-benefit profile with regard to intussusception. Based on these results, selective vaccination against rotavirus AGE can be favorable on all criteria, provided that the vaccine is effective in a population with MRC.

We subsequently evaluated whether vaccination indeed offered protection against rotavirus disease in RIVAR eligible infants. Based on efficacy trials among healthy term and preterm infants, a conservative vaccine effectiveness of 60-80% was anticipated. In the RIVAR project the human rotavirus vaccine (HRV, Rotarix, GSK Biological SA, Belgium) was used. By comparing the vaccinated versus unvaccinated RIVAR cohort we were able to assess rotavirus vaccine effectiveness among MRC infants (**chapter 4**). In contrast to the vaccine efficacy trials, HRV was not significantly protective against severe rotavirus AGE (vaccine effectiveness 30%; 95%CI -36;65%) in this study, and no impact on rotavirus hospitalizations was observed. As the numbers were however small, a post-hoc analysis was added for all-cause AGE and rotavirus AGE of any severity, but comparable and non–significant effects were observed, suggesting that rotavirus vaccine performance is minimal in infants with MRC. The upper 95% confidence limit of rotavirus vaccine effectiveness was 65% in our study, as opposed to a mean estimate of 90% for healthy infants in high-income settings.[5,6] In addition, lower 95% bound vaccine effectiveness estimates for healthy infants are 76-84%.[5,6] We therefore conclude that HRV effectiveness is significantly lower in MRC infants and this finding signifies the need for risk-group specific research.

Moreover, we found that serious adverse events that were possible vaccine reactions[7] occurred more frequently than previously described in the population with MRC, at a rate of 0.25 per 100 vaccine doses (**chapter 5**). The majority of adverse events were gastrointestinal. Possible causality was based on the temporal relationship with HRV administration and biological plausibility in terms of their pathophysiology. Overall, more (gastrointestinal) adverse events were reported among vaccinated premature infants as opposed to non-rotavirus vaccinated (RR 1.07, 95%CI 1.04;1.10). In the group of infants with a gestational age below 27 weeks, who were vaccinated off-label, rotavirus vaccination was generally well tolerated and no safety signals were observed. Acknowledging the combined effectiveness and safety results, clinicians should weigh the risks and benefits of rotavirus vaccination for the individual infant with MRC.

Furthermore, there was no evidence of benefit due to non-specific effects of rotavirus vaccination (**chapter 6**). Live-attenuated vaccines, like HRV, have been associated with beneficial non-specific effects. This phenomenon is attributed to trained immunity, a vaccine induced modification of the innate immune system that reduces the risk and/or severity of disease by non-target infections. In our study, HRV was not protective against acute hospitalization when excluding admissions for AGE (hazard ratio: 0.91, 95%CI 0.76;1.16). In addition, we did not

observe a reduction in cumulative days hospitalized or incidence of acute respiratory illness, as would be expected on the basis of trained immunity mechanisms.

Finally, the implementation strategy used for the RIVAR project yielded a vaccination coverage of 52% (95%CI 51;54%) with a wide variation in coverage between infants with different MRCs and between hospitals (**chapter 7**). In the Netherlands, routine childhood vaccinations are delivered via youth health care professionals in well-baby clinics. Setting the indication for, and administering rotavirus vaccination selectively to medical risk infants required a different infrastructure. We therefore implemented this targeted vaccination program in secondary and tertiary pediatric medical care centers. Based on evaluation surveys among parents and health care professionals (HCP), and in-depth interviews with involved HCP we provided suggestions for improvement of a hospital-based targeted rotavirus vaccination program for medical risk infants. This included an elaborate educational program with a dedicated on-site physician to raise awareness, nationally implemented recommendations to avoid too much variability in local hospital policies and, dependent on the existing local immunization structure and setting, involvement of youth HCP for counseling and vaccine delivery.

General discussion

The decision making process on rotavirus vaccination in the Netherlands has been a long and bumpy road. What we have learned throughout the RIVAR project and from its results is ultimately reflected in the reversed ministerial decree on implementation of rotavirus vaccination, and a renewed request to the Dutch Health Council to revise its advisory statement.[8]

The first rotavirus vaccination advisory statement, years before the RIVAR study started, dated from 2007 and concluded that there was insufficient evidence for the added value of universal rotavirus vaccination, given unknowns about genotype epidemiology and cost-effectiveness in the Netherlands.[9] In 2013 rotavirus vaccination was again reviewed by the Health Council, however no consensus was reached and a formal report was never published.[10,11] In 2017, the Health Council advised to implement rotavirus vaccination, at least for infants with MRC.[12] A year later, the Ministry of Health decided to implement a selective rotavirus vaccination program by 2019, which was later postponed to 2020.[13,14] While preparations were in progress, the preliminary results of the RIVAR project were communicated to the National Institute of Public Health and the Ministry of Health. This led to the decision on 30 April 2020 to cancel the implementation and to request an updated advice from the Health Council, incorporating lessons learned from the RIVAR project.[8,15] At the time of writing of this discussion, the new advisory statement is pending and no rotavirus vaccination program is implemented in the Netherlands, contrary to the situation in over 100 countries worldwide (**figure 1**).[16]

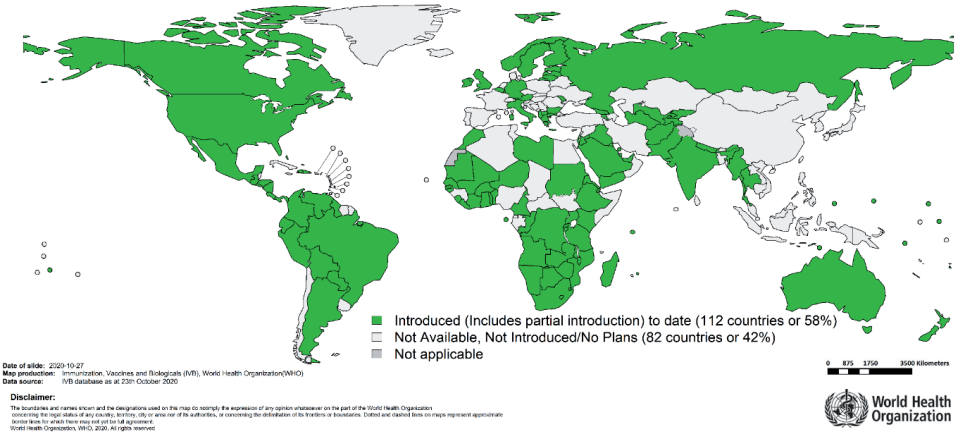


Figure 1. Rotavirus vaccine global introduction status. 2020 @WHO.

In the following paragraphs the lessons learned from the RIVAR project and its results will be discussed, related to previous literature and translated into future (clinical and research) directions.

Vaccine effectiveness

The most remarkable finding of this thesis is the low rotavirus vaccine effectiveness for infants with MRC. The results of this study appear in sharp contrast to results from previous (pre-licensure) efficacy studies in (subgroups of) medical risk populations. Importantly, efficacy studies (randomized controlled trials) are usually performed in highly selected populations under strictly controlled conditions, whereas in daily practice the intervention applies to more heterogeneous populations. The RIVAR project was specifically designed as an observational phase IV (post-licensure) effectiveness study that is suited to provide real world evidence for a heterogeneous, high-risk population. Where traditional observational study designs may suffer from bias due to confounding by indication, the quasi-experimental design of the RIVAR study was chosen to appropriately avoid this. Therefore, these results are considered representative and generalizable.

Differences between the current study and prior "positive" effectiveness studies in medical risk populations are presented in **table 1**.

Table 1. Differences in study -procedures, -population and -period between RIVAR and prior positive rotavirus vaccine effectiveness studies

	RIVAR	IVANHOE[17]	Dahl et al[18]
Study procedures			
Design	Before-after cohort	Active hospital based surveillance	Longitudinal administrative data
Data collection	Prospective	Prospective	Retrospective
Vaccine	Rotarix	RotaTeq	RotaTeq and Rotarix
Exposure	At least one dose	Vaccine introduction	Receipt of at least one dose rotavirus vaccination
Adjustment	Seasonal variation by rotavirus detections from weekly sentinel surveillance	Variation in rotavirus epidemiology by using an unvaccinated population	Seasonal trends by birth month-year in annual and peak season
Statistical analysis	Cox regression	Poisson regression	Poisson regression
Outcome	Severe rotavirus AGE	Rotavirus hospitalization	Rotavirus hospitalization
Study population			
Inclusion criteria	Premature infants 24-36+6 weeks Low birthweight Congenital disorders Or combination of all above	Premature infants 25-36+6	(very) Low birthweight <1500 or <2500 grams
Gestational age	Mean (SD): 32+5 weeks+days (3+5)	Median (range): 34.7 weeks (30.2-35.6)	n/a
Birthweight	Median (IQR): 1830 g (822-2838)	Median (range): 2320 g (1575-2670)	n/a
Number of participants	1482	217	78,288
Vaccination coverage	84.5%	41.9-45.2%	64-82%
Outcome events	38	27	n/a
Main outcome estimate	30% (95%CI -36;65%)	62% (95%CI 45;73%)	90-100% (95%CI n/a)
Study period			
Time	2014-2019	2002-2010	2001-2015
Country	The Netherlands	France	North-America
Circulating rotavirus strains	G2P4, G3P8, G9P8, G4P8[19–21]	G1P8, G9P8[22]	G1P8, G3P8[23], G12P8[24,25]
Universal rotavirus vaccination	No	Within study area, from 2007 onwards	Yes, from 2006 onwards

Abbreviations: AGE= acute gastroenteritis, SD = standard deviation, n/a = not available, IQR = interquartile range, CI = confidence interval.

Changing rotavirus epidemiology

One of the possible explanations for the low vaccine effectiveness is the change in rotavirus epidemiology. Globally, the introduction of rotavirus vaccines has substantially changed the epidemiology.[26–28] Furthermore, in the Netherlands and other non-vaccinating countries epidemiology of rotavirus was altered as well. In general, rotavirus epidemiology is influenced by vaccination, climate and temperature changes, birthrates, previous rotavirus seasons and size of susceptible populations.[29–31] Changes observed in recent years in both rotavirus vaccinating and non-vaccinating countries include a shift from annual high endemic peaks towards biennial, lower and later peaks.[28,32] Strain diversity changed from primarily G1P8 genotype dominance, to alternating high prevalence of G2P4, G3P8, G4P8 and G9P8 in the more recent years.[19–21] This change in circulating genotypes is thought to be the result of vaccine-induced selective pressure.[33]

Rotavirus vaccination is less well effective towards (partly) heterotypic strains, that were circulating more after 2014. During the RIVAR study period less than 14% of rotavirus detections by national surveillance sentinel laboratories were tested as G1P8 strain, while the fully heterotypic G2P4 strain became more prevalent with 12%.[19,34,35] This altered landscape of rotavirus strain distribution may have contributed to our low vaccine effectiveness estimates (**table 1**). While early on, rotavirus vaccine effectiveness estimates against partly heterotypic strains were 74-87% and 85-94% against fully heterotypic strains (compared to 89-95% against homotypic strains).[36–38] Recent estimates from the era of altered strain diversity are not available. In general, there is a lack of research on rotavirus vaccine performance or effectiveness in more recent years. Within five years after the first rotavirus vaccines were globally introduced, 24 primary studies reported estimates of vaccine effectiveness in different geographic regions. In the window between five to ten years after vaccine introduction only eight studies reported on vaccine effectiveness and no studies have yet been published that cover the period beyond ten years post-introduction.

However, in light of the substantial changes in rotavirus strain distribution, continued monitoring of vaccine effectiveness is warranted. For influenza, a European Influenza Surveillance Scheme (EISS) exists. Strain-specific and overall vaccine effectiveness reports are published for each influenza season based on the available clinical and epidemiological data.[39–41] This aids in monitoring the virus, mismatch with vaccine strains and circulating strains in Europe. For rotavirus, the National Respiratory and Enteric Virus Surveillance System (NREVSS) and New Vaccine Surveillance Network (NVSN) in North America provided reports on clinical and epidemiological data of rotavirus until 2016.[25,42] In Europe, EuroRotanet (a network of collaborating laboratories)[43] already collects information on rotavirus types co-circulating in Europe. Integration of these data in vaccine performance studies seems feasible. Active surveillance of rotavirus epidemiology should be combined with monitoring vaccine effectiveness to better understand the impact of strain replacement on vaccine performance and burden of disease.

Infant population characteristics

Another possible explanation for the lower vaccine effectiveness is related to the study population. Some host-factors are known to influence the rotavirus vaccine immune response, including gut dysbiosis, genetic factors and intestinal coinfections. While these associations have mainly been established based on studies in developing countries,[44] they may also be relevant for infants with MRC. For instance, gut dysbiosis may also exist in medical risk infants because of prematurity, antibiotic treatment or critical illness. Microbiome composition is additionally thought to differ from term infants, depending on gestational age. These differences, also in microbiota with positive effects on immune training, were described to exist at six weeks of age (the time point of first rotavirus vaccination).[45] In addition, premature infants have impaired functioning of the mucosal barrier, and innate and adaptive immune system.[46] This may contribute to decreased effectiveness of mucosal vaccines in premature infants as was demonstrated for oral polio vaccines.[47,48] Furthermore, infants with congenital cardiovascular pathologies, that comprised the largest group of congenital disorders in our study population, are known to be immunocompromised pre- and post- cardiac bypass surgery, or may suffer from genetic disorders affecting the immune system and consequently rotavirus vaccine immune response. Serum anti-rotavirus IgA testing, as was performed in the pre-licensure clinical efficacy trials,[49] and their geometric mean titer would add valuable information to assess the immune responses in infants with MRC.

In summary, the RIVAR study population included more vulnerable infants with regard to gestational age, birthweight and comorbidities, compared to other studies among specific risk populations (**table 1**), which may explain the lower vaccine effectiveness. In addition, these studies were performed in settings with universal rotavirus vaccination, where herd protection potentially contributed to measured vaccine effects.

To improve rotavirus vaccine performance among medical risk infants, alternative vaccination strategies should be explored. The novel parenteral rotavirus vaccines may offer a solution.[50] Vaccine responses to other parenteral childhood vaccinations were adequate in a subset of the prematurely born infants participating in RIVAR.[51] Alternatively, the rotavirus vaccination schedule could be adapted to improve immune responses, for instance by adding a third dose for Rotarix or by changing intervals between dosing.

Non-specific effects of vaccination

For live-attenuated vaccines, some studies have reported beneficial non-specific effects. Trained immunity is the proposed mechanism by which live-attenuated vaccines enhance the innate immune response to subsequent and non-target infections.[52,53] The RIVAR study population would greatly benefit from such non-specific effects, as these infants are at increased risk of respiratory infections and hospitalizations. However, we did not find significant beneficial effects on hospitalization for non-target diseases or on incidence of acute respiratory infections after

rotavirus vaccination in medical risk infants. So far, inconclusive evidence is reported on the overall benefit of (live-attenuated) childhood vaccines on non-target diseases[54,55] and the mechanisms that could mediate the non-specific effects have not yet been fully elucidated. Therefore, further evidence is needed before these effects could be considered for inclusion in cost-benefit analyses. For rotavirus, the combined data from the rotavirus vaccine phase III efficacy trials analyzed with non-AGE acute hospitalization or hospitalization for respiratory infection as outcome, should be suitable to provide more definite answers on the protection of rotavirus vaccination against non-target diseases.

Hospital-based targeted vaccination

The hospital-based targeted rotavirus vaccination strategy resulted in suboptimal overall vaccination coverage and several hurdles were encountered as identified in the survey and in-depth interviews. Parents of medical risk infants were insufficiently reached and providing quality of care by timely and personal vaccine counseling proved difficult to achieve for all eligible infants. Among the cohort-study participants however, better counseling was feasible with the aid of a dedicated RIVAR researcher and resulted in a much higher vaccination coverage of 85%. It is however unlikely that this level of support could be maintained in a national roll-out of this hospital-based vaccination strategy. At the time of writing, only two countries, Croatia and Spain, have implemented targeted vaccine programs for rotavirus vaccination.[56,57] No estimates on vaccination coverage or effectiveness from these countries have been published.

Alternative strategies to deliver rotavirus vaccination to medical risk infants therefore need to be considered. In the Netherlands the national immunization program is invested with well-baby clinics and executed by youth HCP. Using this infrastructure for rotavirus vaccination of infants with MRC is possible. However, due to (prolonged) hospital stay and frequent post-discharge outpatient visits, many MRC infants do not receive care by youth HCP within the tight age restrictions of first dose administration of rotavirus vaccine. Therefore, some kind of cooperation between youth HCP and hospital care will be necessary, which already proved difficult to implement in practice.[14]

Implications for vaccine policy and future research

The two main aims of the RIVAR project were to assess feasibility and effectiveness of a selective rotavirus vaccination strategy targeting infants with MRC. The achieved reduction of severe rotavirus acute gastroenteritis was limited and the feasibility of selective hospital-based vaccination proved suboptimal. In this paragraph, I will weigh protective effects (direct, indirect and non-specific), safety profile, different vaccination strategies and cost-effectiveness in order to arrive at recommendations for future rotavirus vaccination policy for medical risk infants.

Overall benefit of rotavirus vaccination for medical risk infants

Rotavirus vaccination for infants with MRC in this study did not result in a significant reduction in hospitalization due to rotavirus AGE, although a 30% reduction (the point estimate of our study) could have some clinical relevance. In addition, no difference in incidence of rotavirus AGE of any severity was observed between vaccinated and unvaccinated infants. Vaccination coverage using a hospital-based targeted vaccination strategy reached 52%. Therefore, the assumptions on vaccination effectiveness and coverage in the updated cost-effectiveness analysis (**chapter 3**) no longer apply. It is highly unlikely that targeted rotavirus vaccination would be cost-effective from either a healthcare or societal perspective at the free market price given the vaccine effectiveness estimate of 30%. Targeted vaccination could be more favorable if reductions in hospitalizations could be achieved through non-specific effects. However, such non-specific beneficial effects of rotavirus vaccination could not be demonstrated in our study.

Safety and tolerability profile

Some safety signals were detected in our study and have also been described earlier.[58] An evaluation of reports from the vaccine adverse event reporting systems in America and Europe covering ten years, concluded that most adverse events following rotavirus vaccination were gastrointestinal, non-serious and were already included in the Summary of Product Characteristics (SPCs), like vomiting and diarrhea (n>1000). Respiratory tract infections, Kawasaki disease and neurological disorders were also reported, although causality is difficult to establish and the authors recommend further investigation. The reported odds ratios, for rotavirus vaccines compared to other vaccines, were 8.8, 14.6 and 2.3 for respiratory tract, Kawasaki and neurological diseases respectively. These passive adverse event surveillance databases do not include information on patient characteristics (such as presence of MRC) and stratified risk assessment for comparison was therefore not possible. Our tolerability results also showed most adverse events were gastrointestinal and non-serious (i.e. did not require healthcare attendance). Yet the few severe (mainly gastrointestinal) adverse events we observed cannot be ignored.

Risk-benefit ratios

The combined results on vaccine effectiveness, overall health benefits and safety risks of rotavirus vaccination for infants with MRC warrant recalculation and weighing of the risk-benefit ratios. If we conservatively consider only those serious adverse events (SAE) for which a link with other routine national immunization program vaccines is unlikely given the nature of events (gastrointestinal), there were eight vaccine related SAE among 2077 vaccinated infants (described in **chapter 5**). This translates to a population attributable risk of vaccine related SAE after rotavirus vaccination of 0.4%. Which means that four in 1000 vaccinated

MRC infants experience a SAE. The potential benefit of vaccination we calculate based on a 30% vaccine effectiveness and a 7.6% incidence of severe rotavirus AGE up to 18 months of age (derived from rotavirus incidence of 14.6 per 100 person years and 43% severe disease in the unvaccinated population as described in **chapter 2**). This leads to a 2.3% population attributable risk reduction of severe rotavirus AGE by vaccination in medical risk infants. Jointly, these calculations result in a risk-benefit ratio of 1:6, meaning that per induced SAE six severe rotavirus AGE cases were prevented. In this comparison of risks and benefits we ignored all non-serious adverse events, that occur at one in 10 rotavirus vaccinated infants. Our previous analyses which assumed over 80% vaccine effectiveness and higher AGE incidence,[4] described in **chapter 3**, resulted in a far more favorable risk-benefit ratio of targeted vaccination.

Some further discussion is needed on infants born after 32 weeks of gestation and term infants with congenital disorders. Within RIVAR the focus was on extreme vulnerable medical risk infants with prolonged care, i.e. infants should still receive care at time of first dose rotavirus vaccination. Consequently, our results cannot be extrapolated to healthy and stable premature infants without prolonged postnatal care. This includes mostly infants born after 32 weeks of gestation. For moderately premature infants it might be best to rely on the prior effectiveness studies (**table 1**) and pre-licensure trials of Omenaca and Goveia et al.[59,60] In these trials, 303 and 2070 premature infants were studied for immunogenicity and efficacy of rotavirus vaccination respectively. Only a small proportion had a gestational age below 32 weeks and none had comorbidities. IgA seroconversion rate after two doses of Rotarix was 85.7% (95%CI 79.0;90.9%)[59] and efficacy against rotavirus AGE of any severity was 73% (95%CI -2.2;95.5%) after three doses of RotaTeq.[60]

Another group that could benefit more from rotavirus vaccination includes the subgroup within RIVAR of term infants with congenital disorders. The point estimate for vaccine effectiveness in this group was slightly higher (hazard ratio: 0.51). However, due to fewer participants in the subgroups the estimates are less precise. For these infants, evidence from the post-licensure studies of Javid and Fang et al should also be considered.[61,62] These two studies showed sufficient seroconversion and an acceptable safety profile of rotavirus vaccination for infants with intestinal disorders or failure.

Vaccination strategy

Based on the RIVAR study, vaccination of infants with MRC is no longer cost-effective and the estimated risk-benefit ratio gives reason for concern. In order to protect these infants from rotavirus disease, an alternative vaccination strategy should be considered. Routine universal rotavirus vaccination or universal mass vaccination, as 107 countries worldwide have implemented,[16] could be such a strategy. With universal rotavirus vaccination included in the national immunization program at well-baby clinics, indirect effectiveness (herd effect)

could protect medical risk infants. Herd effect is achieved via decreased transmission in the population if a sufficient fraction has been vaccinated. This prevents disease occurring among unvaccinated individuals, and occurs in a setting with universal vaccination. Estimates of herd effect from universal rotavirus vaccination varied between two and 77% per season in a North-American study,[28] a meta-analysis reported 48% (95%CI 39;55%) overall indirect effectiveness among children below five years of age.[63] In addition, the population with underlying medical conditions or perinatal morbidity is mostly affected by nosocomial rotavirus infection early in life.[3] Due to frequent hospitalization and prolonged admission duration, their risk of in-hospital rotavirus acquisition increases. Universal rotavirus vaccination was reported to reduce 72% of nosocomial rotavirus infections per year compared to no vaccination.[64]

For future research, I propose that the following five suggestions are taken into consideration:

a) The (changing) epidemiology of rotavirus. Two studies underlined the need for studying rotavirus strain diversity and continuation of genotype surveillance.[29,65] Surveillance of rotavirus epidemiology and corresponding vaccine effectiveness is advised in order to monitor changes in circulating strains and its effect on vaccine performance.

b) Vaccine performance should be separately assessed for specific medical risk populations as evidence from general or trial populations may not necessarily be generalizable. This thesis demonstrated that separate studies in specific at-risk populations can provide valuable information in order to guide policy on vaccine administration, programs and implementation.

c) Given the poor vaccine effectiveness in our study population, alternative types of rotavirus vaccines, which are currently still in development (**figure 2**), should be considered.[50] Parental subunit vaccines or inactivated vaccines could improve immune responses in medical risk infants and hopefully deliver sufficient protection.

d) The microbiome association with rotavirus immune response. This should be verified in infants as there are several hypotheses from animal and human studies that immunity is influenced by the gut microbiota.[66–69] The microbiota is a potential stimulant,[45] and a potential target for interventions to promote the immune response needed for (mucosal) rotavirus vaccination in infants with MRC.

e) Rotavirus serum IgA levels in medical risk infants after vaccination. Serum IgA antibody titer is considered the best correlate of protection, and rotavirus vaccine performance as reported by a meta-analysis of efficacy trials.[49] A lower rotavirus serum IgA titer in our population would corroborate the hypothesis of an altered immune response in infants with MRC.

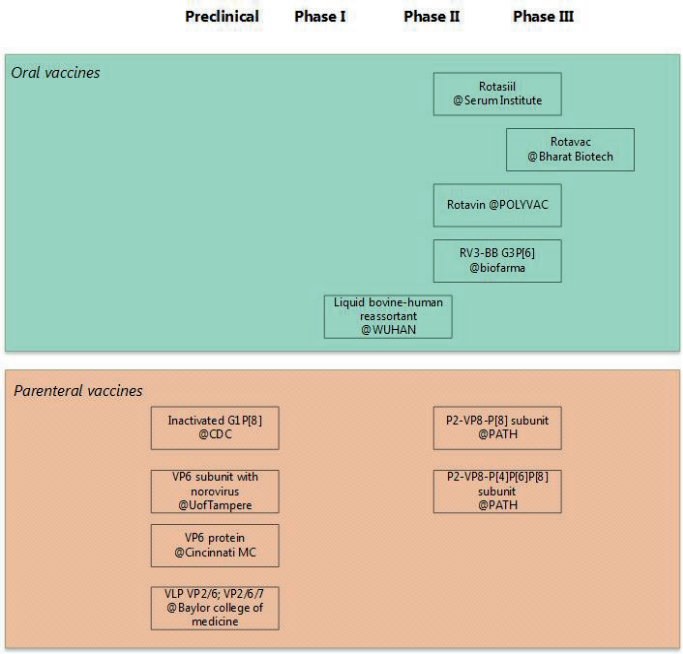


Figure 2 Rotavirus vaccine development pipeline. Based on Burke et al - *Curr Opin Infect Dis* 2019

In the RIVAR study the full safety-effectiveness-implementation spectrum of rotavirus vaccination for infants with MRC was evaluated. Therefore, for this specific patient population, guided recommendations can be made. Non-specific effects of rotavirus vaccination are ignored in this recommendation, because these could not be confirmed in our study but we acknowledge that further research is required. Considering the combined (cost-) effectiveness, safety and feasibility results I would advise a universal rotavirus vaccination strategy excluding premature infants below 32 weeks of gestation and premature infants with comorbidities. At high vaccination coverage, this strategy could yield sufficient indirect effectiveness (herd effect), and reduction in nosocomial infections for the extreme vulnerable medical risk infants, as well as substantial reductions in rotavirus disease in the total infant population, resulting in cost and healthcare benefit. The existing national immunization program infrastructure can be used, guaranteeing quality of parent counseling and high uptake in the population. Because the most extremely vulnerable infants with MRC are excluded, administration within age restrictions of rotavirus vaccination will generally be feasible at well-baby clinics. Rotavirus vaccine effectiveness in healthy premature and term infants with congenital (gastrointestinal) pathology has been studied satisfactory, even though newer studies in the current epidemiology landscape are needed.

Summarizing conclusion

Rotavirus vaccine (cost-) effectiveness and its safety profile among infants with medical risk conditions (MRC) and the implementation of a targeted rotavirus vaccination program have been studied and evaluated in this thesis. This population of infants with MRC should be prioritized for prevention since their disease burden is highest and substantial, even in a well-developed country like the Netherlands. However, a hospital-based vaccination program targeted exclusively towards these medical risk infants showed limited protection and efficiency. Vaccine performance is subject to host characteristics and changing epidemiological conditions, which warrants population specific research and continued surveillance of vaccine effectiveness. The limited protection from current oral rotavirus vaccines among infants with MRC emphasize the need for alternative and optimized preventive strategies for rotavirus disease.

References

1. Kotloff KL. The Burden and Etiology of Diarrheal Illness in Developing Countries. ***Pediatr Clin North Am***. 2017;64(4):799-814. doi:10.1016/j.pcl.2017.03.006

2. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. ***Emerg Infect Dis***. Published online 2003. doi:10.3201/eid0905.020562

3. Verhagen P, Moore D, Manges A, Quach C. Nosocomial rotavirus gastroenteritis in a Canadian paediatric hospital: Incidence, disease burden and patients affected. ***J Hosp Infect.*** Published online 2011. doi:10.1016/j.jhin.2011.04.020

4. Bruijning-Verhagen P, Mangen M-JJ, Felderhof M, et al. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. ***BMC Med***. 2013;11(112). doi:10.1186/1741-7015-11-112

5. Hungerford D, Smith K, Tucker A, et al. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. ***BMC Infect Dis.*** 2017;17. doi:10.1186/s12879-017-2613-4

6. Burnett E, Parashar UD, Tate JE. Real-world effectiveness of rotavirus vaccines, 2006-19: a literature review and meta-analysis. ***Lancet Glob Heal.*** 2020;8(9):e1195-e1202. doi:10.1016/S2214-109X(20)30262-X

7. Organization WH. Causality Assessment of an Adverse Event Following Immunization (AEFI): User Manual for the Revised WHO Classification (Second Edition).; 2018. http://www.who.int/vaccine_safety/publications/aefi_manual.pdf?ua=1

8. Blokhuis P. Changes in Neonatal Screening and Vaccination.; 2020. https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2020Z07778&did=2020D16656

9. Toenders WGM. CFH-Rapport Beoordeling Rotavirus RIX4414 (Rotarix). Vol 3.; 2007.

10. Gezondheidsraad (Health Council of the Netherlands). Het individuele, collectieve en publieke belang van vaccinatie. Published online 2013:1-86.

11. de Vrieze J. Het vaccinatieprogramma van de overheid is te behoudend. ***de Groene Amsterdammer.*** Published online 2019.

12. Moerkamp AH., van Gool WA, Dutch Health Institute. Note of Dutch Health Council and Institute of Health by advices on vaccination against rotavirus. Published online 2017.

13. Blokhuis P. Offering rotavirus vaccine to risk group infants. Lett to Parliam. Published online 2018:1-2.

14. Blokhuis P. Postponement of rotavirus vaccination for risk groups. Letter to Parliament. Published 2019. Accessed February 26, 2021. https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2019D20882

15. Blokhuis P. Aanvraag Gezondheidsraad Update Rotavirus-Advies.; 2020.

16. World Health Organization. Vaccine Introduction Status. Published 2020. Accessed February 8, 2021. www. who.int/immunization/monitoring_surveil lance/ VaccineIntroStatus. pptx?ua=1

17. Roué JM, Nowak E, Le Gal G, et al. Impact of rotavirus vaccine on premature infants. ***Clin Vaccine Immunol.*** 2014;21(10):1404-1409. doi:10.1128/CVI.00265-14

18. Dahl RM, Curns AT, Tate JE, Parashar UD. Effect of rotavirus vaccination on acute diarrheal hospitalizations among low and very low birth weight US infants, 2001-2015. ***Pediatr Infect Dis J***. 2018;37(8):817-822. doi:10.1097/INF.0000000000001930

19. Schurink-van t Klooster TM, de Melker HE. The National Immmunisation Programme in the Netherlands: Surveillance and developments. ***Natl Inst Public Heal Environ***. Published online 2019:102-125. doi:10.1007/978-94-6265-282-8_2

20. Thomas S, Donato CM, Roczo-Farkas S, Hua J, Bines JE. Australian Rotavirus Surveillance Program: Annual Report, 2019. ***Commun Dis Intell.*** 2021;(45). https://pubmed.ncbi.nlm.nih.gov/33573535/

21. Staat MA, Payne DC, Parashar UD. Continued evidence of the impact of Rotavirus Vaccine in Children Less than 3 Years of age from the US New Vaccine Surveillance Network-a multi-site active surveillance program, 2006-2016. ***Clin Infect Dis***. Published online 2020:16. doi:10.1017/CBO9781107415324.004

22. Ituriza-Gomara M, Hungerdorf D. EuroRotaNet: Annual report 2018. EuroRotanet. Published online 2019. https://www.thl.fi/documents/533963/1527557/EuroRotaNetAnnualReport6th_2014.pdf/7e4386c0-0e09-4e18-8576-95031eaf2680

23. McDonald SM, McKell AO, Rippinger CM, et al. Diversity and Relationships of Cocirculating Modern Human Rotaviruses Revealed Using Large-Scale Comparative Genomics. ***J Virol.*** 2012;86(17):9148-9162. doi:10.1128/jvi.01105-12

24. Payne DC, Parashar UD. Chapter 13 Rotavirus. In: Vaccine Preventable Disease Surveillance Manual. ; 2014:1-16.

25. Bowen MD, Mijatovic-Rustempasic S, Esona MD, et al. Rotavirus strain trends during the postlicensure vaccine era: United States, 2008-2013. J Infect Dis. Published online 2016. doi:10.1093/infdis/jiw233

26. Markkula J, Hemming-harlo M, Savolainen-kopra C, Vesikari T. Continuing rotavirus circulation in children and adults despite high coverage rotavirus vaccination in Finland. ***J Infect.*** Published online 2019. doi:10.1016/j.jinf.2019.09.009

27. Maguire JE, Epi M, Appepi M, Glasgow K, Hons B, Glass K. Rotavirus Epidemiology and Monovalent Rotavirus Vaccine Effectiveness in Australia : 2010 – 2017. 2019;144(4):2010-2017. doi:10.1542/peds.2019-1024

28. Pindyck T, Tate JE, Parashar UD. A decade of experience with rotavirus vaccination in the United States – vaccine uptake, effectiveness, and impact. ***Expert Rev Vaccines***. Published online 2018. doi:10.1080/14760584.2018.1489724

29. Donato CM, Roczo-Farkas S, Kirkwood CD, Barnes GL, Bines JE. Rotavirus disease and genotype diversity in older children and adults in Australia. ***J Infect Dis***. Published online 2020:1-11. doi:10.1093/infdis/jiaa430

30. Hahné S, Hooiveld M, Vennema H, et al. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. ***Euro Surveill.*** 2014;19.

31. van Gaalen RD, van de Kassteele J, Hahne SJM, Bruijning-Verhagen P, Wallinga J. Determinants of Rotavirus Transmission: A Lag Nonlinear Time Series Analysis. ***Epidemiology.*** 2017;28(4):503-513. doi:10.1097/ede.0000000000000654

32. Verberk JDM, Pijnacker R, Bruijning-Verhagen P, et al. Biennial Pattern of Rotavirus Gastroenteritis in The Netherlands and a Shifting Age Distribution Following a Low Rotavirus Season, 2010-2016. ***Pediatr Infect Dis J***. 2018;37:248-250. doi:10.1097/INF.0000000000001880

33. Roczo-Farkas S, Kirkwood CD, Cowley D, et al. The impact of rotavirus vaccines on genotype diversity: A comprehensive analysis of 2 decades of australian surveillance data. ***J Infect Dis.*** 2018;218(4):546-554. doi:10.1093/infdis/jiy197

34. Thanh HD, Tran VT, Lim I, Kim W. Emergence of Human G2P[4] Rotaviruses in the Post-vaccination Era in South Korea: Footprints of Multiple Interspecies Re- assortment Events. doi:10.1038/s41598-018-24511-y

35. Mukhopadhya I, Murdoch H, Berry S, et al. Changing molecular epidemiology of rotavirus infection after introduction of monovalent rotavirus vaccination in Scotland. ***Vaccine***. Published online 2017. doi:10.1016/j.vaccine.2016.11.028

36. Braeckman T, Herck K Van, Meyer N, et al. Effectiveness of rotavirus vaccination in

prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: Case-control study. ***BMJ***. Published online 2012. doi:10.1136/bmj.e4752

37. Cortese MM, Immergluck CL, Held M, et al. Effectiveness of Monovalent and Pentavalent rotavirus vaccine. ***Pediatrics.*** 2013;7(1):13-20. doi:10.5152/ced.2013.04

38. Payne DC, Boom JA, Staat MA, et al. Effectiveness of Pentavalent and Monovalent Rotavirus Vaccines in Concurrent Use Among US Children <5 Years of Age, 2009-2011. HHS ***Public Heal***. 2013;57(1):13-20. doi:10.1093/cid/cit164.Effectiveness

39. Rose A, Kissling E, Emborg HD, et al. Interim 2019/20 influenza vaccine effectiveness: Six European studies, September 2019 to January 2020. ***Eurosurveillance***. 2020;25(10):1-14. doi:10.2807/1560-7917.ES.2020.25.10.2000153

40. Pebody RG, Zhao H, Whitaker HJ, et al. Effectiveness of influenza vaccine in children in preventing influenza associated hospitalisation, 2018/19, England. ***Vaccine***. 2020;38(2):158-164. doi:10.1016/j.vaccine.2019.10.035

41. Arkema JM, Meijer A, Meerhoff TJ, Van Der Velden J, Paget WJ. Epidemiological and virological assessment of influenza activity in Europe, during the 2006-2007 winter. ***Euro Surveill.*** 2008;13(34):1-7. doi:10.2807/ese.13.34.18958-en

42. Tate JE, Haynes A, Payne DC, et al. Trends in national rotavirus activity before and after introduction of rotavirus vaccine into the national immunization program in the United States, 2000 to 2012. ***Pediatr Infect Dis J***. 2013;32(7):741-744. doi:10.1097/INF.0b013e31828d639c

43. EuroRotaNet. No Title. Accessed January 9, 2018. http://www.eurorota.net/

44. Lee B. Update on rotavirus vaccine underperformance in low- to middle-income countries and next-generation vaccines. ***Hum Vaccines Immunother.*** 2020;00(00):1-16. doi:10.1080/21645515.2020.1844525

45. Chernikova DA, Madan JC, Housman ML, et al. The premature infant gut microbiome during the first 6 weeks of life differs based on gestational maturity at birth. ***Pediatr Res.*** 2018;84(1):71-79. doi:10.1038/s41390-018-0022-z

46. Baxter D. Impaired functioning of immune defences to infection in premature and term infants and their implications for vaccination. ***Hum Vaccin.*** Published online 2010. doi:10.4161/hv.6.6.12008

47. Pagano JS, Plotkin SA, Cornely D. The response of premature infants with type 3 attenuated poliovirus. ***J Pediatr***. 1994;65(2):12337-12343.

48. Keller R, Dwyer JE, Oh W, D'Amodio M. Intestinal IgA neutralizing antibodies in newborn infants following poliovirus immunization. ***Pediatrics.*** 1996;43(3):330-339.

49. Patel M, Glass RI, Jiang B, Santosham M, Lopman B, Parashar U. A systematic review of anti-rotavirus serum IgA antibody titer as a potential correlate of rotavirus vaccine efficacy. ***J Infect Dis***. 2013;208(2):284-294. doi:10.1093/infdis/jit166

50. Burke RM, Tate JE, Kirkwood CD, Steele AD, Parashar UD. Current and new rotavirus vaccines. ***Curr Opin Infect Dis***. 2019;32(5):435-444. doi:10.1097/QCO.0000000000000572

51. Rouers EDM, Bruijning-Verhagen PCJ, van Gageldonk PGM, van Dongen JAP, Sanders EAM, Berbers GAM. Association of Routine Infant Vaccinations With Antibody Levels Among Preterm Infants. ***Jama***. 2020;324(11):1068-1077. doi:10.1001/jama.2020.12316

52. Benn CS, Netea MG, Selin LK, Aaby P. A Small Jab - A Big Effect: Nonspecific Immunomodulation By Vaccines. ***Trends Immunol.*** 2013;34(9):431-439. doi:10.1016/j.it.2013.04.004

53. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. ***Nat Rev Immunol.*** 2020;20(6):375-388. doi:10.1038/s41577-020-0285-6

54. Kandasamy R, Voysey M, McQuaid F, et al. Non-specific immunological effects of selected routine childhood immunisations: Systematic review. ***BMJ***. 2016;355. doi:10.1136/bmj.i5225

55. Higgins JPT, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: Systematic review. ***BMJ.*** 2016;355. doi:10.1136/bmj.i5170

56. Tešović G. Childhood vaccinations in Croatia. ***Period Biol***. 2012;114(2):149-166.

57. ECDC. Rotavirus infection: Recommended vaccination schedule. ***ECDC***. Published 2021. Accessed February 24, 2021. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=32&SelectedCountryIdByDisease=-1

58. Bonaldo G, Noseda R, Ceschi A, Vaccheri A, Motola D. Evaluation of the safety profile of rotavirus vaccines: a pharmacovigilance analysis on American and European data. ***Sci Rep.*** 2020;10(1):1-9. doi:10.1038/s41598-020-70653-3

59. Omenaca F, Sarlangue J, Szenborn L, et al. Safety, Reactogenicity and Immunogenicity of the Human Rotavirus Vaccine in Preterm European Infants: A Randomized Phase IIIb Study. ***Pediatr Infect Dis J.*** 2012;31(5). doi:10.1097/INF.0b013e3182490a2c

60. Goveia MG, Rodriguez ZM, Dallas MJ, et al. Safety and Efficacy of the Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine in Healthy Premature Infants. ***Pediatr Infect Dis J.*** 2007;26(12):1099-1104. doi:10.1097/INF.0b013e31814521cb

61. Javid PJ, Sanchez SE, Jacob S, McNeal MM, Horslen SP, Englund JA. The safety and immunogenicity of rotavirus vaccination in infants with intestinal failure. ***J Pediatric Infect Dis Soc.*** Published online 2014. doi:10.1093/jpids/pit060

62. Fang AYW, Tingay DG. Early observations in the use of oral rotavirus vaccination in infants with functional short gut syndrome. ***J Paediatr Child Health.*** 2012;48(6):512-516. doi:10.1111/j.1440-1754.2011.02227.x

63. Rosettie KL, Vos T, Mokdad AH, et al. Indirect Rotavirus Vaccine Effectiveness for the Prevention of Rotavirus Hospitalization: A Systematic Review and Meta-Analysis. ***Am J Trop Med Hyg***. Published online 2017. doi:10.4269/ajtmh.17-0705

64. Zlamy M, Kofler S, Orth D, et al. The impact of Rotavirus mass vaccination on hospitalization rates, nosocomial Rotavirus gastroenteritis and secondary blood stream infections. ***BMC Infect Dis***. 2013;13(1). doi:10.1186/1471-2334-13-112

65. Bányai K, László B, Duque J, et al. Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: Insights for understanding the impact of rotavirus vaccination programs. ***Vaccine***. 2012;30(SUPPL. 1):122-130. doi:10.1016/j.vaccine.2011.09.111

66. Harris VC, Haak BW, Handley SA, et al. Effect of Antibiotic-Mediated Microbiome Modulation on Rotavirus Vaccine Immunogenicity: A Human, Randomized-Control Proof-of-Concept Trial. ***Cell Host Microbe.*** 2018;24(2):197-207.e4. doi:10.1016/j.chom.2018.07.005

67. Harris V, Ali A, Fuentes S, et al. Rotavirus Vaccine Response Correlates with the Infant Gut Microbiota Composition in Pakistan. ***Gut Microbes***. Published online 2017. doi:10.1080/19490976.2017.1376162

68. Harris VC. The Significance of the Intestinal Microbiome for Vaccinology: From Correlations to Therapeutic Applications. ***Drugs***. Published online 2018. doi:10.1007/s40265-018-0941-3

69. Harris VC, Armah G, Fuentes S, et al. Significant Correlation Between the Infant Gut Microbiome and Rotavirus Vaccine Response in Rural Ghana. ***J Infect Dis***. 2017;215(1):34-41. doi:10.1093/infdis/jiw518

Appendices

A

Dutch summary

Nederlandse samenvatting

Introductie

Rotavirus is een belangrijke oorzaak van acute gastro-enteritis (AGE) bij kinderen. Rotavirus AGE kenmerkt zich door acuut ontstaan van diarree, koorts en/of overgeven. De ziektelast is hoog, vooral vanwege dehydratie, dat vooral bij zuigelingen kan optreden. In Nederland is het rotavirus verantwoordelijk voor 1900-3400 ziekenhuisopnames per jaar en vijf tot zes doden op kinderleeftijd. Deze ziektelast wordt in ontwikkelde landen, zoals Nederland, vooral ervaren door kinderen die te vroeg of te klein zijn geboren of kinderen met een aangeboren afwijking. Kinderen met een van deze drie medische risico aandoeningen hebben een verhoogd risico op ernstige complicaties als gevolg van rotavirus AGE.

Sinds 2006 zijn er werkzame, levend verzwakte orale vaccins tegen rotavirus beschikbaar voor zuigelingen, RotaTeq en Rotarix. Deze vaccins verminderen het risico op ernstige rotavirus AGE met meer dan 80%. De vaccins worden over het algemeen goed verdragen. Er is echter een klein verhoogd risico op invaginatie (een acuut ziektebeeld waarbij een deel van de darmen in elkaar schuift) in de eerste zeven dagen na de eerste dosis. Het risico op invaginatie wordt geschat op 1.1 tot 2.7 per 100.000 rotavirus gevaccineerde kinderen. De Wereldgezondheidsorganisatie (WHO) adviseert universele vaccinatie tegen rotavirus voor zuigelingen, vanwege de gunstige risico-batenverhouding van vaccinatie. In Nederland is er tot op heden geen rotavirusvaccinatie programma, in tegenstelling tot de situatie in meer dan 100 landen wereldwijd. De Gezondheidsraad heeft in september 2017 een advies uitgebracht waarin zij positief staat ten opzichte van universele vaccinatie en het rotavirusvaccin in ieder geval adviseert voor kinderen met een medische risicofactor. De minister van Volksgezondheid besloot in 2018 een gericht rotavirusvaccinatie programma te implementeren voor deze groep kwetsbare kinderen. Dit programma zou in juni 2020 starten. Echter, op basis van de voorlopige resultaten van dit proefschrift, werd in april 2020 de implementatie voor onbepaalde tijd uitgesteld en werd de Gezondheidsraad opnieuw om advies gevraagd over rotavirusvaccinatie, met inachtneming van de onderzoeksgegevens zoals beschreven in dit proefschrift.

In dit proefschrift wordt het Risk-group Infant Vaccination Against Rotavirus (RIVAR) project beschreven. In dit project werd rotavirusvaccinatie aangeboden aan zuigelingen met medische risico aandoeningen met als doel de vaccin effectiviteit, veiligheid en haalbaarheid van dit programma te bestuderen. De groep zuigelingen die in het RIVAR project werd onderzocht was gedefinieerd als zuigelingen met 1) een of meer medische risico aandoeningen: prematuriteit (geboren voor 36 weken zwangerschapsduur), een laag geboortegewicht (minder dan 2500 gram) en/of, een ernstige aangeboren afwijking. En 2) ontvangen van (poli-) klinische zorg (tussen zes en 14 weken postnatale leeftijd) in een deelnemend ziekenhuis. In totaal namen dertien ziekenhuizen op 15 locaties deel aan het RIVAR project. Het RIVAR project was ontworpen om twee hoofdvragen te beantwoorden en bestond uit de implementatie van een

rotavirusvaccinatie programma gecombineerd met een voor-na cohort studie. De eerste vraag was, wat is de vaccin effectiviteit van rotavirusvaccinatie bij zuigelingen met een medische risico aandoening? En de tweede, is een gericht rotavirusvaccinatie programma in de tweede- en derdelijnszorg haalbaar? Als secundaire doelen werden de vaccin veiligheid en potentiele niet-specifieke effecten van rotavirusvaccinatie bepaald. Deze vragen werden beantwoord, nadat eerst de ziektelast van rotavirus in de samenleving werd geschat voor deze populatie kinderen met een medische risicofactor en de kosten-effectiviteitsanalyse werd herzien.

Samenvatting van het onderzoek in dit proefschrift

Om een uitgangsmeting te hebben en te kunnen prioriteren voor preventie strategieën, beoordeelden we de ziektelast van acute gastro-enteritis (AGE), en pathogeen specifieke AGE, voor zowel episoden die thuis plaatsvonden als waarvoor een arts werd geraadpleegd. Hiertoe gebruikten we de data van het rotavirus ongevaccineerde RIVAR cohort (**hoofdstuk 2**). De ziektelast in de samenleving door rotavirus was niet eerder systematisch onderzocht, en beschikbare informatie over rotavirusinfecties in de populatie kinderen met medische risico aandoeningen was verkregen uit studies in een ziekenhuis omgeving. We vonden dat de incidentie van AGE onder kinderen met een medische risicofactor gelijk was als voor gezonde kinderen, echter de ernst met betrekking tot symptomen, zorggebruik en ziekenhuisopname was twee tot drie keer verhoogd. Rotavirus en norovirus waren de meest gedetecteerde pathogenen, en rotavirus veroorzaakte het ernstigste ziektebeloop. Daarbij komt dat AGE in deze populatie leidde tot belangrijk maatschappelijke impact, weerspiegeld in 30% absentie van kinderopvang en ouderlijk werkverlies/verzuim. We concludeerden dat, vergeleken met studies in gezonde kinderen, de AGE ziektelast in de samenleving voor medisch risico kinderen aanzienlijk verhoogd was.

Vervolgens hebben we de bestaande kosten-effectiviteitsanalyse van rotavirusvaccinatie in Nederland opnieuw berekend, waarbij de verandering in rotavirus epidemiologie, de lagere aantallen ziekenhuisopnamen en de nieuwe schattingen van ziektelast werden meegenomen (**hoofdstuk 3**). Naar schatting zou universele rotavirusvaccinatie de grootste reductie geven in rotavirus ziektelast voor de gehele populatie. Echter, gerichte vaccinatie van zuigelingen met een medische risico aandoening was kostenbesparend in de primaire en sensitiviteitsanalyses, en had het gunstigste risico-baten profiel met betrekking tot invaginatie. Gebaseerd op deze resultaten zou gerichte vaccinatie tegen rotavirus AGE gunstig zijn op alle criteria, mits het vaccin effectief is in een populatie met een medische risicofactor.

Aansluitend evalueerden we of het vaccin inderdaad bescherming bood tegen rotavirusziekte in zuigelingen met een medische risicofactor. Op basis van eerdere schattingen over vaccin

werkzaamheid onder gezonde a terme en prematuur geboren zuigelingen, werd een conservatieve vaccineffectiviteit van 60-80% verwacht. In het RIVAR project werd het humaan rotavirus vaccin (HRV, Rotarix, GSK Biological SA, België) gebruikt. Door de gevaccineerde en ongevaccineerde cohort deelnemers aan de RIVAR studie onderling te vergelijken konden we de rotavirusvaccin effectiviteit voor zuigelingen met een medische risico aandoening bepalen (**hoofdstuk 4**). In tegenstelling tot de eerdere onderzoeken, was HRV minder beschermend tegen ernstige rotavirus AGE (vaccin effectiviteit 30%; 95% betrouwbaarheidsinterval (BHI) -36;65%) in deze studie, en er werd geen impact op rotavirus ziekenhuisopnames geobserveerd. Omdat de geobserveerde aantallen laag waren, en een groot deel van de AGE episoden niet op rotavirus waren getest, werd een post-hoc analyse gedaan voor AGE ongeacht oorzaak en rotavirus AGE ongeacht ernst. Dit leverde vergelijkbare en niet significante uitkomsten. Samenvattend suggereren de resultaten dat de werking van rotavirusvaccinatie minimaal is in zuigelingen met een medische risicofactor. De bovengrens van het 95% betrouwbaarheidsinterval was 65% in onze studie. Dat wijkt substantieel af van de gemiddelde waarden van 90% effectiviteit die doorgaans voor gezonde zuigelingen worden gevonden in hoog-inkomen landen, waarbij de ondergrens van de 95% betrouwbaarheidsin¬tervallen 76-84% is. Daarom concludeerden we dat de HRV effectiviteit beduidend lager is in risico kinderen en onderstreept deze bevinding het belang van risicogroep specifiek onderzoek.

Ook is er gekeken naar het voorkomen van bijwerkingen bij kinderen met een medische risico aandoening na rotavirusvaccinatie. We vonden dat ernstige bijwerkingen, geduid als mogelijke vaccinreacties, met een voorkomen van 0.25 per 100 toegediende vaccindoses, vaker optraden dan eerder was beschreven voor de populatie zuigelingen met een medische risico aandoening (**hoofdstuk 5**). De meerderheid van de bijwerkingen waren gastro-intestinaal van aard. Mogelijke causaliteit was gebaseerd op de tijdsrelatie met HRV toediening en biologische plausibiliteit wat betreft de pathofysiologie. Globaal werden er meer (gastro-intestinale) bijwerkingen gemeld voor gevaccineerde premature zuigelingen vergeleken met ongevaccineerden (relatieve risico 1.07, 95% BHI 1.04;1.10). In de kleine groep van 27 zuigelingen geboren na een zwangerschapsduur van minder dan 27 weken, die ondanks hun korte amenorroeduur off-label gevaccineerd waren, werd rotavirusvaccinatie goed verdragen en waren geen veiligheidssignalen. De effectiviteits- en veiligheidsresultaten gezamenlijk beschouwend, adviseren wij dat zorgverleners de risico's en voordelen van rotavirusvaccinatie voor kinderen met een medische risico aandoening steeds per individuele casus afwegen.

Eveneens hebben we onderzocht of rotavirusvaccinatie gunstige niet-specifieke effecten veroorzaakt (**hoofdstuk 6**). Levend-verzwakte vaccins, zoals HRV, worden geassocieerd met positieve niet-specifieke effecten. Dit fenomeen wordt toegeschreven aan getrainde immuniteit, een vaccin geïnduceerde modificatie van het aangeboren immuunsysteem dat het risico op

en/of ernst van ziekte door een niet-doelwit infectie (i.e. een infectie anders dan waartegen het vaccin beschermd) vermindert. In onze studie was HRV niet beschermend tegen acute ziekenhuisopname wanneer opname voor AGE werd geëxcludeerd (hazard ratio: 0.91 95% BHI 0.76;1.16).Verder vonden we geen reductie in cumulatief aantal opgenomen dagen of incidentie van acute luchtweginfecties, zoals kan worden verwacht op basis van getrainde immuniteit mechanismen. Concluderend vonden wij geen aanwijzingen voor positieve niet-specifieke effecten na rotavirusvaccinatie onder kinderen met een medische risico aandoening.

Tenslotte, de implementatie strategie voor het RIVAR project leverde een vaccinatiegraad van 52% op (95% BHI 51;54%) met een grote variatie in vaccinatiegraad tussen zuigelingen met verschillende medische risicofactoren en tussen ziekenhuizen (**hoofdstuk 7**). In Nederland worden de standaard kindervaccinaties aangeboden via de jeugdgezondheidszorg bij consultatiebureaus. Het stellen van de indicatie voor, en het toedienen van rotavirusvaccinatie gericht op zuigelingen met medische risico aandoening past niet binnen deze infrastructuur en dit vereiste derhalve een andere aanpak. Daarom werd dit gerichte vaccinatieprogramma geïmplementeerd in tweede- en derdelijns pediatrische ziekenhuizen. Gebaseerd op evaluatie enquêtes onder ouders en zorgverleners, en diepte-interviews met betrokken zorgverleners gaven we suggesties voor verbetering van een ziekenhuis-gebaseerd gericht rotavirusvaccinatie programma voor medisch risico zuigelingen. Deze suggesties omvatten een uitgebreid onderwijsprogramma voor betrokken artsen en verpleegkundigen met een toegewijde zorgverlener ter plaatse om inbedding in de reguliere zorg te bewerkstelligen, nationale uitvoeringsrichtlijnen om variatie tussen ziekenhuizen te voorkomen en, afhankelijk van de bestaande infrastructuur en locatie, het betrekken van de jeugdgezondheidszorg voor counseling en vaccintoediening.

De rotavirusvaccinatie (kosten-) effectiviteit, het veiligheidsprofiel voor zuigelingen met een medische risico aandoening en de implementatie van een gericht rotavirusvaccinatie programma werden bestudeerd en geëvalueerd in dit proefschrift. Deze populatie van kinderen met een medische risicofactor zou voorrang moeten krijgen op preventie, aangezien de ziektelast hoog en substantieel is, zelfs in een goed ontwikkeld land als Nederland. Echter, een ziekenhuis-gebaseerd vaccinatie programma exclusief gericht op deze zuigelingen toonde matige bescherming en efficiëntie en is derhalve niet meer kostenbesparend. De werking van vaccins is afhankelijk van gastheer eigenschappen en veranderende epidemiologische condities, welke populatie specifiek onderzoek en continue surveillance van vaccineffectiviteit noodzakelijk maken. De matige bescherming van de huidige orale rotavirusvaccins voor kinderen met een medische risico aandoening benadrukt de noodzaak voor alternatieve en geoptimaliseerde preventieve strategieën voor rotavirus.

Contributing authors

Caterina Band
Department of Pediatrics, Spaarne Gasthuis, Hoofddorp and Haarlem, the Netherlands

Marloes van Beurden
Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Marc Bonten
Julius Center for Health Sciences and Primary Care; Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands

Louis Bont
Department of Pediatrics, University Medical Center Utrecht, Utrecht, the Netherlands

Patricia Bruijning-Verhagen
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; Center of Epidemiology and Surveillance of Infectious Diseases, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Carin Dassel
Department of Pediatrics, Deventer Hospital, Deventer, the Netherlands

Sandra Fokkert
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Rolina van Gaalen
Department of Epidemiology and Surveillance, Center for Infectious Diseases Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Marieke Hemels
Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands

Margit Heslinga
Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Marlies van Houten
Department of Pediatrics, Spaarne Gasthuis, Hoofddorp and Haarlem, the Netherlands

Anne van Kempen
Department of Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands

Elly Kleinlugtenbeld
Department of Pediatrics, Albert Schweitzer Hospital, Rotterdam, the Netherlands

Don Klinkenberg
Department of Epidemiology and Surveillance, Center for Infectious Diseases Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Marie-Jose Mangen
Department of Epidemiology and Surveillance, Center for Infectious Diseases Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Hester de Melker
Department of Epidemiology and Surveillance, Center for Infectious Diseases Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Obbe Norbruis
Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands

Dasja Pajkrt
Department of Pediatrics, Amsterdam University Medical Center, Amsterdam, the Netherlands

Roan Pijnacker
Center of Epidemiology and Surveillance of Infectious Diseases, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Gea van Putten
Department of Pediatrics, University Medical Center Utrecht, Utrecht, the Netherlands

Elsbeth Rouers
Center of Epidemiology and Surveillance of Infectious Diseases, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Maaike van Rossem
Department of Pediatrics, Rijnstate Hospital, Arnhem, the Netherlands

Rob Schuurman
Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands

Jacqueline van der Sluijs
Department of Pediatrics, Maxima Medical Centre, Veldhoven, the Netherlands

Helene Stas
Department of Pediatrics, Maasstad Hospital, Rotterdam, the Netherlands

Carla Tims-Polderman
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Gerdien Tramper-Stranders
Department of Pediatrics, St. Franciscus Hospital, Rotterdam, the Netherlands

Janneke Verberk
Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands

Arine Vlieger
Department of Pediatrics, St. Antonius Hospital, Nieuwegein, the Netherlands

Shannon Watkins
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Gijs van Well
Department of Pediatrics, Maastricht University Medical Center, Maastricht, the Netherlands

Margreet Wessels
Department of Pediatrics, Rijnstate Hospital, Arnhem, the Netherlands

Lydeke Zwart
Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

List of publications and conference presentations

Scientific publications not included in this thesis:

Rouers, E. D. M., Berbers, G. A. M., Dongen, J. A. P. Van, Sanders, E. A. M., & Bruijning-verhagen, P. (2019). Timeliness of immunisations in preterm infants in the Netherlands. ***Vaccine***, 37(39), 5862–5867. https://doi.org/10.1016/j.vaccine.2019.08.006

Rouers, E. D. M., Bruijning-Verhagen, P. C. J., van Gageldonk, P. G. M., van Dongen, J. A. P., Sanders, E. A. M., & Berbers, G. A. M. (2020). Association of Routine Infant Vaccinations With Antibody Levels Among Preterm Infants. ***Jama***, 324(11), 1068–1077. https://doi.org/10.1001/jama.2020.12316

Gunawan, S., Wolters, E., van Dongen, J., van de Ven, P., Sitaresmi, M., Veerman, A., Mantik, M., Kaspers, G., & Mostert, S. (2014). Parents' and health-care providers' perspectives on side-effects of childhood cancer treatment in Indonesia. ***Asian Pacific Journal of Cancer Prevention***, 15(8). https://doi.org/10.7314/APJCP.2014.15.8.3593

Mostert, S., Gunawan, S., Van Dongen, J. A. P., Van De Ven, P. M., Sitaresmi, M. N., Wolters, E. E., Veerman, A. J. P., Mantik, M., & Kaspers, G. J. L. (2013). Health-care providers' perspectives on childhood cancer treatment in Manado, Indonesia. ***Psycho-Oncology,*** 22(11). https://doi.org/10.1002/pon.3314

Mostert, S., Gunawan, S., Wolters, E., van de Ven, P., Sitaresmi, M., van Dongen, J., Veerman, A., Mantik, M., & Kaspers, G. (2012). Socio-economic status plays important role in childhood cancer treatment outcome in indonesia. ***Asian Pacific Journal of Cancer Prevention***, 13(12). https://doi.org/10.7314/APJCP.2012.13.12.6491

Scientific conferences:

27-05-2021	Presentation (e-poster discussion) on Rotavirus vaccine effectiveness among infants with medical risk conditions in the Netherlands, online at ***European Society of Pediatric Infectious Diseases annual meeting***
26-09-2020	Presentation (e-poster) on Implementing a hospital-based rotavirus vaccination program for medical risk infant: an evaluation, and Individual parent counseling results in high rotavirus vaccination coverage among infants with severe medical conditions, online at ***European Society of Pediatric Infectious Diseases annual meeting***
09-05-2019	Presentation (oral) on Safety and tolerability of rotavirus vaccination among extremely preterm infants in the Netherlands, in Ljubljana, Slovenia, at ***European Society of Pediatric Infectious Diseases annual meeting***

24-04-2019	Presentation (oral) on Rotavirus incidence and burden of disease among risk-group infants in the Netherlands, in Riga, Latvia, at ***European Expert Meeting on Rotavirus Vaccination***
15-06-2018	Presentation (pitch) on Acute gastro-enteritis: incidentie en ziektelast onder hoog-risico kinderen, in Arnhem, the Netherlands, at ***Nederlandse Vereniging voor Kindergeneeskunde congres***
31-05-2018	Presentation (e-poster discussion) on Rotavirus disease burden among high-risk infants in the Netherlands, in Malmo, Sweden, at ***European Society of Pediatric Infectious Diseases annual meeting***
26-05-2017	Presentation (e-poster) on Rotavirus incidence among high-risk infants in the Netherlands, in Madrid, Spain, at ***European Society of Pediatric Infectious Diseases annual meeting***
22-03-2017	Presentation (poster) on Rotavirus hospitalizations in the absence of rotavirus vaccination, in Utrecht, the Netherlands, at ***European Expert Meeting on Rotavirus Vaccination***
13-01-2012	Presentation on Health-care providers' perspectives on childhood cancer treatment, in Manado, Sulawesi, Indonesia, for all employees of the pediatric hematology-oncology ward of Prof Dr RD Kandou hospital

Acknowledgements/Dankwoord

"***La dolce far niente***" *– a way of life, which the Italians master.*

(vertaling: het zoete nietsdoen)

Het ontstaan van dit proefschrift is mede mogelijk gemaakt door vele knappe koppen, meewerkende handen en onvermoeide supporters. Gedurende de viereneenhalf jaar achter een bureau en in het veld (van Emmen tot aan Doenraede) hebben vele mensen meegeholpen of bijgedragen aan de RIVAR studie. Mijn dank aan eenieder is groot en zonder jullie allen was het niet tot zo'n resultaat gekomen, een aantal personen benoem ik hier in het bijzonder.

Dank voor de bijdrage aan het ontstaan van dit proefschrift.

Prof. dr. M.J.M. Bonten, Beste Marc. Onze eerste ontmoeting was op mijn eerste werkdag, dit gaf naar mijn idee blijk van jouw vertrouwen in Patricia. En volgens mij heb je dat vertrouwen in de hele groep collega's die je om je heen hebt verzameld. Onze een-op-een meetings gingen gepaard met weinig woorden, en ook op woensdag morgen was je vaak to the point, raak en direct, met soms wat nazorg. Dank dat ik deel mocht uitmaken van jouw onderzoeksgroep en ik hoop een beetje van je onderzoeksbril/perspectief/geest mee te nemen in mijn verdere carrière.

Dr. P.C.J. Bruijning-Verhagen, Beste Patricia, dank voor deze kans die je me hebt geboden. Zonder jouw scherpe kijk, inschatting, support en zetjes in de goede richting was ik onderweg verdwaald. Je gaf me de ruimte om te groeien, veel te leren en me ook persoonlijk te ontwikkelen. Ik neem een voorbeeld aan jouw doorzettingsvermogen, functioneren als duizendpoot, kritische en scherpe blik en het combineren van werk en privé. Ik neem vele lessen en adviezen van de afgelopen jaren met me mee.

De lezerscommissie, prof. dr. A.M.C. van Rossum, prof. dr. J. Frenkel, prof. dr. M.C.J. Sturkenboom, prof. dr. E.A.M. Sanders en dr. H. de Melker, allen hartelijk dank voor de tijd die u heeft genomen voor het uitgebreid lezen en beoordelen van dit proefschrift.

Aan alle coauteurs, die eerder al met naam en affiliatie zijn benoemd, dank voor de reacties en suggesties ter verbetering van de losse manuscripten. Zo bleek, naïeve ogen zien veel meer en dragen bij aan een beter resultaat.

Alle (hoofd-) onderzoekers en research medewerkers in de deelnemende ziekenhuizen, en

in het bijzonder Caterina, Gea, Carin en Marieke wil ik vanuit de grond van mijn hart danken. In dertien ziekenhuizen op vijftien locaties in Nederland hebben vele mensen zich ingezet voor het kunnen starten van deze studie, het uitvoeren, werven van deelnemers, faciliteren en vaccineren van zuigelingen. Het was leuk, soms lastig, soms moeilijk, interessant, uitdagend en soms teleurstellend om de studie tot zijn einde te brengen. Maar jullie gaven niet op, en nu is het resultaat daar. Met als kers op de taart een Gezondheidsraad advies, waar velen van jullie je vast in kunnen vinden.

Het RIVAR studie team in UMC Utrecht, Carla, Lydeke, Marloes, Diana. Zonder jullie hulp en inzet voor de logistieke, administratieve en data technische afhandeling was het in het water gevallen. Ontelbare keren hing ik aan de telefoon of typte ik een mail met een verzoek tot hulp. Daar tegenover stond koffie en taart bij de overleggen en een praatje op de gang. Veel dank!

Elsbeth verdient het om hier apart te noemen, aan het begin van haar promotietraject heeft zij geholpen met het opzetten van de RIVAR studie. En aan het begin van mijn traject heeft ze me dan ook op weg geholpen. Daarna kwam een periode met vele huisbezoeken in heel Nederland om bloedafnames te doen voor haar PRIEMA studie. Ik heb goede herinneringen aan onze samenwerking, en veel dank.

Alle werk- en wetenschappelijke studenten, Margit, Renee, Sandra, Auke, Lisanne, Emily, Shannon, Ella, Esther, Anemone, Judith, Lina en Sander. Veel dank voor het bellen van deelnemers, klaarmaken van ontlastingssample pakketten, vaccinatiesets, compleet maken van datasets, tackelen van data cleaning problemen en uitvoeren van sub-analyses. Ik heb veel mogen leren van het samenwerken en begeleiden van jullie stages.

En bovenal alle ouders van- en RIVAR deelnemende kinderen, zonder jullie geen resultaat. Dank jullie wel voor deelname aan de studie, het invullen van de maandelijkse vragenlijsten en jullie betrokkenheid. Het is af. De meeste kinderen zijn inmiddels al (veel) ouder dan drie, dus het heeft even geduurd...

Dank voor de support tijdens het tot stand komen van dit proefschrift.

Alle infectie epi onderzoekers, WMM-ers, XEWMM-ers, PedID Epi-ers, dank voor de inhoudelijke discussies, scherpe observaties, blogs, journal clubs, congres bingo kaarten en micaffe koffies. Het is gek om zo op afstand af te sluiten, maar gelukkig hadden we nog een corona pubquiz en wijn- en bierproeverij.

Dank aan alle kamergenoten in het Stratenum en van Geuns over de jaren heen, en speciaal aan Marian, Denise, Tess en Tessa. *Marian, thank you for the mental support in good times and the bad. Sitting across your desk in the office and side by side during the Epi master made my day. I hope Paris treats you well!* Denise, dank voor jouw plantjes, koffies, kerstversiering, just keep swimming en valley of shit- support. De PhD reddingsboei hebben we samen bedacht en heeft voor goede dingen gezorgd, dank je wel! Tess, tegenover je zitten, sparren en samen de laatste loodjes afronden heeft me vaak geholpen. Ik hoop binnenkort ook jouw verdediging bij te wonen! Tessa, ontzettende speedy gonzales, precies in vier jaar je PhD afgerond en met wat voor traject en ook in de VvE visitatiecommissie. Je was wat dat betreft mijn voorbeeld. *Que te vaya bien*!

Veel vrienden en vriendinnen hebben ook jarenlang mijn PhD perikelen aangehoord of gedaan alsof. Dank voor jullie support lieve amigo's van het Haganum, van de studie, uit het jaar, uit het huis, uit de co-groep en de st jean suipers. De paranifmen moet ik natuurlijk even in het bijzonder noemen. Lieve Pien, we kennen elkaar nu 25 jaar en dat betekent dat we vele ups en downs samen hebben doorstaan. Ik kan me geen betere vriendin voorstellen en ben heel blij dat je naast me staat op deze dag! Lieve Nus, in een 08 rollercoaster hebben wij elkaar grondig leren kennen en we gaan nu de tweede verdediging samen aan. Van de hei tot aan de hemel!

Lieve schoonfamilie, de goede en grote tribe van Beer: Stien, de Pekels, de sleutels. Dank voor jullie support en aanhoren van, in de afgelopen jaren. In die tijd heeft ook een gigantische gezinsuitbreiding plaatsgevonden, dus wellicht gaan we wat rustiger vaarwater tegemoet..

Lieve familie, de van Dongens, Stoutens, de Goossens-en, Feijtes, de GVD, skiclub de Vetklep, veel dank voor jullie steun en liefde. En in het speciaal, natuurlijk Oma Leentje, die nu 93 is! Ik ben ontzettend blij met alle familie en dankbaar voor de fijne en mooie momenten die we samen hebben.

The House of Nerdi's, lieve Liek, Ka, pap en mam. Dank voor jullie onvermoeide vertrouwen en wijze raad. Lieve Lieke, mijn grote kleine zus, altijd scherp en grappig. Lieve Karel, mijn brootje, te lief en stoer tegelijk. Lieve papa, op je 57e gepromoveerd en vol met adviezen, niks is te gek en vol vertrouwen. Lieve mutti, de slimme dokter, advocaat van de duivel en altijd voor me klaar met support en vertrouwen.

Lieve Beer, Sam en Kees, er blijven bijna geen woorden over. Sammie, stuiterbal en kleine doerak. Keesje, stoute wijsneus en "bal". En mijn liefste Beer, dank voor je eindeloze steun, raad, vaak grappig en liefde. Ik ben trots op hoe we het met zijn vieren doen!

Curriculum vitae

Josephine, call name Fien, van Dongen was born in Amsterdam on September 5th 1989. She grew up in Amsterdam, Addis Ababa (Ethiopia), Cochabamba (Bolivia), Katwijk and Voorburg. She attended secondary education at Gymnasium Haganum in the Hague and graduated in 2007. After a gap year with voluntary work in La Paz (Bolivia) and travelling South America, she studied Medicine at the Vrije Universiteit Amsterdam. As part of the Medicine master she did a research internship at a pediatric hospital in Manado (Indonesia) and travelled South-East Asia. After obtaining her medical degree in 2015, she started working as non-training resident at the pediatrics department of Reinier de Graaf Gasthuis and later Onze Lieve Vrouwe Gasthuis.

She became a PhD candidate in 2016 at the Epidemiology of Infectious Diseases group of prof. dr. Marc Bonten, Julius Center of UMC Utrecht, co-supervised by dr. Patricia Bruijning-Verhagen. Besides her PhD, she completed the postgraduate master in Epidemiology, with a specialization in Infectious Disease epidemiology at Utrecht University. She was also member of the VvE visitation committee that reviews epidemiology curricula of Dutch universities, assisted in teaching epidemiology to medical students and supervised bachelor and master research internships. As of April 2021, she is applying for a doctor in training residency in Pediatrics.


RIVAR