Rotavirus infection and vaccination in Norway

– epidemiological studies of infection and intussusception events before and after vaccine introduction

Tone Bruun

Oslo, January 2020

Department of Infection Control and Vaccines, Norwegian Institute of Public Health

and

Faculty of Medicine, University of Oslo

NIPH
Norwegian Institute of Public Health

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-791-8

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

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Acknowledgements

The research that this thesis is based on was conducted during 2014-2019 as part of my work at the Norwegian Institute of Public Health.

First, I will thank Elmira Flem, who was my main supervisor until March 2019. Thank you for your support and guidance, for sharing of your competence and experience in the field of vaccine research, and for your confidence in me. I am deeply grateful to Preben Aavitsland, for agreeing to step in as my main supervisor when Elmira started a new job. Your support, encouragement and scientific feedback have been invaluable. I will also thank my co-supervisor Per Nafstad, for your interest in my project and wise counselling along the way, which I highly appreciate.

This work would not have been possible without Terese Bekkevold, who has coordinated the project –always patient and helpful, and also contributed scientifically. I am also very grateful to Susanne Dudman, Moustafa Gibory and other colleagues at the Department of Virology for their contributions in planning the study and analysing samples. Thanks to Sara Viksmoen Watle and Ingun Heiene Tveteraas for helping me validating diagnoses against medical journals. It was a pleasure travelling around the country with you. Beatriz Valcarcel Salamanca, your contribution with the statistics has been invaluable. Furthermore, I want to thank Richard White and Liliana Vazquez Fernandez for methodological assistance, and Birgitte Freiesleben de Blasio for updating and running the rotavirus transmission model from her previous studies.

Important parts of the project were performed in collaboration with hospitals around the country. All the enrolled children and their families deserve a warm thank for their contribution to the studies. A special thank goes to colleagues at the paediatric and microbiological departments at the sentinel surveillance hospitals: Oslo University Hospital Ullevål, Stavanger University Hospital, St. Olavs University Hospital, Østfold Hospital and Akershus University Hospital. I am really grateful for your contributions and for enlightening discussions along the way. The project (and this thesis) would not have been possible without the data and samples you collected at the hospitals.

Thanks also to all my colleagues and friends at the Norwegian Institute of Public Health. What an enjoyable and stimulating place to work! A particular thanks to my running mates, for important contributions to my physical and mental health. And Oliver, thanks for reading most of the manuscript and providing valuable comments and suggestions.

The contributions of all my co-authors are much appreciated. Thanks for inspiring discussions and useful input to the studies and the papers.

I am very grateful to my family and friends for support and encouragement. In particular I am grateful to my dear father, for always being there, forever interested in me and my work. You have always been an important inspiration for me.

Finally, a special thanks to Kim, Jakob and Mari for your love and support. Kim, your ability to enjoy life and see the humor in almost everything saves me on a regular basis (as does your technical support). Jakob and Mari, thank you for putting my work in perspective, inspiring me, challenging me and making me a better person.

Tone Bruun, January 2020

Abbreviations

AGE	Acute gastroenteritis
ACIP	Advisory Committee on Immunization Practices (in the US)
CDC	Centres for Disease Control and Prevention (in the US)
CI	Confidence interval
ED	Emergency departments
EPC	Emergency primary care provider (out-of-hours)
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration (in the US)
GBD	Global Burden of Disease Project
GP	General practitioner
HBGA	Histo-blood group antigens
ICD-10	Tenth revision of the International Classification of Diseases
ICPC-2	Second edition of the International Classification of Primary Care
IQR	Interquartile range
IR	Incidence rate
IRR_a	Adjusted incidence rate ratio
KUHR	National Health Economics Administration Database
NIPH	Norwegian Institute of Public Health
NPR	Norwegian Patient Registry
OR	Odds ratio
PCR	Polymerase chain reaction
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
RV1	The monovalent vaccine Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium)
RV5	The pentavalent vaccine RotaTeq® (Merck & Co., Inc., Kenilworth, NJ, USA)
RVGE	Rotavirus gastroenteritis
RT-PCR	Reverse transcription polymerase chain reaction
SAGE	World Health Organization Strategic Advisory Group of Experts (on immunization)
SYSVAK	The Norwegian Immunization Registry

VE	Vaccine effectiveness
WHO	World Health Organization
WRE	Winter residual excess method

Summary

Rotavirus is the most common cause of severe acute gastroenteritis (AGE) among young children globally. In 2006, two rotavirus vaccines were licensed internationally. By 2009, the World Health Organization (WHO) recommended that all countries include rotavirus vaccines in their national immunization programs, and in October 2014, Norway so incorporated the vaccine into its program. However, at the time of writing, two thirds of European countries have not added the vaccine. As the licensed rotavirus vaccines seem to be associated with a small risk of intussusception, and the risk seems to be age-dependent, the vaccine is administered under strict age limits (the first dose given by maximum 12 weeks of age and the second dose by 16 weeks of age). The overall aim of this thesis is to understand the burden of rotavirus disease in Norway, the benefits of routine vaccination, and the potential risk of intussusception associated with vaccination. Exclusive use of the monovalent vaccine, high vaccination coverage from the start, and the analysis of data from the Norwegian population-based registries provides a valuable opportunity to evaluate the impact of this vaccine in a low-mortality setting. In addition to registry studies, we conducted prospective laboratory-based surveillance of children hospitalized for AGE to assess the rotavirus burden before vaccine introduction and the vaccine effectiveness against rotavirus hospitalizations. We estimated baseline incidence of intussusception, and the numbers of expected vaccine-associated intussusception cases compared with estimated numbers of averted rotavirus cases. Our work shows that rotavirus was the primary cause of severe AGE in children <5 years of age in Norway, and constituted a substantial public health burden before introduction of the vaccine. We estimated that 4.0 (95% CI: 4.0–4.2) inpatient and 2.3 (95% CI: 2.2–2.3) outpatient cases per 1,000 children <5 years of age were seen in hospital with rotavirus disease each year during 2009-2013, whereas 30.6 (95% CI: 30.3–30.8) rotavirus cases per 1,000 children <5 years of age were treated in primary care. The annual rotavirus mortality rate before vaccine introduction was 0.17 (95% CI: 0.04–0.29) deaths per 100,000 children <5 years of age, corresponding to one death every second year in Norway. Intussusception was confirmed to be a rare disease among Norwegian infants (37.1 (95% CI: 31.2–43.8) cases/year per 100,000 children <1 year of age) before vaccine introduction. We estimated that 1.3 (95% CI: 0.7–2.0) vaccine-associated intussusception cases were expected to occur in the 2016 birth cohort under the current age limits for vaccine administration, and that 1,360 rotavirus hospitalizations would be averted for each vaccine-associated intussusception case. Extension of the age limits to 16 weeks for the first vaccine dose and 24 weeks for the second dose (the maximum age according to the manufacturer), leading to more children being vaccinated at an older age, would result in roughly one additional intussusception case annually in the vaccinated cohort. Finally, our data demonstrate a substantial impact of rotavirus vaccination on severe AGE among children four years after vaccine

introduction; AGE hospitalizations in children <5 years of age were reduced by 45% in the post-vaccine period compared with the pre-vaccine years (IRRa 0.55; 95% CI: 0.49-0.61), attributable to a high vaccine effectiveness established in our study. The effectiveness against hospital admission for rotavirus gastroenteritis after two vaccine doses was 76% (95% CI: 34-91%) using test-negative controls, and 75% (95% CI: 44-88%) using community controls. In conclusion, routine rotavirus vaccination of Norwegian children has successfully reduced the burden of severe acute gastroenteritis requiring hospital care. Administering rotavirus vaccines beyond current age limits in Norway would lead to a marginal increase in intussusception cases, offset by the benefits of vaccination.

List of papers

1. Burden of rotavirus disease in Norway: Using national registries for public health research. Bruun T, Salamanca BV, Bekkevold T, Vainio K, Gibory M, Haugstad KE, Rojahn A, Jakobsen K, Storvold G, Lunde A, Stordal K, Kanestrom A, Eidem MO, Dollner H, Skanke LH, Nordbo SA, Sivertsen HC, Gilje AM, Haarr E, Flem E. *Pediatric Infectious Disease Journal*. 2016; 35 (4): 396-400.

2. Intussusception among Norwegian children: What to expect after introduction of rotavirus vaccination? Bruun T, Watle SSV, Tveteraas IH, Flem E. *Vaccine*. 2019; 37 (38): 5717-23.

3. Impact of the rotavirus vaccination program in Norway after four years with high coverage. Bruun T, Salamanca BV, Bekkevold T, Døllner H, Gibory M, Gilje AM, Haarr E, Kran AB, Leegaard TM, Nakstad B, Nordbo SA, Rojahn A, Stordal K, Flem E. Manuscript submitted, January 17th 2020. *Pediatric Infectious Disease Journal.* Publish Ahead of Print, 2020 Dec 15.

1 Introduction

1.1 Rotavirus infection

1.1.1 The virus

Gastroenteritis has been a common cause of morbidity and mortality in young children throughout the history. In 1929, Zahorsky described the "Winter vomiting disease", suggesting that viral infection could be the cause of this frequently observed illness with symptoms of vomiting and diarrhoea, later confirmed by Kapikian's discovery of norovirus in 1972 (1) and the discovery of rotavirus by Bishop and colleagues in 1973 (2) as causes of acute gastroenteritis (AGE) particularly occurring in the winter months. Rotaviruses affect primarily young children, whereas noroviruses affect people of all ages (3). Before 1973, no infectious agent was identified in about 80% of the children admitted to hospital with severe AGE during these winter epidemics (2). The search for a virus as the cause of AGE began in the late 1960s. It was assumed that viruses were important since bacteria seldom were associated with winter epidemics (1).

In May 1973, at Royal Children's Hospital in Melbourne, Australia, Ruth Bishop, Geoffrey Davidson, Ian Holmes and Brian Ruck identified, by electron microscopy, viral particles in the epithelial cells lining the upper villous surface of duodenal mucosa in children with AGE (4). The virus was also identified by electron microscopy of faecal extracts (5) and the wheel-like structure seen in the microscope led to the name Rotavirus (from the Latin, rota, meaning wheel) (2). Rotavirus belongs to the Reoviridae family.

The virus is a non-enveloped double-stranded RNA virus (figure 1). The virus particles are complex, with three concentric protein layers around the genome of 11 RNA-segments, which encode six structural viral proteins (VP1, VP2, VP3, VP4, VP6 and VP7) and six non-structural proteins (NSPs) (6).

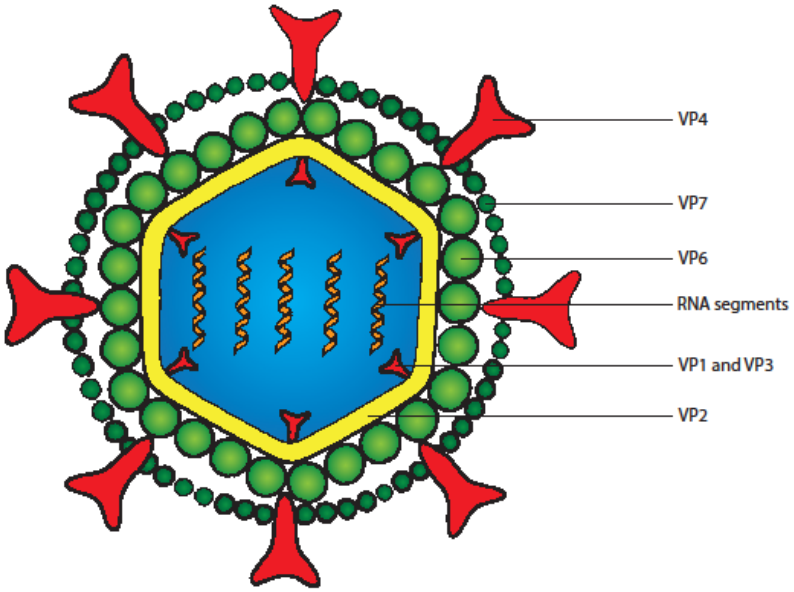


Figure 1. The structure of rotavirus. Illustration by Mari Bruun Ånonsen

Ten different rotavirus species (A–J) have been classified on the basis of sequence and antigenic properties of VP6, with A as the most common cause of infections in children (6). Species A can be further classified. The outer shell of the virus contains two proteins that determine the strain: a glycoprotein (G-type antigen or VP7) and a protease-sensitive protein (P-type antigen or VP4) (7). These induce neutralizing antibody responses and are the basis of the nomenclature system used for species A rotavirus strains. G-types can be identified using enzyme immunoassays (EIAs) and are known as serotypes, or by sequencing and are then described as genotypes. The two methods give concordant results, and viruses are referred to by their G serotype (G1, G2, G3 etc.). EIA serotyping is less reliable for P-types, so these are often determined using polymerase chain reaction (PCR) and referred to by their P genotype (P[4], P[6] etc.) (7). Based on this classification system more than 30 G genotypes and more than 40 P genotypes of species A rotavirus have been identified (8). During the pre-rotavirus vaccine era 1996-2007, five globally common strains accounted for a total of 75% of all strains recovered from patients (G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]) (9). The same strains dominate today, together with the emerging strain G12P[8] (6, 10-12). Strain distribution varies by geography (6). Co-infection of a host cell with multiple viruses may result in genome reassortment and virus evolution (6). Rotavirus is a segmented RNA virus, and have (similar to influenza virus) capacity for reassortment during co-infection, whereby segments are exchanged among different viral strains (13). One source of rotavirus strain diversity is the introduction of animal rotavirus genes through reassortment (14). A review of African studies published during 1997–2006, found a greater diversity of circulating rotavirus strains than in many other regions, likely reflecting genome reassortment between co-infecting rotaviruses and zoonotic transmission (15). Some studies show

increased genotype diversity following vaccine introduction, and suggest that the vaccines exert evolutionary pressures that influence the diversity of circulating rotavirus strains (10, 16). Other studies do not find any consistent pattern indicative of selection pressure resulting from vaccine use (17).

Isolation and cultivation of rotavirus from clinical faecal specimens is difficult (18).

1.1.2 The interaction between the virus and the host

Pathogenesis

Rotavirus infects and replicates in mature enterocytes in the mid and upper part of the villi and in enteroendocrine cells of the small intestine (19, 20). Inflammation of the intestine is generally mild compared to that for other intestinal pathogens. The fluid and electrolyte secretion associated with rotavirus infection is probably caused by several mechanisms, including both malabsorptive and secretory components, resulting both from the direct effects of virus infection and the host response (19, 20). Rotavirus replication stimulate release of serotonin, which can activate brain structures that induce nausea and vomiting (21). Viremia and extraintestinal replication occur in children with rotavirus gastroenteritis (RVGE) but the impact of systemic rotavirus infection on disease burden remains to be determined (6, 22).

Histo-blood group antigens (HBGAs) expressed on the surface of host cells mediate virus attachment and influence susceptibility of individuals to rotavirus, dependent on the rotavirus P genotype (23, 24). This insight might explain differences in rotavirus epidemiology among different populations and likely also some of the differences in protection from rotavirus vaccines (6).

Immunity

One episode of rotavirus infection does not guarantee lifelong protective immunity. In a Mexican study, two natural rotavirus infections (whether symptomatic or asymptomatic) appeared to provide complete protection against subsequent moderate-to-severe RVGE (25). Protection was predominantly against the homotypic strain. In Guinea-Bissau, a primary rotavirus infection conferred 70% protection against subsequent rotavirus diarrhoea (26). In India, however, the protection against moderate-to-severe disease was only 57% after two infections and 79% after three infections, with no evidence that protection was homotype-specific (27). All three studies showed less effect against mild or asymptomatic infections. It seems like the first exposure to rotavirus induces predominantly homotypic antibody response and as the number of RVGE episodes increases, children develop broader heterotypic responses, even if the infections comprise only a restricted number of G types (28, 29). Both non-immunological (e.g. HBGA expression) and

immunological factors affect the susceptibility to rotavirus infection (6). Contribution of the innate immunity for protection against rotavirus infection is indicated by animal studies, but few data are available on the significance in humans (6, 29, 30). A variety of animal models have demonstrated that acquired immunity is important (7). Studies suggest that both cell-mediated and humoral factors are important, but the mechanisms of immunity are not completely understood (3, 7, 30). Both the monovalent and the pentavalent vaccine, used globally, protect against strains not included in the vaccines (31-36). Association between rotavirus antibody levels and protection has not proven to be complete, suggesting that factors other than antibodies are important for providing protection (30). The ability of rotavirus antibodies after natural infection to neutralize rotavirus remains unclear, and the correlation between post-vaccination rotavirus antibody titres and protection against rotavirus infection is even less evident (30).

1.1.3 Clinical features, diagnostics and treatment

The clinical picture of rotavirus infection

Following an incubation period (the interval between virus exposure and symptom onset) of 1–3 days, the onset of RVGE is usually abrupt. The main features of the disease are watery non-bloody diarrhoea and vomiting, often accompanied by fever, abdominal cramps and malaise (3, 6, 37). The disease is most often self-limiting and lasts between 2-5 days (3). However, without timely and appropriate treatment, diarrhoea and vomiting can lead to severe dehydration, hypovolemic shock and death. Disease severity is dependent on several factors, including the host's immune status (38). Asymptomatic infections do occur, particularly in neonates, presumably because of maternal antibodies transferred through the placenta or breast milk (6). Chronic gastroenteritis can be seen in immunocompromised children (3, 6). Rotavirus is mainly recognized as a childhood disease, however the virus can also cause disease in adults. In adults, the course is usually mild and moderate in severity, but can be severe in immunocompromised patients (39, 40).

Non-gastrointestinal conditions linked to rotavirus infection

Extraintestinal spread of rotaviruses can occur and result in viremia and, rarely, central nervous system disease (6, 38). Rotavirus disease has been linked to childhood seizures, and rotavirus vaccination is found to be associated with a significant reduction in risk of seizure requiring hospitalization or emergency care in the post-vaccination period (41). Rotavirus infection has also been proposed to trigger type 1 diabetes mellitus and coeliac disease in genetically susceptible children (42, 43). In Australia, the number of incident cases of type 1 diabetes mellitus decreased by 15% in the cohort of children born after the introduction of rotavirus vaccine into the routine immunization program (44), a finding that builds on human and animal studies implicating a role of

rotavirus in the development of type 1 diabetes mellitus in genetically susceptible children (45). A retrospective study of recipients of rotavirus vaccine and placebo in the Rotavirus Efficacy and Safety Trial (REST), found no difference in the occurrence of type 1 diabetes mellitus between the groups, but the prevalence of coeliac disease was significantly higher in placebo recipients (1.11%; CI: 0.78%-1.6%) than in vaccine recipients (0.60%; CI: 0.38%-0.93%) (p=0.027) (46). In the Environmental Determinants of Diabetes in the Young (TEDDY) study, gastrointestinal infections increased the risk of coeliac disease autoimmunity in children with genetic susceptibility, and the risk of coeliac disease autoimmunity was found to be reduced in children vaccinated against rotavirus (47).

Diagnostics

RVGE is difficult to distinguish from AGE caused by other enteric viruses or bacteria by clinical presentation alone, and laboratory testing is required for a specific diagnosis. Several techniques can be used for direct detection of viral antigen or RNA in faecal specimens, including immunochromatographic tests, enzyme immunoassays (EIA) and reverse transcription polymerase chain reaction (RT-PCR). Commercially available EIA tests, based on detection of the VP6 antigen, are typically used in clinical laboratories, and most of these tests have high sensitivity and specificity (48, 49). In research and public health laboratories these assays are often complemented by RT-PCR, which also permit genotyping and detection of vaccine virus strains (6, 50, 51). EIA usually can detect viral shedding within one week after disease onset, while RT-PCR can detect virus RNA for a longer period (6). Of importance, the EIA result correlates better with the presence of symptomatic disease, and RT-PCR results should be carefully interpreted (3, 52). Severe rotavirus disease in young children may be followed by extended excretion of rotavirus after recovery (53). One study found 29% asymptomatic children <1 year of age were positive for rotavirus using RT-PCR (54). The performance of each test depends on the “gold standard” method used for comparison, and different tests commonly yield different results when used to test the same specimen (48, 49).

Treatment

There is no specific treatment for rotavirus infection. Vomiting and diarrhoea may lead to dehydration, which often can be treated with oral rehydration therapy. Severe cases require hospitalization for intravenous fluid treatment. WHO recommends continued breastfeeding in infants and zinc supplement for children <6 months of age in developing countries, where zinc deficiencies are common (55, 56).

1.1.4 Transmission, prevention and control

Transmission

The mode of transmission is mainly faecal-oral directly through close person-to-person contact, but transmission can also occur indirectly via contaminated fomites and possibly by droplets (6, 57-59). The virus can also transmit through contaminated food or water (58, 60). The infectious dose is small, and few virus particles are needed to cause infection in susceptible individuals (61). Rotavirus is stable and can retain infectivity for several hours on the skin (62) and may remain viable in the environment for weeks or months if not disinfected (58, 63).

Prevention and control

The incidence of rotavirus disease has been observed to be similar in both industrialized and developing countries, largely unaffected by water supply, sanitation or hygiene (64). Compared with other causes of childhood diarrhoea, the burden of rotavirus disease has not diminished with improvements in sanitation, hygiene and access to healthcare. The increasing role of rotavirus as the aetiology of severe AGE among children is likely caused by the fact that it is mainly transmitted from person to person and difficult to control compared to bacterial and parasitic agents (65, 66). Development of rotavirus vaccines has provided opportunities for prevention of severe RVGE. Since 2006, rotavirus vaccines has been introduced worldwide, but still 57% of all children in the world (over 70 million) lack access to the vaccines (67).

1.1.5 Rotavirus-related outcomes used in research

Two main clinical scoring systems have been used for the determination of the severity of RVGE in clinical trials and epidemiological studies, the 20-point Vesikari scoring system and the 24-point Clark scoring system (68, 69). In both systems, scoring is based on the presence and severity of symptoms like duration of diarrhoea, frequency of stools, rectal temperature and signs of dehydration. In a comparison between the two systems, they did not correlate in their definition of severe cases, which may affect the comparability between research studies using different scales (70). The Vesikari score has become the most commonly used scoring system in rotavirus vaccine efficacy studies and a modified Vesikari score has been shown to be suitable for studies that include different healthcare systems and populations (71, 72). Such scoring systems are also used in observational studies, often in addition to other rotavirus-related outcomes. In case-control studies, frequently used to evaluate vaccine effectiveness post-licensure, common outcomes of interest are consultation or hospitalization for AGE with laboratory-confirmed rotavirus infection, or only a positive rotavirus stool sample as reported by a laboratory (73-75). Impact studies, which compare rotavirus-related

outcomes before and after vaccine introduction, often study the number/incidence rates of hospitalized all-cause AGE cases, hospitalized RVGE cases, rotavirus or all-cause AGE emergency care contacts, laboratory tests positive to rotavirus, proportion of tests positive to rotavirus or RVGE reported through routine surveillance (74-76). Rotavirus-related outcomes are most often studied in children <5 years of age.

1.1.6 Epidemiology

Data on the incidence of diarrhoea and its causes over time are insufficient, especially in high-burden settings. Data can be difficult to compare and extrapolate between countries. Studies are often conducted in selective and possibly unrepresentative populations, diagnostic tests have varying sensitivity and specificity, and the reported hospitalizations rates may be influenced by the access to care. It is also difficult to assign a cause of death for children with multiple conditions. As a consequence, estimates presented here are largely based on models.

Pre-vaccination era

Global burden of all-cause gastroenteritis

In 2000, approximately 1,400 million diarrhoea episodes and 2.1 million diarrhoea deaths were estimated to occur worldwide per year among children <5 years of age (77). In 2008, the estimated number of deaths were 1.4 million (78). Gastroenteritis and diarrhoea are present in all regions and populations. However, the largest morbidity and mortality occurs in low-income countries. The proportion of deaths in children <5 years of age attributable to diarrhoea demonstrates a declining trend with increasing income level (77).

Global burden of rotavirus gastroenteritis

The epidemiology of RVGE differ by country and region. However, almost every child in the world, irrespective of where they live, was in the pre-vaccine era infected with rotavirus at least once during their first years of life (25, 56, 79). In 1985, de Zoysa and Feachem suggested that rotavirus accounted for 6% of diarrhoea episodes and 20% of deaths caused by diarrhoea in children <5 years of age in developing countries (64). The proportion of diarrhoea hospitalizations attributable to rotavirus has demonstrated an increasing trend with increasing income level. Parashar et al. found that the median rotavirus proportion among diarrhoea hospitalizations in low-income countries in 2000 was 20%; for low-middle income countries, 25%; for high-middle income countries, 31%; and for high-income countries, 34% (77). Through networks of hospital-based sentinel rotavirus surveillance sites in all WHO-regions, WHO found that overall approximately 40% (range 34%–45%) of hospitalizations for diarrhoea among children <5 years worldwide were due to rotavirus infections

in 2001-2008 (80). Annually, during the pre-vaccination era 1986–2000, more than 2 million children <5 years of age were hospitalized for rotavirus infections and 352,000–592,000 died each year (77). Nosocomial rotavirus infections represent a significant problem, but studies are limited and do not allow complete overview of the burden (81). One meta-analysis from 2012 found that the overall incidence of nosocomial RVGE in Europe and North America was 7 cases per 1,000 hospitalizations among children <5 years of age before the implementation of rotavirus vaccination programs (82).

Age distribution

Overall, children 4-23 months of age are said to have the greatest risk for severe RVGE (3). The age distribution varies between countries but tends to be younger in low-income/high-mortality settings (6). In a recent large review of the age distribution of rotavirus disease in children <5 years of age before the introduction of rotavirus vaccination, the median age of rotavirus-positive hospital admissions was 38 weeks (IQR: 25-58 weeks) in countries with very high child mortality and 65 weeks (IQR: 40-107 weeks) in countries with very low or low child mortality (83). Only 3% of the rotavirus-positive admissions in countries with very high child mortality were in the first 10 weeks of age. Infections in the first 3 months of life are generally mild, probably because of protection from maternal antibodies (3). Adults can also be infected with rotavirus, but the disease is usually mild because of the increasing immunity with each subsequent infection (3). Immuno-compromised adults can have a variable course from symptomless to severe and sustained rotavirus infection (40).

Seasonality

In 1990, Cook et al. demonstrated that rotavirus had a distinct seasonal peak in countries with temperate climates but was year-round in tropical settings (84). Later it was found that in most high-income countries, rotavirus epidemiology is seasonal, whereas in low-income countries the disease pattern is more likely to be year-round (85). Country income level was more predictive of the seasonality than other factors like latitude or geographical location. Other have demonstrated that high transmission rates and high birth rates could explain a relative lack of seasonality in poor countries (86).

The burden of rotavirus gastroenteritis in Europe

In Europe, mortality from RVGE is low, but rotavirus resulted in an estimated 87,000 hospitalizations and 700,000 outpatient visits in children <5 years of age each year in European Union countries in the pre-vaccination era (87). Overall, RVGE was estimated to account for 28%–52% of AGE cases in Europe, responsible for up to two-thirds of hospitalizations and emergency department consultations, and one-third of primary care consultations, for AGE among children <5 years of age (88). In the other Scandinavian countries, with similar healthcare systems as in Norway, they found

estimates of RVGE hospitalizations per 1,000 children <5 years of age to be 3.7-3.9 in Sweden (89, 90) and 2.4-2.8 in Denmark (91, 92).

The burden of rotavirus gastroenteritis in Norway

In Norway, a national assessment of rotavirus disease burden was published in 2009 (93, 94). The study evaluated rotavirus epidemiology in hospitalized children using retrospective data from the Norwegian Patient Registry on children <5 years of age hospitalized with AGE during 1995–2004, and data on children <5 years of age admitted with AGE to three hospitals during 2006–2008 prospectively surveyed for rotavirus in stool samples. Rotavirus was found to be the most frequent cause of hospitalization for AGE in children <5 years of age, accounting for 63% of all cases. The annual incidence of rotavirus-associated hospitalizations was estimated to be 3.0 admissions per 1,000 children <5 years of age, resulting in estimated 900 (range 735–1,092) hospitalizations, 7,248 (range 4,530–9,060) primary care consultations, and 28,992 (range 21,744–36,240) home care episodes per year. This study also documented that the majority (61%) of all hospitalized cases with confirmed rotavirus infection were children aged 6–23 months. The mean duration of hospital stay among rotavirus cases was 1.3 days. In Norway, RVGE showed a clear seasonality with a marked increase from March through May.

The economic burden of rotavirus infection in Norway has been shown to be substantial before vaccine introduction, both from a healthcare perspective and a societal (including also payments by parents and workdays lost) perspective (95). Using post-discharge interviews with caregivers of 282 of the children hospitalized with AGE in our sentinel study, Edwards et al. found that work absenteeism and healthcare use before and after hospitalization due to RVGE imposed considerable productivity losses and a substantial burden on the healthcare sector (96).

Post-vaccination era

According to the latest estimates from the Global Burden of Disease project (GBD), despite a growing number of countries introducing the rotavirus vaccine since 2006, rotavirus is by far the leading aetiology responsible for diarrhoea incidence and mortality in children and adults. The study estimated that rotavirus was responsible for more than 258 million episodes (95% UI, 193-341 million) and nearly 130,000 deaths (95%UI, 104,500-155,600) of diarrhoea among children <5 years of age in 2016 and the third leading pathogen associated with mortality in this age group, behind the malaria parasite (517,000 deaths) and Streptococcus pneumoniae (359,000 deaths) (97). The GBD results have been compared with other estimates, and the Child Health Epidemiology Research Group (CHERG), the WHO, and the Centres for Disease Control and Prevention (CDC) estimated even higher number of deaths from rotavirus (98). Tate et al. (WHO/CDC) estimated that the number of rotavirus deaths in children <5 years of age was 215,000 in 2013, having declined from 528,000 in

2000. They concluded that the majority of countries that had used rotavirus vaccine during the study period were low-mortality countries and the impact of rotavirus vaccine on global estimates of rotavirus mortality had been limited (99).

Several studies have found or predicted a biannual pattern in the rotavirus incidence after vaccine introduction (75, 100-102), including a Norwegian model using data from the sentinel surveillance in our project (103). Such a pattern can be explained by accumulation of unvaccinated susceptible children over two successive years.

1.2 Rotavirus vaccination

1.2.1 The RotaShield story

Within a few years after rotavirus was discovered, development of vaccines against the virus started. In the late 1980s, Albert Kapikian and colleagues at the US National Institutes of Health (NIH) developed RotaShield® (Wyeth-Ayherst), an oral, live attenuated, tetravalent rotavirus vaccine (RRV-TV) (104). The vaccine was approved by the Food and Drug Administration (FDA) and licensed for use in the US in August 1998. In the article "The First Rotavirus Vaccine and the Politics of Acceptable Risk", Jason L. Schwartz examines the history of RotaShield®, with particular attention to decision making regarding its use in the US and globally. He reviewed and analysed meeting transcripts, conference reports, government and scientific publications, media coverage, and other sources, in addition to interviewing several of those who participated in decisions regarding the vaccine (105). He calls for greater attention on how the decision makers and their expert advisers evaluate evidence in medicine and public health and translate it into regulations and policy. According to Schwartz, Wyeth's hope was to establish a profitable market in the US, which could subsidize later rollout of the vaccine to regions with greater burden of rotavirus-related disease. Before the FDA approval there were questions about cases of intussusception (see figure 2 and section 1.2.3) observed during clinical testing. Five cases of intussusception were found among the recipients of the vaccine, compared with none in the placebo groups, but the difference in these rates between vaccinees and controls was not statistically significant. The finding was mentioned in the package insert (106) but not among the adverse reactions listed in the FDA press release when the vaccine was licensed. Neither was it the focus for the post marketing studies that Wyeth was instructed to conduct by the FDA. The vaccine was recommended for routine childhood immunization in the US for administration at 2, 4 and 6 months of age, by the Advisory Committee on Immunization Practices (ACIP) in March, 1999 (107). By June, of that year, the Vaccine Adverse Event Reporting System (VAERS) had received 12 reports on intussusception cases potentially related to RotaShield®, and the

CDC oriented ACIP about plans to investigate vaccine-associated intussusception cases. In July, CDC decided to recommend that the vaccine should be temporarily suspended (108). This announcement led to additional reports of intussusception submitted the following weeks, and in the end, results of several studies suggested a substantial increased risk of intussusception after vaccination (approximately 10 cases per 100,000 vaccinees), with the greatest risk after the first dose (105, 109, 110). Wyeth recognized that the vaccine recommendations were about to be withdrawn, and withdrew RotaShield® from the market on October 15th, 1999, one week before ACIP stated that they no longer recommended routine immunization of infants with the vaccine (111). During the ACIP meeting there were discussions about what consequences the withdrawal would have for future testing and use of the vaccine in developing nations where the potential benefits were much larger, and the participants recognized that the indirect effects of their decision likely would have implications outside the US. The ACIP members wanted to emphasize that their recommendations in the US should not necessarily be applied elsewhere, but the instructions from the CDC director were to have "a statement that is as clear and concise and unambiguous as possible". The final statement was published in November 1999 (112). Schwartz describes the debate in the following years, about the scientific and ethical issues related to testing and use of RotaShield® in developing countries, and how the ACIP decision made the vaccine politically nonviable in these countries, possibly also because Wyeth didn't prioritize continued testing or distribution of the vaccine (105). According to Albert Kapikian, when WHO held a meeting in 2000 to assess the future of RotaShield® in developing countries, the health ministers said "they didn't want their population to be seen as second-class citizens. If it was not good enough for US kids, it was not good enough for their infants either" (113). In retrospect it is remarkable that there were (basically) no discussions regarding the risks and benefits of RotaShield® during the ACIP meeting in October 1999, and that the statement only addressed the significantly increased intussusception risk. There was no explanation about whether a specific threshold of risk was exceeded, or any other considerations (105). Years later, it became evident that concerns about public perception and the overall vaccination program were factors important for the outcome. The story of RotaShield® led to large clinical trials powered to detect intussusception risks of a similar magnitude, and thorough post-marketing surveillance, for the rotavirus vaccines that were licensed later and that are now in use.

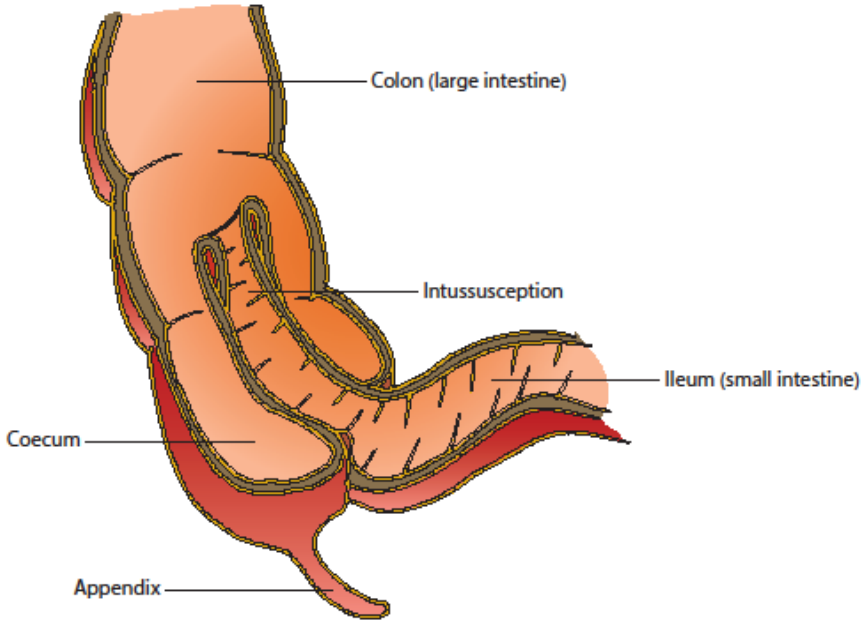


Figure 2. Intussusception, the main cause of bowel obstruction in infants and young children. It occurs when one segment of the bowel becomes enfolded within another segment, and can restrict blood supply to the affected area. In infants and young children, this occurs most commonly in the ileocoecal region. Without treatment, the condition can cause ischemia, perforation and death. Some cases resolve spontaneously. The underlying aetiology in the majority of infants is not clear (114, 115). Illustration by Jakob Bruun Ånonsen

1.2.2 Current rotavirus vaccines and new developments

Two rotavirus vaccines in use worldwide

After RotaShield®, no rotavirus vaccine was available until 2006, when two vaccines were licensed following large trials on efficacy and safety (116, 117). Rotarix® (GSK Biologicals) is an oral monovalent vaccine based on a live attenuated human rotavirus strain, G1P[8], which is recommended as two doses administered between 6 and 24 weeks of age (preferably both doses before 16 weeks) with an interval of at least 28 days between each one. RotaTeq® (Merck & Co., Inc.) is an oral pentavalent human-bovine vaccine that includes five live reassortant rotavirus strains (G1, G2, G3, G4 and P1[8]). RotaTeq® is recommended as three doses administered between 6 and 32 weeks of age (preferable before 20-22 weeks) with an interval of at least 28 days between each dose; the first dose should be given before 12 weeks of age. In Europe, as the vaccine-attributable risk of intussusception seems to be age-dependent, the first dose of rotavirus vaccine is recommended between 6 and 12 weeks of age, preferably at the age of 6-8 weeks (118). These two vaccines are still the only rotavirus vaccines in wide use globally.

Efficacy in clinical trials

The efficacy of a vaccine is usually defined as the percentage reduction of the disease rate among those who are vaccinated according to the recommended schedule compared to those who are

unvaccinated, generally measured under ideal conditions in a placebo-controlled randomized trial, with the intention to establish the biologic performance capacity of the vaccine (119).

Pre-licensure trials for Rotarix® were primarily conducted in Latin-America, and showed efficacy of 85% against severe RVGE (116). A European trial demonstrated an efficacy of 90% against severe disease and 96% against rotavirus hospitalization (120). A clinical trial for RotaTeq® conducted across three regions (Europe, the US and Latin America) demonstrated an efficacy of 98% against severe RVGE (117). However, a combined estimate on efficacy against severe rotavirus diarrhoea from high-mortality countries (Bangladesh, Vietnam, Ghana, Kenya and Mali) was only around 67% in the first year of life and 34% in the second year of life (121). Both vaccines have demonstrated cross-protection to strains not included in the vaccines (32-36). A Cochrane review of all trials of the currently used vaccines found that in the first two years of life, Rotarix® prevents more than 80% of severe cases of rotavirus diarrhoea in low-mortality countries and 35-63% of severe rotavirus diarrhoea in high-mortality countries (122). The same review found that Rotarix® probably also prevents 37-41% of severe cases of all-cause diarrhoea in low-mortality countries and 18-27% of severe cases of all-cause diarrhoea in high-mortality countries. Similar results were found for RotaTeq® (except for all-cause diarrhoea in low-mortality countries where no studies were found). With regard to safety, neither vaccine was associated with any serious adverse events during the pre-licensure trials, including intussusception. The reasons for reduced efficacy in high-mortality countries are not well known; factors may include nutritional deficiencies, altered gut microbiota, interference by maternal antibodies, co-administration of oral poliovirus vaccine, histo-blood group antigens, diverse rotavirus strain types and co-infections (123).

Introduction status

Following licensure of these vaccines, a number of countries have included rotavirus vaccine in their national immunization programs. American and European countries and Australia were the first to introduce the vaccine, but countries in other regions followed, many with support from the GAVI Alliance (a public-private partnership which provides vaccine financing to poor countries). In 2009, WHO recommended that rotavirus vaccines should be included in all national immunization programs (124). When we started our project at the beginning of 2014, just after the Norwegian decision on rotavirus introduction, 56 countries had introduced the vaccine, 16 with support from GAVI (125). In 2019, at the time of writing, 99 countries have introduced the vaccine in their national immunization programs, 47 with support from GAVI (67, 126). Around one third of European countries have introduced the vaccine. Still, 77 million children lack access to rotavirus vaccines globally (67).

Impact and effectiveness in routine use

Vaccine effectiveness measures the same percent reduction in the rate of disease as vaccine efficacy, but under routine use of the vaccine in the "real world". Effectiveness often differs from the efficacy because the study population and program implementation are not perfectly controlled (119). Impact usually measures the reduction in disease at population level following introduction of the vaccine, and can be expressed as the percentage reduction or absolute change in the disease rate (119). It is most commonly measured by comparison of the same population before and after vaccine introduction, and is dependent on the vaccine effectiveness, coverage and herd effect (when part of the population is vaccinated against a disease, leading to reduced transmission in the community, and lower risk of disease also in unvaccinated persons).

Countries that have introduced universal rotavirus vaccination have experienced substantial reductions in rotavirus disease burden (33, 74, 127-129). GBD estimated that 27.8% of children <5 years of age were vaccinated against rotavirus in 2016, preventing more than 28,000 deaths (95% UI, 14,600-46,700), and found that full use of the rotavirus vaccine could have averted an additional 83,200 deaths (95% UI, 37,000-168,000) (97). There is evidence that rotavirus vaccination also has a herd immunity effect (130-133). However, vaccine safety concerns have been considered a barrier to introduction and implementation of the vaccine (134). For example, French health authorities withdrew their vaccine recommendations in 2015 after two intussusception deaths temporally related to rotavirus vaccination (135).

In Europe, vaccine effectiveness estimates vary. In high-income countries like Finland, Belgium, Germany and Spain, vaccine effectiveness against hospitalization has been estimated to be between 86% and 96% (128, 136-139), while in settings with less resources, the estimates are lower; In Armenia, vaccine effectiveness against hospitalization was 62% and in the Republic of Moldova 79% among children <2 years old (140, 141). In 2009, Finland was the first Nordic country to introduce rotavirus vaccination, and a 93% drop in rotavirus-coded hospitalizations and a 69% drop in all-cause AGE hospitalizations were seen after five years among children <5 years of age (142). In Belgium the mean incidence of all-cause AGE hospitalizations was found to decrease by 27% between the pre- and post-vaccination period (143). In a review of data from 2006 to 2014, Karafillakis et al. found reductions in rotavirus hospitalizations in European countries ranging from 65% to 84% (74).

A meta-analysis on US data from 2006 to 2017, showed a vaccine effectiveness against hospitalizations or emergency department visits for RotaTeq® at 84% and Rotarix® at 83% (102). A study of 62 US paediatric hospitals, comparing all-cause diarrhoea hospitalizations during two post-vaccine seasons with data from three pre-vaccine seasons, found 50% and 29% reductions among children <5 years of age in the 2007-2008 and 2008-2009 seasons respectively, while rotavirus-coded

hospitalizations, decreased by 83% and 66% (144). Another US study using insurance databases from 2001-2009 showed comparable results (145).

A few researchers have studied rotavirus vaccine impact through socio-demographic variables, with divergent results. One study in the UK showed that the vaccine's impact was greatest among the most deprived populations, despite lower vaccine uptake in those groups (146). In Canada, despite similar vaccination coverage among all children, disadvantaged socio-economic groups appeared to have a less pronounced AGE reduction (147). The study showed that children living in neighbourhoods with more low-income families had significantly lower vaccine effectiveness against AGE hospitalizations compared to neighbourhoods with lower rates of low-income families (148). Also, in a study from Israel, the vaccine effectiveness was greater in children who belonged to higher socioeconomic status levels (149).

Lower effectiveness is demonstrated in low-income countries such as in Sub-Saharan Africa. In Burkina Faso the adjusted vaccine effectiveness for RotaTeq® against rotavirus hospitalization was 58% in children 6-11 months of age and 19% in children ≥12 months (150); in Malawi 62% among vaccine-eligible children overall (151); In Tanzania 53% in children 5–23 months of age overall, and 66% in children requiring IV rehydration (152). However, even if the relative effect estimates are smaller in high-mortality settings than in low-mortality settings, a greater number of AGE episodes are prevented in these settings as the baseline rates are much higher.

Post-licensure studies suggest similar effectiveness of RotaTeq® and Rotarix® (35, 153). Partial vaccine series are also shown to be effective for both vaccines in routine use, but with lower VE than a full series (102, 138, 154-156).

Two recently prequalified rotavirus vaccines

In addition to Rotarix® and RotaTeq®, WHO has recently prequalified two other rotavirus vaccines; Rotavac® (Bharat Biotech, Hyderabad, India; prequalified in 2018) and ROTASIIL® (Serum Institute of India PVT. LTD., Pune, India; prequalified in 2018) are currently only in use in India (both) and Palestine (only Rotavac®) (157). Rotavac® demonstrated 56% efficacy against severe RVGE in Indian infants; there was insufficient power to evaluate an association with intussusception (158). ROTASIIL® is heat-stable, which makes it suitable for use in low-income countries, where refrigeration can be difficult. In Niger, the vaccine showed 67% efficacy against severe RVGE (159); In India efficacy was 33% (160). None of the studies were powered to evaluate the risk of intussusception. Nationally licensed vaccines exist in China and Vietnam, and several other rotavirus vaccine candidates are in the pipeline. One is intended to be given to neonates, others under development are nonreplicating parenterally administered rotavirus vaccines (157).

1.2.3 Rotavirus vaccination and intussusception

Intussusception is the most common cause of bowel obstruction in infants and young children, which without treatment can cut off the bowel's blood supply and cause ischemia, perforation, and ultimately death (see figure 2).

Baseline incidence of intussusception

Diagnosis and treatment of intussusception vary substantially between countries. In a review published in 2013, from 82 studies across the world, an annual mean intussusception incidence of 74 per 100,000 children <1 year of age (range: 9-328) was reported, with a peak incidence among infants 5-7 months of age. (161). There are large variations in the background incidence reported from different countries and regions, including variations over time within the same country. For example, in Denmark, a population-based cohort study showed that the incidence rate decreased from 16 cases per 10,000 person-years in 1980 to 8.5 cases per 10,000 person-years in 2000 (162). In Norway, intussusception was studied previously in two counties (Rogaland and Hordaland), showing a mean incidence of 14-20 cases per 10,000 children <14 years of age per year (163).

Vaccine-associated intussusception risk

Because RotaShield® was associated with an increase in the risk of intussusception following vaccination, large clinical trials were carried out with Rotarix® and RotaTeq®. According to the recently updated Cochrane review, 119,114 children participated in Rotarix® trials and 88,934 children in the RotaTeq® trials, with no evidence of increased risk of intussusception (122). The risk of intussusception following RotaShield® (approximately 10 cases per 100,000 vaccinees) seemed to be higher in infants who received their first dose after 3 months of age (109, 110, 164). The recommended dosing schedule for RotaShield® in the US resulted in many children receiving vaccine between three and seven months of age, a peak period for naturally occurring intussusception (107). Restricting vaccination to those younger than 3 months old would probably have reduced the risk (165). As a consequence, the first dose for both Rotarix® and RotaTeq® was administered in children <3 months of age, to avoid the background peak age for intussusception, in clinical trials as well as post-licensure. In 2009, WHO recommended that rotavirus vaccines should be initiated for infants between the age of 6 and 15 weeks, with all doses being completed by 32 weeks (166). Nevertheless, post-licensure investigations in some countries revealed that currently licensed rotavirus vaccines appears to be associated with a small risk of intussusception of 1–6 cases per 100,000 vaccinees (167-172). The vaccine-attributable risk seems to be highest in the first week following the first dose (173). The risks are substantially lower than those associated with RotaShield®, but cannot be truly compared because of the different age windows for vaccine administration. Several studies confirm

that adherence to upper age limits for vaccine administration may reduce the likelihood of vaccine-associated intussusception (171, 174). Whether the risk of vaccine-associated intussusception relative to the baseline rates increases with age is not completely understood, but data we have found has not indicated an effect of age on the intussusception risk (109, 172).

Results vary, and a recently published study among infants 28 to 245 days of age from seven low-income sub-Saharan African countries, found that the risk of intussusception during three weeks after administration of monovalent human rotavirus vaccine was not higher than the background risk of intussusception (175). A question that has been raised is whether children with rotavirus vaccine-associated intussusception may be predisposed to the condition, and that the vaccine trigger intussusception to occur earlier, offset by a lower risk later in infancy. Simonsen et al. found no evidence of an increased rate of intussusception admissions during the RotaShield® period, but observed an increase in admissions at 2–4 months of age that was offset by a decrease among older infants during the period compared to the previous data period. They concluded that the high risk reported in the first week after RotaShield® did not translate into the expected overall effect on intussusception admission rate (176). Other studies have similar findings (177-179). A recently published systematic review and meta-analysis found no significant association of vaccination with increased risk of intussusception compared with placebo among infants for up to 2 years after vaccination, and suggests that rotavirus vaccination is not associated with an elevated risk of intussusception (180).

Following a benefit-risk modelling analysis in 2012, WHO decided to no longer universally recommend the age restrictions, but allow countries to remove them in settings where mortality benefits outweigh the risk (56) . In low- and middle-income countries the number of lives saved by removing the age restrictions for rotavirus vaccination would far outnumber the potential vaccine-associated intussusception deaths the age restrictions could prevent (121). A recently published modelling study from low- and middle-income countries showed that a neonatal schedule, where the first two vaccine doses are given as early as possible, would have the fewest excess intussusception deaths and favourable benefit–risk ratios compared with other schedules (181).

1.2.4 Introduction of rotavirus vaccination in the Norwegian immunization program

Already in 2006, when Rotarix® and RotaTeq® were first licensed in Europe, the Norwegian Institute of Public Health (NIPH) started an evaluation to consider introduction of rotavirus vaccine in the national immunization program. An expert group led by the NIPH, with representatives from clinical, laboratory and public health services, concluded in 2011 that routine rotavirus vaccination should be

introduced in Norway (182). One member of the group, the representative of the national nurses' association, believed that the evidence for health and economic benefits was insufficient. The majority of the group found that the disease burden, particularly the number of hospitalizations, and the safety profile of the vaccine, were arguments to support the introduction of the vaccine. The Norwegian Research Centre for Health Services conducted separately an economic analysis, and concluded that it was unlikely that rotavirus vaccination would be cost-effective in Norway from a healthcare perspective. However, from a societal perspective (including indirect costs like productivity loss due to parental absence from work), vaccine introduction was likely to be cost-effective (183). The NIPH estimated that the vaccine prices would be lower after introduction than the price the analysis was based on. After the recommendation from the NIPH working group in 2012, the National Council for Priority Setting in Healthcare decided, with a small majority, that the disease was not serious enough to justify introduction into the national immunization program (184). However, in 2013, based on recommendations from the NIPH, the Ministry of Health and Care Services took a political decision to introduce the vaccine (185). To minimize the risk of intussusception, Norway adopted strict age limits for vaccine administration. The first dose is recommended at 6 weeks of age with a maximum age limit of 12 weeks, and the second dose is recommended at 12 weeks with a maximum limit of 16 weeks. An interval of at least 28 days is advised between doses.

1.3 Introduction of new vaccines – a complex decision

Vaccination is said to be one of the most effective and successful public health tools to prevent disease and premature death. Still, vaccination is a cause of controversy. In fact, we have seen that trust in vaccines seems to have declined worldwide during recent years. More parents are hesitant about giving vaccines or choose to delay vaccination of their children. Countries that were close to eliminating measles, have seen a resurgence of the disease in the last few years (186). Reasons behind this phenomenon are complex, but vaccine hesitancy and resistance are surely part of the explanation. We have not seen the same in Norway, but the situation in other European countries is of concern, and reminds us about the vulnerable trust in vaccines and the importance of understanding the underlying determinants for parents' vaccine decisions. A large study on worldwide attitudes to immunizations showed particularly negative vaccine-safety perceptions in the European region (187). Except for France and Italy, the Western and Northern European countries express less concern about vaccine safety than Eastern and Southern European countries. Vaccine hesitancy is defined by the Strategic Advisory Group of Experts (SAGE) Working Group as "delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is

complex and context specific, varying across time, place and vaccines. It includes factors such as complacency, convenience and confidence." (188). They summarize the determinants in a model with three key domains: 1. Contextual influences – including historic, socio-cultural, environmental, health system/institutional, economic or political factors; 2. Individual and group influences – including influences arising from personal perception of the vaccine or influences of the social/peer environment; and, 3. Vaccine and vaccination-specific issues which are directly related to the characteristics of the vaccine or the vaccination process (189). Evidence on the risk-benefit ratios of vaccines is important, but not enough to achieve and retain public confidence and adequate vaccination coverage in the future. Psychological, social, and political factors also affect public trust in vaccines (190).

Is any threat that can be reduced by vaccines, worth the effort? In the book "Immunization –How vaccines became controversial", Stuart Blume claims that the transition from vaccine development based in the public sector, to the privatization of the vaccine industry, has given rise to a loss of faith in vaccination. Before, the only aim was to prevent the major life-threatening diseases, whereas the industry today is increasingly oriented to profit maximization, with the objective of convincing the world that there is a need for more and more vaccines (191).

According to the European Society for Paediatric Infectious Diseases, the reasons for introducing rotavirus vaccination in Europe is mainly the burden of disease (118), and deaths occurring from RVGE in previously healthy infants are not acceptable given the high standard of European healthcare. It is easier to defend introduction of rotavirus vaccines in countries with high rotavirus mortality rates. In low-mortality/high-income countries, rotavirus infection is usually perceived as a mild disease. Some believe that rotavirus vaccine is not needed in Norway, because of the high-quality and accessible healthcare, and potential side-effects of the vaccine. However, without treatment rotavirus infection is a severe disease also in Norway. Rotavirus affects all children. Other control measures have limited effect on the burden. Also, Norwegian paediatricians tell about severe dehydrated children, requiring urgent appropriate care to prevent death. Yet, it is important to keep in mind that public confidence in the vaccination program as a whole is vulnerable and not to be taken for granted.

Even comparable settings, like the Nordic countries, with similar infrastructure, healthcare services, disease burden and health economic evaluations, arrive at different decisions. Other factors than the scientific evidence may also influence the decision, like national priorities and traditions (185).

Since June 2019, the vaccine recommendation process in Norway are guided by a new system, including a standardised and transparent assessment of available evidence. Recommendations are

developed by the Scientific Reference Group for National Immunisation Programs, which also serves as a National Immunisation Technical Advisory Group (NITAG) reporting to the NIPH (192).

2 Aims and objectives

The overall aim of this project was to evaluate the introduction of rotavirus vaccination in the Norwegian childhood immunization program.

The specific aims for each study were:

1. (Paper I) Assess the burden of AGE and RVGE among Norwegian children before the introduction of rotavirus vaccination in the national immunization program, with specific objectives as follows:
    - Estimate the incidence of AGE- and RVGE-related primary care and hospital contacts among children <5 years of age
    - Estimate the rotavirus proportions among AGE-related primary care and hospital contacts in children <5 years of age
    - Estimate the mortality of RVGE among children <5 years of age
    - Describe RVGE cases by age, gender, geography, season and disease severity
2. (Paper II) Assess the risk of intussusception associated with rotavirus vaccination in Norway against the benefits of the program, under current and extended age limits, with specific objectives as follows:
    - Validate intussusception coded hospitalizations among children <2 years of age during the pre-vaccine period
    - Estimate the baseline incidence and age distribution of intussusception among children <2 years of age
    - Estimate the number of expected vaccine-associated intussusception cases under current age limits for vaccine administration
    - Estimate the number of expected vaccine-associated intussusception cases under extended age limits for vaccine administration
    - Compare the number of expected vaccine-associated intussusception cases with the number of expected rotavirus cases averted by vaccination
3. (Paper III) Assess the impact of the monovalent rotavirus vaccine under routine use in Norway, with specific objectives as follows:
    - Estimate effectiveness of the rotavirus vaccine against laboratory-confirmed rotavirus hospitalization in children <5 years of age
    - Estimate age-specific rate reductions in AGE episodes in primary and hospital care in the post-vaccine period compared with the pre-vaccine years

3 Materials and methods

This section describes the data sources and methods that we used for this work. More details about the methods for each of the studies are described in the papers. The potential and limitations of the chosen methods are discussed in the discussion section.

3.1 An overview of the studies

Paper	Study design/type	Data sources	Inclusion of study participants	Epidemiological measures
Paper I. Burden of rotavirus disease in Norway – Using national registries for public health research	a. Descriptive registry-based study	a. Health registries	a. Population-based and retrospective	a. AGE and RVGE incidence and RVGE specific mortality (prior to vaccine introduction)
	b. Descriptive surveillance study	b. Tailor-made hospital-based surveillance system	b. Prospective in selected hospitals	b. Rotavirus proportion among AGE hospitalizations (prior to vaccine introduction)
Paper II. Intussusception among Norwegian children: What to expect after introduction of rotavirus vaccination?	Descriptive and predictive registry-based study	Health registries (data validated against medical records	Population-based and retrospective	-Intussusception incidence (prior to vaccine introduction) -Annual number of predicted vaccine-associated intussusception cases -Annual number of predicted rotavirus episodes averted by vaccination
Paper III. Impact of the rotavirus vaccination program in Norway after four years with high coverage	a. Case-control study	a. Tailor-made hospital-based surveillance system	a. Cases and controls: consecutively	a. Rotavirus vaccine effectiveness (=1 – odds ratio)
	b. Etiologic time-trend study	b. Health registries	b. Population-based and retrospective	b. AGE incidence rate ratio

Table 1. Overview of the study design/type, data sources, inclusion and epidemiological measures

3.2 Setting

This work was carried out in Norway, a country with 5.3 million inhabitants (193). According to Statistics Norway, the population has increased substantially the last decades due to immigration, relatively high fertility and few people in the elderly age groups (194). Population growth peaked in 2011 and 2012, but has since then declined sharply. The population in Norway is getting older. While only about 8% of the population was aged 67 and more in 1950, today it is almost 15%. The fertility rate has declined during recent years, and is now at a record low (1.6 in 2018). 6% of the population is <5 years of age. 92% of all children aged 1–5 are in kindergarten. The under-five mortality rate of Norway has declined gradually during the last decades, to 2.6 deaths per 1,000 live births in 2018.

In Norway, public health services are divided into primary and specialized healthcare. Primary care deals with general health issues and is provided locally by general practitioners (GP), out-of-hours emergency primary care (EPC) providers, public health clinics and the school health service. Specialized healthcare provides specialists and hospital care. All residents in Norway are entitled to be registered as a patient with a primary doctor (GP). Appointments with specialists and hospitals require referral from a primary healthcare provider. Most hospitals in Norway are public hospitals, funded and owned by the state through hospital trusts. A small number of hospitals are privately owned, but most of these are also publicly funded through contracts with the hospital trusts.

Vaccines provided through the childhood immunization program are voluntary and provided free of charge in public health clinics and schools, to children and adolescents up to the age of 20. The vast majority receive the vaccines recommended through the program. In December 2018, the national coverage for rotavirus vaccine was 95% for one dose and 93% for two doses (195). The first dose of measles, mumps and rubella (MMR) vaccine is usually given at 15 months, without an upper age limit, and 96% of Norwegian children receive the first dose by two years of age.

Data collection for this work started in the beginning of 2014, just after the Ministry of Health and Care Services decided to introduce rotavirus vaccine in the national childhood immunization program. The studies are based at the NIPH. For the sentinel surveillance study, researchers from the NIPH collaborated with healthcare personnel from paediatric and microbiological departments at five major hospitals in Norway. The NIPH is a government agency and research institute under the Ministry of Health and Care Services, which monitors the health of the population and works to improve general health through health promotion and prevention of disease. Control and prevention of communicable diseases are important tasks for the institute, and the main activities include surveillance of infectious diseases, recommendations and programs for vaccination and vaccine supply, monitoring vaccination coverage and adverse events following immunization.

3.3 Data sources

To ascertain the baseline disease burden of AGE and RVGE in Norway, the impact of the rotavirus vaccine after introduction, and the baseline intussusception rates, we collected data from several health registries and databases. We also performed active rotavirus surveillance at selected hospitals. See table 1 for a general overview of the data sources. In the following sections, all the data sources are described more in depth.

3.3.1 Registry-based data

Primary care

The Norwegian Health Economics Administration (HELFO) is responsible for control and payment of reimbursement claims from general practitioners (GP) and out-of-hours emergency primary care (EPC) providers, and administers the national database for the reimbursement of health expenses (KUHR) (196). For all claims, HELFO collects information on provider type (GP, EPC), patient (personal ID number, age, sex, place of residence), type of contact (ordinary consultation, home visit, phone consultations etc.), and diagnoses coded with the second edition of the International Classification for Primary Care (ICPC-2). Data are collected regularly (usually every second week). The personal ID number have been included only since 2006. The completeness of data is expected to be high. Misclassification of health conditions in this database may however occur, as the ICPC system uses codes for both symptoms and specific diseases, and reimbursement is not dependent on the ICPC codes reported.

We examined all primary care (GP and EPC) consultations for Norwegian children <5 years old with the ICPC-2 codes corresponding to gastroenteritis as the main diagnosis during the period from January 1st 2009 to December 31st 2013 for **paper I** and from January 1st 2009 until December 31st 2018 for **paper III**. Consultations were selected using the following ICPC-2 codes:

- D10 (Vomiting)
- D11 (Diarrhoea)
- D70 (Gastrointestinal infection)
- D73 (Gastroenteritis, presumed infectious)

The following variables were extracted for each consultation, in addition to the ICPC code: personal ID number, date of birth, sex, type of healthcare provider (GP, EPC), type of contact, place of residence (county) and date of consultation.

Hospital admissions

The Norwegian Patient Registry (NPR) is a national database of all hospitalizations occurring in public and private hospitals in Norway (155). Reporting of data to the registry from somatic hospitals is considered to be complete since 1990. The information recorded for each hospitalized patient includes type of contact (inpatient and outpatient, where outpatient usually are defined as staying in the hospital for less than five hours), name of the hospital, patient information (personal ID number, age, sex, place of residence), date of admission and discharge, outcome (dead or alive), procedure codes and diagnoses coded according to the 10th revision of the International Classification of Diseases (ICD). Personal ID number is available for each patient since 2008. Data are reported regularly (at least every four month). The completeness of data is expected to be high. The ICD codes form the basis of reimbursement.

We examined all hospital admissions in Norwegian children <5 years old with the ICD-10 codes corresponding to AGE of bacterial, parasitic, viral or presumed infectious aetiology as the primary diagnosis (defined as the main reason for the hospital treatment), including the specific code for rotavirus infection, during the period from January 1st 2009 to December 31st 2013 for **paper I** and from January 1st 2009 until December 31st 2018 for **paper III**. Admissions were selected using the following ICD-10 codes:

- A080 (Rotavirus enteritis)
- A081, A082 (Norovirus and adenovirus enteritis)
- A083-A084 (Other or unspecified viral enteritis)
- A000-A059 (Bacterial enteritis)
- A060-A079 (Parasitic enteritis)
- A085, A090, A099 (Other, presumed infectious enteritis)

We also selected admissions with the ICD-10 dehydration code E86 as the main discharge diagnosis in combination with one of the gastroenteritis codes as one of the secondary discharge diagnoses (defined as conditions that exist simultaneously with the main condition or develop during the treatment period, and must be taken into account or have consequences for patient management).

For each hospitalization, data was extracted on the patient's personal ID number, date of birth, sex, type of contact (inpatient or outpatient), outcome of hospitalization (dead or alive), place of residence (county) and admission and discharge dates.

For the rotavirus disease burden study (**paper I**) we linked the NPR and KUHR data to identify cases treated in both settings.

For the intussusception study (**paper II**), we selected hospital admissions in children <2 years of age during the period January 1999 to December 2017, with the ICD-10 code K56.1 for intussusception listed as any of the discharge diagnoses. Since NPR data reported after 2008 contain the personal ID, admissions during the period 2008-2013 could be linked to patients' hospital medical records. To avoid misclassification and over-estimation, NPR data were validated by review of the medical records for each patient. Information extracted from medical records included admission dates, symptoms, treatments and outcomes. Three study investigators (physicians) from the NIPH reviewed the medical records with support from a local paediatrician at each hospital. Two of the NIPH investigators reviewed each record to reduce observer bias. In case of doubt, we discussed until consensus was reached. Data were entered in a standardized form (Appendix I), and cases were categorized using the internationally accepted Brighton collaboration clinical case definition for intussusception (197).

Vaccination data

The Norwegian immunization registry (SYSVAK) is an electronic immunization registry that records an individual's vaccination status and the overall vaccination coverage (195, 198). The registry has been nationwide since 1995. Public health clinics and other health services that administer vaccines, are responsible for registration in SYSVAK. Registration is mandatory for all vaccines included in the childhood immunization program in Norway. The registry is run by the NIPH who annually sends reports to the municipal health services, including information on children that are incompletely vaccinated according to age, to ensure close follow-up of vaccination coverage and data quality. Information recorded includes the personal ID number, a specific code and name of each vaccine, date of vaccination for each dose, and name and location of the vaccinating unit (public health clinic, GP, etc.).

SYSVAK provided data on vaccination coverage for all three studies (**paper I, II and III**). Vaccination coverage is defined as the proportion of children within a birth cohort (all children residing in the country as of December 31st) who have been fully vaccinated, i.e. who have received all vaccine doses recommended according to the schedule. For the intussusception study (**paper II**), we extracted data on the numbers of vaccinated children by age in weeks in 2016. For the effectiveness study (**paper III**), data on rotavirus vaccination status for all cases and controls, including number of vaccine doses and dates of administration, were verified through linkage with SYSVAK.

Mortality

The national Cause of Death Registry covers all deaths in Norway (199). Physicians are required to complete a death certificate based on ICD codes. Norway implemented the 10th revision of ICD in 1996. The death certificates are run through a semi-automatic coding program which selects the underlying cause of death according to WHO rules. To assess AGE-related and rotavirus-related mortality for **paper I**, we examined data from the registry regarding all deaths in children <5 years of age reported during the period from January 1st 2000 to December 31st 2013 whose death certificates included AGE as the underlying cause of death, using the same ICD-10 codes as we did for hospital admissions in NPR. We also reviewed deaths in the NPR data.

Denominator data

Population data from Statistics Norway are used for denominators in all three sub-studies (**paper I, II and III**), to calculate the incidence of AGE, RVGE and intussusception (193). We used annual numbers of children per January 1st in each one-year age group. For the baseline intussusception rates per age in weeks (**paper II**) and the time series analysis of monthly counts of AGE cases (**paper III**), we assumed a constant birth rate throughout the year. However, usually the birth rates are slightly higher during the spring and summer months in Norway. We assume that this will have little effect on our results.

The denominator should equal the population that the cases come from. When we use national registries and databases to count disease episodes, we assume they cover the whole Norwegian population, and that they are complete.

We mainly present incidence as number of cases per 1,000 or 100,000 children in a specific age group per year. In **paper III**, we calculate the incidence of AGE in the same way, but express it as number of AGE cases per 1,000 person-years (incidence rate). We assume that the number of children January 1st each year in each one-year age group is at risk during the whole year and thereby each of these children contributes to one person-year at risk.

Community controls

For the effectiveness study, we selected controls from SYSVAK, which in this case was used as a source of community controls. Community controls should ideally be selected from a comprehensive population-based list, such as a birth registry, from the community in which the case resides. However, the use of immunization registries is shown to produce valid results in other studies of rotavirus vaccine effectiveness (34, 200). August 25th 2018, we extracted immunization data on all children born after September 1st 2014 that were registered in SYSVAK, lived in the catchment area

of the study hospitals and were ≥56 days of age at the extraction date (see further description on control selection in section 3.4.3).

3.3.2 Sentinel surveillance data

Non-specific ICD codes are widely used in hospitals. By only using data from the health registries, without supplementary information, it was not possible to estimate accurately the incidence estimate of RVGE hospitalizations. In February 2014, we established active sentinel surveillance and collected data on AGE prospectively at four hospitals: Oslo University Hospital Ullevål in Oslo, Stavanger University Hospital in Stavanger, St. Olavs University Hospital in Trondheim and Østfold Hospital in Fredrikstad. The catchment population for these hospitals covered around 31% of all Norwegian children <5 years of age. In December 2015, Akershus University Hospital joined the study, increasing the catchment population to around 40%.

To study AGE and RVGE hospitalizations before vaccine introduction, we collected data during February 2014–January 2015 (vaccination was introduced from mid-October 2014, and we assumed that the impact of vaccination before February 2015 were negligible). Surveillance continued until May 31st 2018 to evaluate the effectiveness of the vaccine through a case-control study during four post-introduction rotavirus seasons. We enrolled children <5 years of age admitted to hospital because of AGE within 10 days of illness onset. AGE was defined as diarrhoea (at least 3 loose stools in a 24-hour period) or vomiting (at least 1 episode in 24 hours). To exclude nosocomial transmitted rotavirus infections, we excluded cases hospitalized in the 48 hours before illness onset. All eligible children were identified by study personnel at the hospital and their parents were asked for permission to enrol the child in the study. We collected health data and stool samples from each patient within the first 48 hours of hospital admission. Surveillance was going night and day, seven days a week. A standard questionnaire (Appendix II) was filled out for each enrolled child based on information extracted from the medical record, including the personal ID number, date of birth, sex, symptoms, temperature, treatment, dates of admission and discharge, and exposures of interest such as attendance at day care, breast feeding pattern and immunodeficiency conditions. For the case-control study, cases were identified among children born on or after September 1st 2014 that tested positive for rotavirus by EIA and RT-PCR within 48 hours after admission and who were ≥56 days of age when admitted to hospital to ensure that they were eligible to receive at least one dose of rotavirus vaccine ≥14 days before admission to hospital. Test-negative controls were selected among children enrolled in the study born on or after September 1st 2014 and who were ≥56 days of age when admitted to hospital, but had a negative faecal specimen on rotavirus.

Viral sampling and laboratory analyses

In the sentinel study, bulk stool or rectal swabs were collected within the first 48 hours of hospital admission, and stored at +4^{o}C until they were tested at the hospital laboratory by commercial immunochromatographic tests (RIDA®QUICK, R-Biopharm, Darmstadt, Germany; VIKIA®, bioMérieux, Marcy l'Etoile, France) or multiplex real-time RT-PCR (RIDA®GENE, R-Biopharm, Darmstadt, Germany; Seegene, Seoul, South Korea). Specimens were then transferred to the national rotavirus reference laboratory at the NIPH for further testing. Samples were tested for rotavirus antigen by enzyme immunoassay (EIA) (RIDASCREEN® Rotavirus, R-Biopharm, Darmstadt, Germany) and then genotyped by multiplex semi-nested RT-PCR (51, 201) at the NIPH. Traditionally, bulk stool specimens are recommended for rotavirus detection but these may be challenging to obtain from young children. The diagnostic performance of rectal swabs compared to bulk stools for the detection of rotavirus by EIA and multiplex semi-nested RT-PCR, was assessed among 265 children enrolled in our study (202). Both EIA and multiplex semi-nested RT-PCR showed a high accuracy, and the conclusion was that rectal swab specimens are appropriate for rotavirus diagnosis and may be used as an alternate specimen type when collection of bulk stools is not feasible. Samples with genotype G1P[8] collected after vaccine introduction, were tested by Rotarix qRT-PCR for the presence of vaccine strain in stool specimens (203), and those who tested positive for the vaccine strain were excluded from the analysis of vaccine effectiveness.

3.4 Data analysis and statistics

As a measure of disease (AGE, RVGE and intussusception) occurrence and changes over time, we estimated annual incidence using the number of disease episodes as numerator and population data from Statistics Norway as the denominator (see the section on denominator data above).

In general, we used 95% confidence intervals (95% CI) to report the statistical inaccuracy of our estimations. Continuous data are presented as medians with range, or means with standard deviation.

3.4.1 Rotavirus disease burden

To assess the burden of rotavirus disease among children <5 years of age before vaccine introduction, we used retrospective data on all-cause AGE from NPR, KUHR and the national Cause of Death Registry, in combination with data from the sentinel surveillance. Two natural rotavirus infections usually provide protection against subsequent moderate-to-severe RVGE, and thus we

included only the first two AGE episodes occurring in the same child during the study period to estimate the RVGE incidence. To calculate the rates of RVGE episodes that required inpatient treatment or led to death, we used the Brandt method (204), applying the proportion of rotavirus-positive inpatient episodes identified during sentinel surveillance to the registry data. To estimate the rates of rotavirus outpatient and primary care episodes, we used the Winter Residual Excess (WRE) method (205), calculating the difference between numbers of gastroenteritis cases occurring during winter months and summer months. All encounters registered within a 10-day period in one patient were considered the same AGE episode. We applied the Vesikari severity scale to classify cases as severe (score of ≥11), moderate (7–10) or mild (<7) (164, 165).

3.4.2 Intussusception before and after rotavirus vaccination

When we calculated the intussusception incidence among children <2 years of age, we included only definite cases, or level 1 of diagnostic certainty according to the internationally accepted Brighton collaboration clinical case definition for intussusception (197), defined by one or more of the following criteria:

- Surgical criteria: The demonstration of invagination of the intestine at surgery
- Radiologic criteria: The demonstration of invagination of the intestine by either air or liquid contrast enema, or the demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on post reduction ultrasound
- Autopsy criteria: The demonstration of invagination of the intestine

Only the first episode of intussusception occurring in each child during the study period was included in the analyses. Others have found that approximately 9%–14% of infants experience recurrent intussusception episodes (206, 207). To predict the baseline intussusception rates by age in weeks (figure 3) we used a Poisson regression model fitted to weekly data on reported intussusception cases using a restricted cubic spline with 6 degrees of freedom to model the non-linear age association.

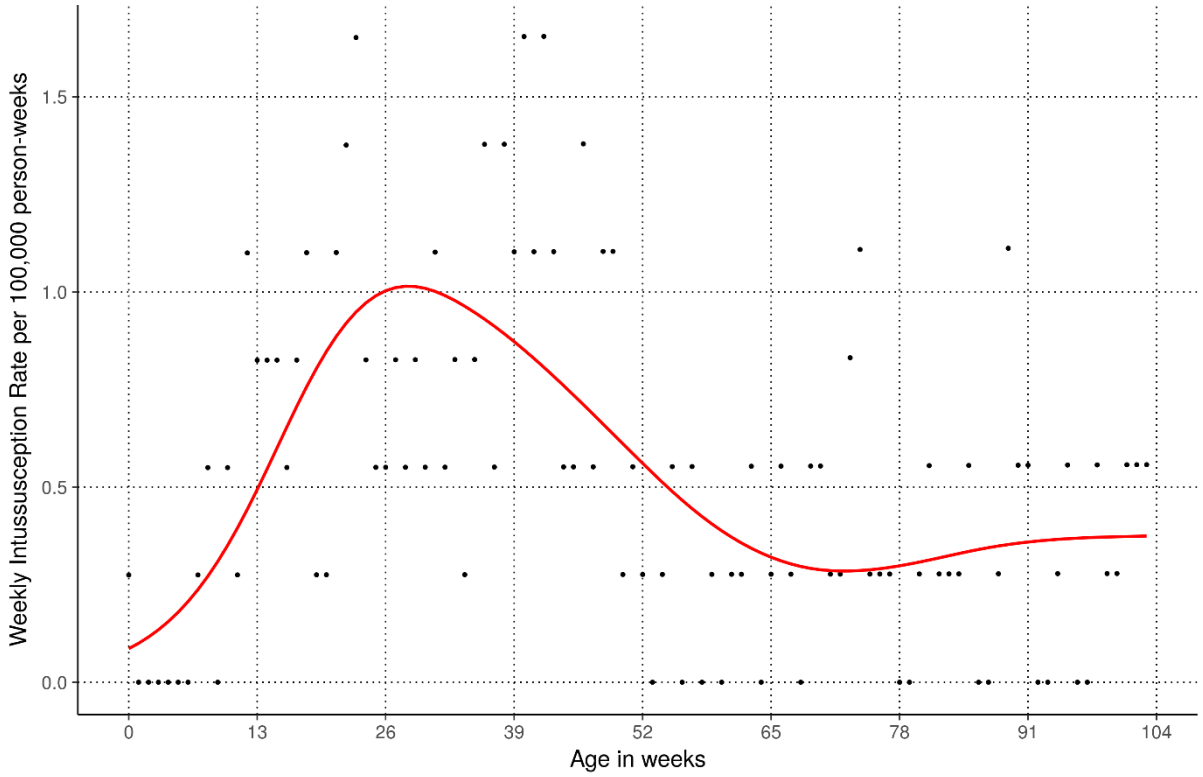


Figure 3. Observed and predicted weekly intussusception rates per 100,000 person-weeks for definite cases <2 years of age hospitalized in Norway, 2008-2013

These rates were used as baseline, when we estimated the expected number of vaccine-associated intussusception episodes during the post-vaccine years 2016-2019. First, we used the number of vaccinated children by age in weeks in 2016 and calculated the risk of naturally occurring intussusception episodes among these children 21 days post-vaccination. Then we applied relative risks for vaccine-associated intussusception 21 days post-vaccination, obtained from a meta-analysis combining results from England, Australia, Mexico, Brazil and Singapore (170). To estimate the number of vaccine-associated intussusception episodes occurring in each birth cohort during 2016-2019, we assumed stable baseline intussusception rates and stable vaccination coverage during the period. We used population data for each year from Statistics Norway (population numbers for 2018 and 2019 were predictions).

Furthermore, we estimated the expected numbers of vaccine-associated intussusception episodes that would occur if the age limits for vaccine administration were extended to 16 weeks of age for the first dose and 24 weeks for the second dose (the maximum age according to the manufacturer), and the vaccination coverage as a consequence increased. We used several scenarios to test the impact of different assumptions about the vaccine uptake and distribution of age at vaccination

under current and extended age limits. We also tested the impact of increasing the vaccine-associated intussusception risk to the upper bound of the confidence interval for the relative risk estimates, and decreasing the risk to the lower bound of the confidence interval. To assess the risk (excess intussusception episodes associated with rotavirus vaccination) against the benefits (averted RVGE episodes among children <5 years of age) of rotavirus vaccination in Norway, we used a dynamic rotavirus transmission model previously published by de Blasio et al. (103, 208), to estimate the number of rotavirus-related outcomes that would be averted by vaccination under current and extended age limits. The model was updated and run by Birgitte Freiesleben de Blasio, who fitted the model using data from our sentinel study from January 2014 to February 2015 and from a previous Norwegian sentinel study from March 2006 to February 2008 (94).

3.4.3 Effectiveness and impact of rotavirus vaccination

Vaccine effectiveness of rotavirus vaccination against hospital admission for rotavirus infection was calculated using case-control design with rotavirus positive cases recruited through the sentinel study after vaccine introduction and two different control groups: test-negative controls and community controls.

Cases were vaccine-eligible children aged ≥56 days at hospital admission (to ensure that they were old enough to have had the opportunity to receive one rotavirus vaccine dose at least 14 days before admission, allowing an immune response) who tested positive for rotavirus by both EIA and RT-PCR. Test-negative controls fulfilled the same criteria as the cases, except were negative for rotavirus by EIA and RT-PCR (See figure 4 for a flow chart of the inclusion of cases and test-negative controls). Community controls were vaccine-eligible children registered in SYSVAK on August 25th 2018, that lived in the catchment area of the study hospitals.

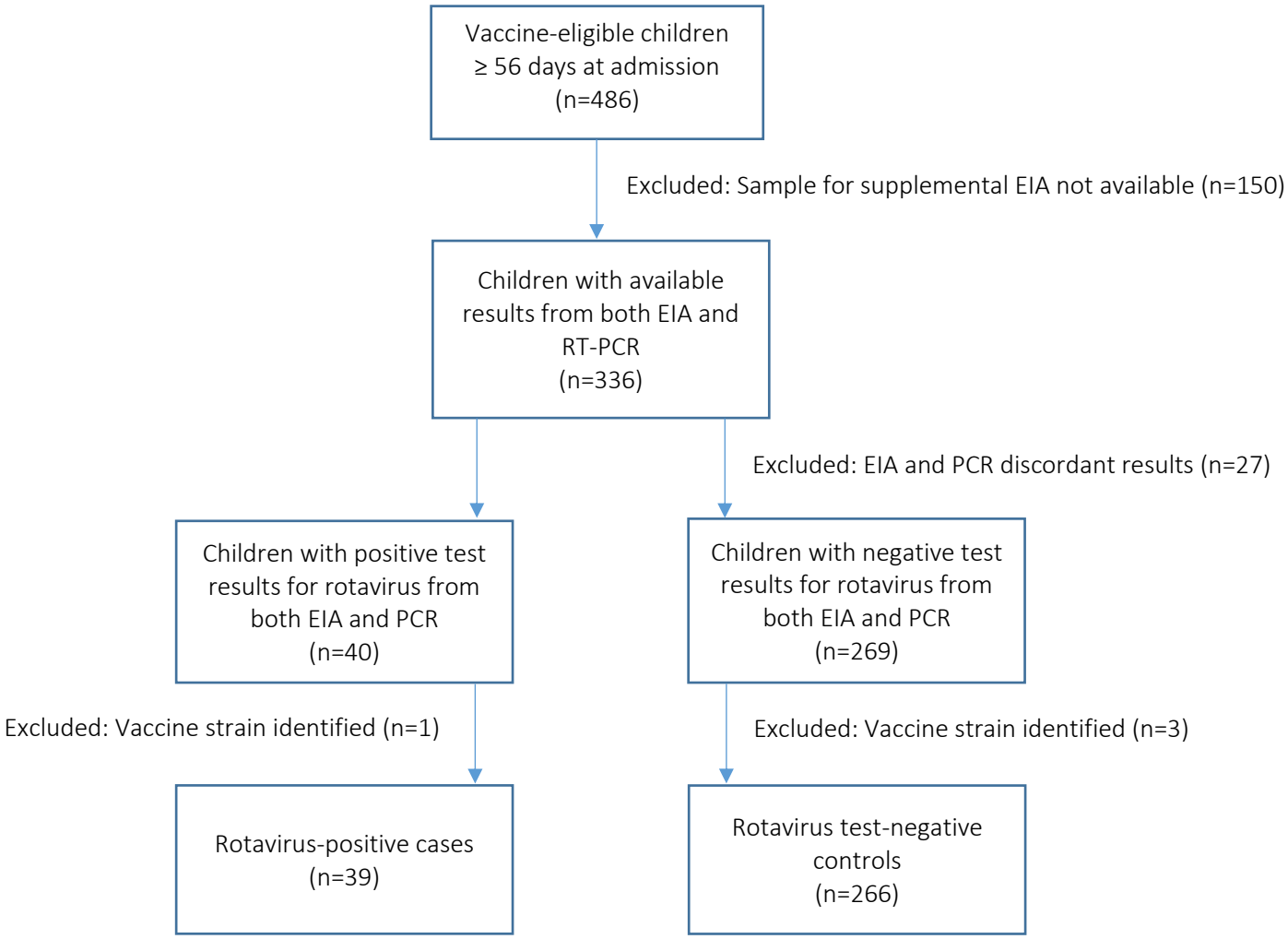


Figure 4. Inclusion of rotavirus positive cases and test-negative controls in the case-control study, Norway 2014-2018

Characteristics of cases and controls in the vaccine effectiveness study were compared using a Wilcoxon rank-sum test for continuous variables and Chi-square test for categorical variables. The reported statistical tests were two-sided, and the significance-level was set at $p < 0.05$.

Odds ratios (OR) (odds of being vaccinated among cases versus the odds of being vaccinated among controls) were calculated by using unconditional logistic regression, and by conditional logistic regression where we matched the cases to controls by age and (for test-negative controls only) admission date. We also adjusted for age and admission date in the analyses. We estimated the vaccine effectiveness against hospital admission for RVGE after two doses, using the formula (1 – OR) × 100%.

To study the impact of vaccine introduction, we used NPR and KUHR data during the years 2009-2018. We assumed that all encounters registered within a 10-day period in one patient were associated with the same AGE episode. We defined the pre-vaccine period as July 2009 to June 2015 and the post-vaccine period from July 2015 to June 2018. We analysed the data by rotavirus epidemiological year, defined as July through June, and conducted age-stratified time series analysis of monthly counts of AGE cases using negative binomial regression, using a similar approach as Thomas et al. (209). The impact was expressed as adjusted incidence rate ratios (IRR_a) compared to the pre-vaccine period.

Statistical analyses were performed using Stata (Stata Corp., College Station, TX, USA), Excel (Microsoft Corp., Redmond, WA, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

3.5 Ethical aspects

The Regional Committee for Medical and Health Research Ethics approved all the studies included in this thesis.

Collection and testing of stool samples for enteric agents and collection of data indicated on the sentinel surveillance study questionnaire (Appendix II) is part of standard medical practice for hospitalized paediatric patients with AGE. Parents were provided an information sheet about the study and given the opportunity to ask questions. For participation, the parents had to provide written informed consent. Consent could be withdrawn at any time. A study-specific biobank was established at the NIPH to store stool samples collected during the study. The samples can be retested and linked to data from the questionnaire and health registries. We have permission to store the stool samples until December 31st 2024, when they will be destroyed. For the registry studies we did not ask for consent. First, it was not feasible because of the high number of patients included. Second, it could have introduced selection bias. The researchers did not see the personal ID number when analysing the data. The Committee for Medical and Health Research Ethics emphasized that we should not collect new information about the individuals registered, only already collected data, thus the project entailed no direct disadvantages for the individuals. The Committee therefore granted exemption from the duty of confidentiality. In the intussusception study, only two researchers had access to each medical record for validation of the intussusception codes, and the data were de-identified immediately after the validation process. We followed data protection procedures of each hospital and the NIPH. To be able to achieve reliable estimates, we did

not seek consent for the validation among the parents of the children, which could have introduced a selection bias.

4 Summary of results

4.1 Rotavirus disease burden before vaccine introduction in Norway

When it was decided to introduce rotavirus vaccination into the Norwegian childhood immunization program, no routine surveillance of RVGE existed. To evaluate the rotavirus vaccination program, we found it important to set up a surveillance platform as soon as possible. **Paper I** presents data on all-cause AGE and RVGE from hospital sentinel surveillance during almost a year before vaccine introduction, in addition to national registry data from a longer pre-vaccine period. We found that before vaccine introduction (during the period 2009-2013), 114.5 (95% CI: 114.0-115.0) AGE episodes per 1,000 children <5 years old were treated in primary care annually. Equivalently, 11.8 (95% CI: 11.6–11.9) AGE episodes per 1,000 children were treated in hospital (inpatients and outpatients). 4.5% of the primary care AGE cases were admitted to hospital within 10 days after hospital admission. Studying rotavirus specifically, we estimated that 30% of the AGE cases in primary care were attributable to rotavirus, while 42% of AGE cases treated as outpatients in hospital were rotavirus-related. Rotavirus was detected in 65% of all collected stool samples (N=318) from inpatients included in the sentinel surveillance. Applying these proportions on the AGE results, we estimated that 30.6 (95% CI: 30.3–30.8) RVGE episodes per 1,000 children <5 years old were treated in primary care each year, while in hospital 4.0 (95% CI: 4.0–4.2) RVGE episodes were treated as inpatients and 2.3 (95% CI: 2.2–2.3) as outpatients per 1,000 children <5 years old annually. The pre-vaccine mortality was 0.17 (95% CI: 0.04–0.29) deaths per 100,000 children, corresponding to 1 death every second year in Norway.

In primary care the highest AGE rates were observed in the northern part of Norway while the lowest rates were in the west. For hospital admissions it was the opposite, with lower rates in the north and higher in the west.

The 207 rotavirus positive inpatients included in the pre-vaccine sentinel surveillance had a median age of 15 months, with children aged <12 months of age accounting for 30%, and children aged 12–23 months old representing 44% of the cases. In the registry data the median age for all-cause AGE cases was 19 months (IQR: 12–31) in primary care and 17 months (IQR: 10-28) in hospital.

Slightly more males were treated for AGE in both primary (male: female ratio 1.14: 1) and hospital (male: female ratio 1.12: 1). In the sentinel study the ratio was 1.28: 1.

The mean Vesikari score among rotavirus positive patients included in the sentinel study in the pre-vaccine period was 13.4 (SD: 2.5), with 87.8% being classified as severe compared with 61.9% among rotavirus-negative patients. The number of rotavirus cases increased during the period December to

May. The same pattern was seen in the registry data, both for all-cause AGE cases in primary care and for hospitalizations coded as rotavirus, other viral and presumed infectious gastroenteritis.

4.2 Rotavirus vaccine-related intussusception among Norwegian children

To detect and assess rare adverse events, such as intussusception, baseline incidence estimates are critical. In **paper II** we present validated baseline intussusception data from Norway. During 1999-2017, 1,512 admissions among children <2 years of age (annual mean 80, range 42–134) were registered in NPR with the intussusception code K56.1. During the 19 years, the annual number of admissions decreased, from 134 in 1999 to 42 in 2017. During the pre-vaccine period of 2008–2013, we found 267 children <2 years of age with an intussusception-coded hospitalization. 195 (73%) of these were defined as intussusception level 1 (definite) according to the Brighton Collaboration Clinical Case Definition. The mean incidence of definite cases was 26.7 (95% CI: 23.1–30.6) cases/year per 100,000 children <2 years and 37.1 (95% CI: 31.2–43.8) cases/year per 100,000 children <1 year of age. The median age of the definite cases <2 years was 9.3 (IQR: 5.6–15.1) months with a peak at 6–7 months of age (see also figure 3 in section 3.4.2). Only four of the cases were <2 months old.

We found that under current age restrictions for rotavirus vaccine administration in Norway, 1.1 (95% CI: 0.5–2.1) vaccine-associated intussusception cases could be expected per 100,000 vaccinees after the first dose, and 1.3 (95% CI: 0.5–2.4) cases per 100,000 after the second dose, in the 2016 birth cohort. This corresponds to a combined estimate of 1.3 (95% CI: 0.7–2.0) intussusception cases in the entire cohort. If the age limits for vaccine administration in Norway were extended to 16 weeks of age for the first dose and 24 weeks for the second dose, we assumed that the vaccination coverage would increase to 96% for one dose and 91% for two doses. With a uniform distribution of age at vaccination (a conservative assumption), 2.2 (95% CI: 1.2-3.5) vaccine-associated intussusception cases were estimated to occur in the 2016 cohort, or less than one additional case compared to the current situation.

Additional scenario analyses gave small differences in the number of expected vaccine-associated intussusception cases, and demonstrated that the estimates were more sensitive to increase in age at vaccination than to an increased vaccination coverage.

Comparing our intussusception data with the modelled number of rotavirus-related outcomes, we found that 1,768 rotavirus hospitalizations (inpatient and outpatient contacts) would be averted per year among children <5 years old under current age limits, meaning that 1,360 rotavirus hospitalizations are averted for each intussusception case associated with the vaccine. Extending the

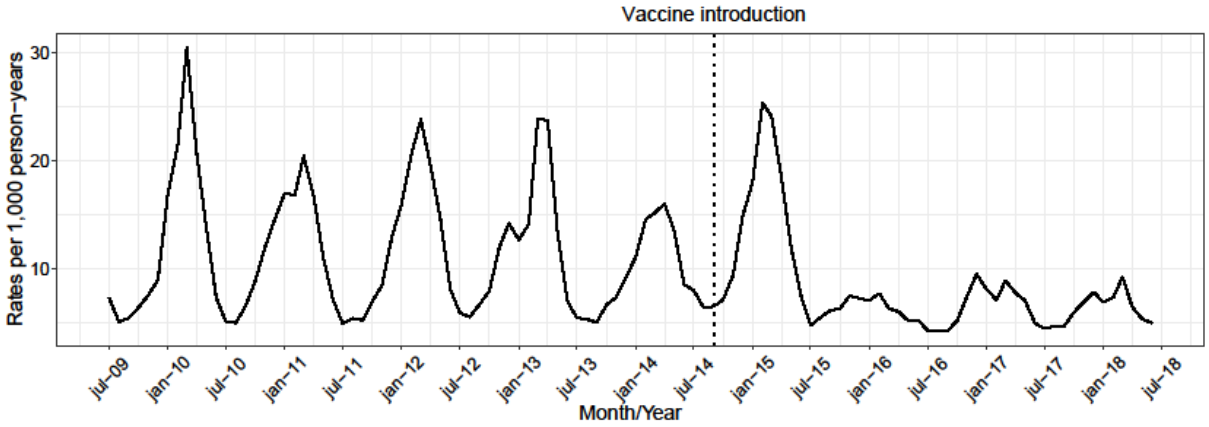
age limits as described above would lead to 98 additional rotavirus hospitalizations averted, and 848 rotavirus hospitalizations averted for each intussusception case.

4.3 Impact and effectiveness of the rotavirus vaccine in Norway

In paper II we used modelled data on rotavirus-related outcomes after vaccine introduction to compare with the estimates on vaccine-associated intussusception. For **paper III**, we collected real data on all-cause AGE and RVGE among children <5 years of age from active hospital surveillance and national health registries, to study the effectiveness and impact of the rotavirus vaccination program in Norway. Overall, we enrolled 39 rotavirus-positive cases and 266 rotavirus-negative AGE controls from the sentinel surveillance for the case-control study. We also collected 113,429 community controls from SYSVAK. Using test-negative controls, we estimated a two-dose vaccine effectiveness of 76% (95% CI: 34-91%) against hospital admission for RVGE among vaccine-eligible children. Restricting the analysis to children <18 months of age, the vaccine effectiveness was 83% (95% CI: 35-96%). In the matched analysis the overall vaccine effectiveness of two vaccine doses was 78% (95% CI: 20-94%). Using community controls, the effectiveness was 75% (95% CI: 44-88%), with similar results in the matched analysis.

Analysing national registry data, we found that the rates of hospital episodes decreased by 45% (IRRa 0.55; 95% CI: 0.49-0.61; $p<0.05$) in children <5 years of age overall. Rates among children <1 year of age decreased by 40% (IRRa 0.60; 95% CI: 0.53-0.69; $p<0.05$), and among children between 4 and 5 years of age (vaccine-ineligible during the whole period) the reduction was 37% (IRRa 0.63; 95% CI: 0.52-0.78; $p>0.05$). The overall rates of all-cause AGE episodes among children <5 years of age in primary care did not drop significantly; the rates were reduced by 10% (IRRa 0.90; 95% CI: 0.85-0.96; $p=0.12$) in the post-vaccine period compared with the pre-vaccine period. In the first post-vaccine epidemiological year, 2015-2016, the primary care rates decreased by 13% overall (IRRa 0.87; 95% CI: 0.82-0.93; $p<0.05$), with significant reductions in all age-cohorts. We found a clear winter seasonality that persisted into the post-vaccine years.

a)



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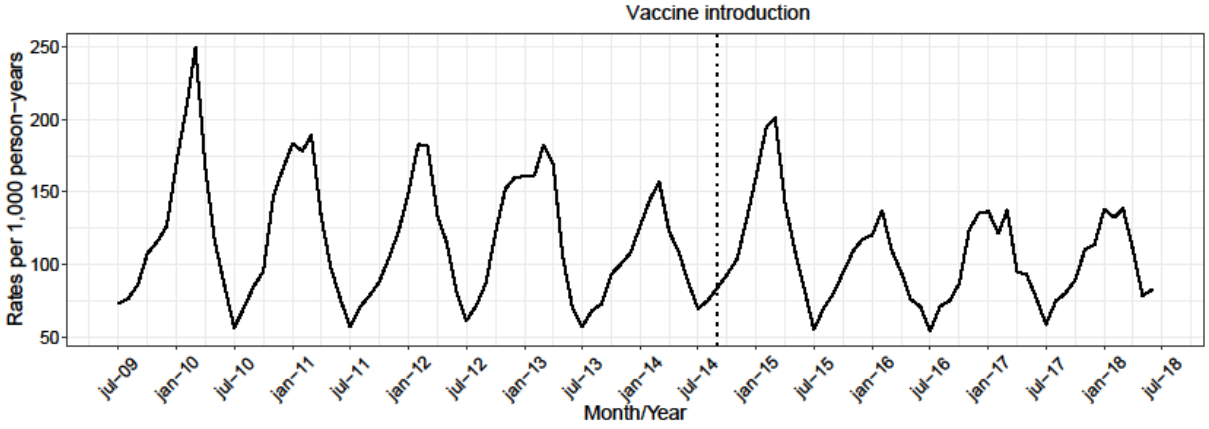

Figure 5. Incidence of AGE cases in a) hospital and b) primary care per 1,000 person-years, Norway July 2009-June 2018

5 Discussion

In this chapter, I will discuss the overall results of the thesis, and the methods used. I will consider the impact and implications of the studies and discuss future perspectives. Parts of the discussion will be more comprehensive than the discussion sections in the papers, but there will also be considerable overlap.

5.1 Discussion of the results

5.1.1 The burden of rotavirus disease –was there really a need for the vaccine in Norway?

In order to establish a baseline for the evaluation of the rotavirus vaccine impact in Norway, we wanted to determine estimates of the rotavirus disease burden prior to the introduction of the vaccine in the national childhood immunization program. RVGE stopped being a notifiable disease in 1991, but a national assessment of the burden of disease associated with rotavirus was published in 2009 (94). In paper I, we conclude that the burden of all-cause AGE and RVGE in Norway was substantial before the vaccine was introduced. Our RVGE hospitalization estimates are higher than in the previous study (94), which may reflect natural trends and changes in hospital referral patterns, but also improved study design (see section 5.2.2 on methodological considerations). The rates are comparable with those reported from our neighbouring countries Denmark (210) and Sweden (89). In other high-income settings, rates vary (88, 211, 212), within the range of what might be caused by varying organization of healthcare services, referral patterns, study inclusion criteria, laboratory methods and other technicalities. Nordic countries, that usually are comparable in terms of demography and healthcare, and also have a quite similar decision-making process for vaccine introduction, have reached different decisions regarding the introduction of rotavirus vaccine. Finland introduced the vaccine into their national immunization program already in 2009, Norway in 2014 and Sweden in 2019, whilst Denmark has decided not to introduce it (185). There are different opinions about whether the consequences of the disease are severe enough to justify universal vaccination of healthy children. Denmark considered low mortality and benign course as an argument against the vaccine, whereas the other countries consider the burden to be high enough to justify its introduction. See section 1.2.4 for further description on the decision-making process in Norway.

The proportion among inpatients with AGE that had a positive diagnosis for rotavirus in our sentinel surveillance (65%) was high. Other high-income countries report proportions from 31% to 69% (88, 89, 210, 211, 213, 214) in inpatient hospital settings, while the proportions in emergency departments and primary care settings in general are lower (88, 213, 214), in keeping with our

findings. The proportion of AGE hospitalizations attributable to rotavirus increases with increasing income level (77). Studies also suggest that the proportion of AGE deaths or severe AGE attributable to rotavirus has increased over time (65, 215-218). This is possibly because the virus is transmitted from person to person and more difficult to control through improvements in hygiene and sanitation, compared to bacterial and parasitic agents, which are most often transmitted through contaminated food or water (65). Also, no specific treatment is available for rotavirus, and oral rehydration therapy can be more difficult to administer in children with severe vomiting, a common symptom in children (65). Norway is a country ranked above the average in income, wealth and health status (219), and has a low incidence of food- and waterborne infections in general (220), making the high rotavirus proportion plausible. The lower proportions among hospital outpatients (42%) and in primary care (30%) show that other enteric agents contribute more to the burden of less severe AGE than in the inpatient setting.

Our mortality estimate is in line with other studies in high-income/low-mortality countries (66, 185).

Data from our sentinel surveillance differ from some high-income countries with respect to the age distribution. The majority of our rotavirus cases are between 1 and 2 years of age, whereas some studies report higher rates among children <1 year of age (221, 222), albeit with few cases in those under three months old. Data from a study in the US show the highest rate among children 6–11 months (223). In Sweden, Denmark and Finland, the age distribution is comparable to ours (89, 91, 210, 224). Rotavirus infection occurs at a younger age in low-income countries than in high-income countries (6, 83). Several factors contribute to the different age distributions. The low rates below 3 months of age is probably because of passive maternal antibodies transferred across the placenta. Breast-feeding traditions vary, and as a consequence also the duration of the protection from maternal antibodies transferred through breast milk. Norway has an extensive breastfeeding tradition; initiation rates are almost universal (98%), and duration of breastfeeding is high, with 65-71% exclusively breastfed children at 3 months of age (225, 226). Another factor can be the age at which children usually attend day-care, and thereby will have increased risk of being exposed to rotavirus. In Norway, parental leave is long, and very few children start attending day-care before they turn one year old (193). The younger age for the severe cases in high-mortality settings can be due to a higher force of infection or age-specific differences in management of RVGE (83).

A review of health economic evaluations worldwide up to 2008 could not conclude whether universal rotavirus vaccination is cost-effective or not (227). In 2018, a study by Bruijning-Verhagen et al. conducted in the Netherlands, concluded that targeted rotavirus vaccination of infants with medical risk conditions (including prematurity, low birth weight, and severe congenital pathology) was a cost-

saving strategy and had the most favourable risk-benefit ratio (228). The same year it was decided to offer vaccination to infants belonging to risk groups in the Netherlands (229). Before implementation in Norway, the Norwegian Research Centre for Health Services conducted an economic analysis and found that universal rotavirus vaccination was cost-effective from a societal perspective, but not from a healthcare perspective (183). The model was based on several assumptions, and the vaccine price was one of the parameters with highest impact on the result, and associated with considerable uncertainty. Vaccines included in the national immunization program in Norway are procured through a governmental tender, and the price of program vaccines are in general lower than the pharmacies' retail price, but the final price is secret. The baseline vaccine price used in the model was set to be 80% of the retail price. In the final recommendation, the NIPH concluded that 50% of the retail price was more likely, based on the experience from other countries that had included the vaccine in their immunization programs (182). With updated data, including data from our study, Edwards et al. found that the ongoing vaccination program was cost-effective from both a healthcare and a societal perspective (103).

5.1.2 Is a small increased intussusception risk acceptable, weighed against the benefits of vaccination?

Although large clinical trials before licensure of the current rotavirus vaccines showed no association with an increased risk of intussusception, post-licensure data from several settings published in 2013 and 2014, just around the time of the decision on rotavirus vaccination in Norway, suggested the possibility of a small increased risk of intussusception after rotavirus vaccination (167, 168, 171, 172). Our study can hopefully form a basis for the safety evaluation of the rotavirus vaccine in the immunization program in Norway. As we discuss in paper II, estimates of the baseline incidence of intussusception varies widely between different countries (161, 162, 169, 230-235), and in Europe the rates tend to have declined, and mortality is rare (162, 230, 233, 236), similar to what we find in our study. Differences by geography and time could be true differences, but the reported rates will also be influenced by varying healthcare utilization patterns, diagnostics and reporting practices. Studies also differ in their case definitions and methods for data collection. Country-specific baseline rates and awareness around the diagnosis, is essential for safety monitoring and assessment of safety signals after rotavirus vaccine introduction. Age-stratified incidence rates are important. Our study was in line with others, showing a peak age for intussusception around age 5-7 months (161, 162, 233, 234, 237), well above the upper age limit for the second dose of rotavirus vaccination in Norway. The validation study showed that the ICD-10 code K56.1 had a relatively high positive predictive value (PPV) among children <2 years of age; 73% of the children with intussusception-

coded admissions had definite intussusception, 80% when probable cases were added, and 81% when possible cases were included. This is not as high as in the Swedish Patient Register (84% for definite cases and 87% including probable cases, among children <3 years of age) (238), or in Switzerland (84% for definite cases; 89% among children <1 year of age) (239). In a health administrative database in Canada, the PPV was 72% for all diagnostic levels (240). Divergent results underscore the importance of knowing the validity of the data in the assessment of intussusception signals arising after rotavirus vaccination.

Our analysis suggests that under the current situation, 1.3 intussusception cases could be expected in association to rotavirus vaccination in the 2016 birth cohort, and that 1,360 rotavirus hospitalizations would be averted for each vaccine-associated intussusception case. A risk-benefit analysis from England reported that vaccination would prevent 375 rotavirus hospitalizations for each additional intussusception admission and 88 rotavirus deaths for each intussusception death caused by the vaccine (241), while a US study estimated the prevention of 1,093 rotavirus admissions for each additional intussusception admission (242), which was closer to our estimate. In France, it was reported that for every intussusception hospitalization and every intussusception death caused by vaccination, 1,624 rotavirus hospitalizations and 743 deaths were prevented by vaccination, respectively (243), while another French study reported a benefit-risk ratio of 214 RVGE hospitalizations prevented for every additional intussusception hospitalization, and 273 RVGE related deaths prevented for each additional intussusception death (244). Most other studies compare RVGE deaths with intussusception deaths. Our data indicate that Norway rarely experience deaths from these diseases and therefore we use hospitalizations as a proxy for severe disease course. The number of both RVGE and intussusception deaths in countries with low mortality will easily be influenced by other factors.

Even with our most pessimistic risk assumption (upper bound of the 95% CI of intussusception risk ratio), there would only be 2.4 excess intussusception hospitalizations under the current age restrictions, giving 737 averted rotavirus hospitalizations for one intussusception case.

Our analyses highlight the value of vaccinating early. The risk of intussusception is assumed to be relative to the baseline incidence, which favours early vaccination, avoiding the peak baseline age for intussusception. In low-income countries RVGE occurs early in life, and a vaccine administered at birth will also have the potential to prevent more cases. A neonatal rotavirus vaccine (RV3-BB) based on a rotavirus strain that was adapted to the new-born gut, was evaluated in a phase IIb immunogenicity and efficacy study, where the first dose was administered at the age of 0-5 days, with very promising results (245).

As mentioned in the introduction, there is still some doubt whether rotavirus vaccination really is associated with an elevated overall risk of intussusception among neonates or infants, or whether rotavirus vaccination may trigger intussusception that would have occurred anyway in the same child.

Even if the risk-benefit ratio increases with extension of the age limits, it is still largely in favour of the vaccine. Yet, given other concerns, the results may not be considered favourable enough to change the recommended age restrictions in Norway. The benefits of rotavirus vaccination and risk of intussusception are not directly comparable. An adverse event caused by an intervention such as vaccination will most likely be perceived more negatively than a condition caused by a failure to intervene.

5.1.3 Is the rotavirus vaccine effective under routine use in Norway, and does it have an impact on the epidemiology?

Rotavirus vaccines have been in use worldwide for more than a decade, and an increasing amount of published data demonstrate high vaccine effectiveness of both RV5 and RV1 in high-income countries, lasting during the first few years of life (33, 34, 102, 128, 136-139, 153, 246-251). Our study shows that two doses with RV1 is effective in routine use also in Norway. Our vaccine effectiveness estimates are in the lower range of what others have found, but our sample size was small, leading to effectiveness estimates with wide confidence intervals. Only one of the 39 cases included in our study were partially vaccinated, so we could not analyse the one-dose effectiveness separately. In the meta-analysis of Pindyck et al. on data from the US during 2006 to 2017, partial RV5 series was shown to be effective (pooled effectiveness, 81%; 95% CI: 75–85%) but had a comparably lower effectiveness than a full series (102), similar to what other studies have found for both RV1 and RV5 (138, 154-156). High effectiveness of partial vaccination is of importance, given the age limits leading to a lower full-dose coverage than the other vaccines in the childhood immunization program.

By looking at the graph showing AGE episodes in hospital care during the years 2009-2018 (figure 5 a), we see the impact of rotavirus vaccination since its introduction in 2014. Our analyses show significant decreases in AGE hospitalization rates among children <5 years of age after vaccine introduction. This was expected, given the large amount of studies from all over the world showing similar results (102, 129, 142, 143). It is nevertheless worth to study the impact at country level, and also whether primary care show similar trends. Evaluation of the impact of rotavirus vaccination has in most studies focused on hospital care, and the impact on primary care is less studied. In our

primary care data, the reductions are less significant. Other studies show that the vaccine impact increases with increasing level of care (102, 146, 209, 252-254). We assume that primary care AGE contacts are caused by a wider panel of microbiological agents, giving milder disease not requiring hospital care, explaining the lower vaccine impact on the AGE burden in this setting. Also, the vaccine is presumably less effective against mild rotavirus disease (35, 255). There is the possibility of a vaccination program-induced shift from severe RVGE requiring hospitalization to milder RVGE treated in primary care.

Reductions among older children in vaccine-ineligible age groups suggest herd effect. Several studies indicate that there is a considerable indirect protective effect of rotavirus vaccination among unvaccinated children and adults (102, 130, 132, 133, 256). We plan future studies in Norway to provide more evidence on the herd immunity effect of the vaccination program.

5.2 Methodological considerations

5.2.1 Registry-based data in general

A strength of our studies is the utilization of the Norwegian population-based health registries, which collect data on all hospital and primary care contacts, causes of death, and vaccinations. Reporting to the registries is mandatory, and the data are likely to be nationally representative. An almost complete study population minimizes selection bias. The large sample size increases the statistical power, which makes studies of rare outcomes, like intussusception, possible. The Norwegian personal ID number enables us to count patients and not only encounters, and thereby identify patients with several healthcare encounters during one disease episode, and link between data sources. Limitations are that the registries contain only data collected in advance –for another reason (such as reimbursement) than the study objective, and provide a limited number of variables, hence necessary information may be unavailable or misclassified. Also, information on data quality is mostly lacking, and it is difficult to know whether a disease case is prevalent or incident. There may be varying coding practices between persons, departments, institutions and over time. Changes in admission practice can change register-based incidence rates. E.g. some hospitals have low-threshold outpatient child clinics, and as a consequence the hospital registry will include more mild disease episodes. Finally, when we use large registries, differences that are not important may become statistically significant, which make it important to carefully interpret small risks.

5.2.2 AGE and RVGE rates

Through improved methods, we update and strengthen the evidence from a previous study on baseline burden of rotavirus disease (94). Using hospital patient registry data, we include both inpatients and outpatients and those with the dehydration code on the main discharge diagnosis combined with a secondary AGE-diagnosis. In addition, we collected primary care data that was not available before. However, using registry data alone has several limitations. It is not routine practice to test all AGE patients for rotavirus, as the result will not alter the choice of treatment, and the rotavirus-diagnostic code will often not be used if the diagnosis is not laboratory-confirmed. To obtain better information about rotavirus hospitalizations, we conducted active, prospective surveillance at four (five from December 2015) sentinel hospitals. We applied the rotavirus proportion established in the sentinel surveillance before vaccine introduction to the hospital registry data, to estimate the annual incidence of rotavirus-associated inpatient hospitalizations (204). The pre-vaccine data from the sentinel study demonstrated a high rotavirus proportion (65%). We excluded AGE cases that did not fulfil the inclusion criteria, and applying this proportion on the all-cause AGE registry data, could have resulted in over- or under-estimation of the rotavirus burden. Using the Winter Residual Excess (WRE) method (205) (comparing the number of AGE cases during the year with the excess during the months when RVGE is most prevalent (December to May)) to calculate RVGE rates for outpatient and primary care contacts, could also have led to inaccurate estimates. If the rotavirus season is indistinct, the method would lead to under-estimation. The sentinel data show that RVGE to some degree occurs throughout the year, however mainly during December to May. On the other side, even if rotavirus is shown to be the main cause of AGE in children <5 years of age, we know that other AGE-agents (e.g. norovirus) giving disease in children, increase during the winter months (257, 258), hence the WRE method could over-estimate the rotavirus rates. Another limitation is that the results might be biased by geographical differences. The AGE hospitalization rates in the north of Norway was lower than in the other regions, while the primary care rates were highest in the north. An explanation may be that the travel distance to hospital in general is much longer in the less densely populated northern Norway. No hospitals in the north of Norway or from rural areas were included in the sentinel study, and the rotavirus proportion may not be representative for the whole country. The short pre-vaccine period in the sentinel study is also a limitation. Ideally, we would start the sentinel study more than a year before vaccine introduction, to capture the year-to-year variation in the incidence of RVGE. However, the previous rotavirus sentinel study established a rotavirus proportion of 63%, close to our estimate (94). Finally, possible selection bias due to incomplete recruitment of patients in the sentinel study could have influenced the results. We do not know the exact recruitment rate, and did not check for representativeness among the recruited patients.

Information about deaths due to AGE in Norway is limited. The Cause of Death Registry is based on the underlying cause of death, reported on the death certificate filled out by the physician that examines the deceased person. Such data are often not of adequate quality, with high use of unspecific codes for the underlying cause of death (259). We applied the rotavirus proportion from the sentinel study, which could be imprecise. If children die outside hospital, we would under-estimate mortality, whereas it is also plausible that severe AGE may be responsible for a higher proportion of AGE hospital admissions than AGE deaths, thus applying rotavirus proportions among hospitalizations to deaths could lead to over-estimation of rotavirus deaths. In general, deaths from RVGE are very rare in the Norwegian setting, and the low death rate is easily influenced by other factors. The experience of our collaborating paediatricians confirms the low estimated death rate, however RVGE as a comorbidity with other causes of death might contribute to mortality while not being the underlying cause of death registered in the Cause of Death Registry.

5.2.3 Baseline intussusception

A strength of our study is the use of comprehensive registry data, and the validation of 96% of all intussusception-coded hospital admissions in Norway during the study period 2008-2013 against the patients' medical records. Validation of intussusception diagnoses against the standardized case definitions from the Brighton collaboration has been described as a reliable method (260, 261). However, there were several limitations to our work. Intussusception rates derived from hospital discharge diagnoses alone have been shown to underestimate the true incidence (262), whereas others found no additional intussusception cases when they searched for possibly miscoded conditions (231). Obviously, the validation does not guarantee an accurate classification. It is a retrospective study, and we had to rely on and interpret the information in the medical records, which was of varying quality. When the two reviewers disagreed, we discussed until we reached consensus, sometimes in collaboration with the local hospital paediatrician. Another possible limitation was that we recorded missing variables as negative, which could lead to fewer confirmed intussusception cases (260). Also, we included only intussusception cases admitted to hospital. We might have lost cases with spontaneously resolved intussusception outside hospital or not diagnosed at the hospital, however the clinical significance of such cases is debatable (239). We did not describe or analyse our data by geography. As we saw in the study on rotavirus disease burden, the hospitalization rates in the north of Norway was lower than in the other regions, possibly caused by longer distances to hospital, which might influence the intussusception rates also.

5.2.4 Intussusception risk versus averted rotavirus outcomes

Given the small intussusception risk reported after rotavirus vaccination, and the small size of the Norwegian birth cohort (approx. 60,000), we decided to use pooled intussusception risk estimates for the monovalent rotavirus vaccine from a meta-analysis combining results from England, Australia, Mexico, Brazil and Singapore (170), applied on our baseline intussusception data during the 1–21 day period after the first and second dose of vaccination. Other researchers have used similar methods (241). We found it important to use experiences from other high-income settings, as we lack local data. However, there are some limitations with this method. The risk estimates are derived from countries with broader age limits than the Norwegian recommendations, hence our post-vaccination numbers could be over-estimated. Secondly, we only assessed the risk during the 21 days after vaccine administration, and did not account for a possible compensatory lower risk later in infancy, which some authors have suggested (176-179). Also, we could have included even more scenario analyses, including the assumption that the risk ratio would be higher outside the age window for vaccine administration. This study was performed before the data collection on rotavirus outcomes post-vaccination were finalized, and therefore we used a model developed and updated by de Blasio et al. (103, 208) to obtain the number of rotavirus-related outcomes that would be averted by the vaccine under current and extended age restrictions. The potential benefits resulting from herd protection were not included in the model, and might have led to under-estimation of the number of rotavirus-related health outcomes in the benefit-risk analysis. However, the importance of herd effect is uncertain, and it would be challenging to include it in the assessment.

5.2.5 Effectiveness and the two control groups

Norway rapidly achieved high vaccination coverage, which is good for the public health, however not ideal for the study. In general, a case-control study is most useful if the coverage is between 20% and 80% (119). If the coverage is very low or very high, unvaccinated persons tend to differ from the source population in ways that may be associated with the risk of disease, independent of vaccination. Our vaccine effectiveness estimates have wide confidence intervals. With such a small number of cases, we could also not assess effectiveness by genotypes, age groups or incomplete vaccination status. The number of controls was limited as well. With a low number of cases, we would ideally match with more than one or two test-negative controls per case, to achieve sufficient power. Nevertheless, both control groups (test-negative and community controls) and both matched and unmatched analyses gave similar effectiveness estimates, which strengthen the reliability of the results. A strength of the study is the use of SYSVAK to obtain reliable information about vaccination status, including accurate dates for vaccine administration, for both cases and controls. Also, using

laboratory-confirmed cases, precise inclusion and exclusion criteria for cases and controls and matching on age and admission date minimize biases. Matching on geography might have improved our results. We did not match on or control for potential confounders like socioeconomic status and access to medical care. It is possible that children with reduced access to healthcare or with parents that refuse to participate in the study, and thereby not included, may have less chances to receive the vaccine, which may result in an under-estimation of vaccine effectiveness when we use community controls (reducing the potential difference in vaccination rates between the cases and controls). One strength of the test-negative design is that it is believed to reduce confounding due to healthcare-seeking behaviour. We could have asked parents for the reason for their refusal, to characterize the group of non-responders. A strength with our study was that we distinguished wild-type infection from excreted vaccine virus, and excluded cases with the vaccine strain. Collection of clinical information allowed us to calculate severity scores, confirming that RVGE hospitalization (94% of the cases were classified as severe according to the Vesikari scoring system) is a relevant proxy for severe RVGE. On the other side, hospitalization is one of the criteria used in the scoring system, hence access to care can affect the score.

There are some limitations and assumptions we make when we use SYSVAK as a source of controls. Population-based lists, such as birth registries, in which the cases are included, can be used to randomly select potential controls (263). However, such lists should obviously be comprehensive, and the basis for the list should not be associated with receipt of vaccines (119), which is exactly what SYSVAK is. Though, SYSVAK captures 98% of the Norwegian child population (264), and vaccination registries are shown to be a suitable source for selection of controls in other studies of vaccine effectiveness (34, 200).

A comparison of the test-negative and traditional case-control study designs by Haber et al. concluded that with the high sensitivity and specificity of EIA tests used to diagnose rotavirus infections, and no evidence that the existing rotavirus vaccines affect the rates of non-rotavirus diarrhoea, using test-negative controls is convenient and reliable for estimation of rotavirus vaccine effectiveness (265). By requiring confirmation of the EIA result with RT-PCR, the risk of misclassification in our study is minimized. The use of test-negative controls is proven to be an efficient and cost-effective approach to estimate rotavirus vaccine effectiveness in several other studies (266-268).

5.2.6 Impact and time series analyses

In addition to the general strength of registry-based studies discussed in section 5.2.1, the multivariable analyses using pre-vaccination data over six years allowed us to control for underlying trends in AGE incidence and healthcare-seeking behaviour.

There are some limitations to consider. The impact study is ecological, and the decrease in AGE rates post-vaccination might be caused by other factors than vaccine introduction, such as testing and coding practices or natural variations in the rotavirus burden. Rotavirus testing and coding practices may change after vaccine introduction, influenced by the knowledge of changed epidemiology. However, all-cause AGE is a broad case-definition, allowing for variation in classification. Although the Norwegian health registries lack information about sociodemographic variables, we had the possibility and ethical approval to link the data to such information from Statistics Norway using the personal ID number, but this was not done because of limited time and resources. Hygiene behaviour, nutritional status and healthcare seeking are factors that might influence the exposure or the susceptibility to the virus, and the healthcare utilization.

5.3 Conclusion and future perspectives

5.3.1 Summary and conclusions

Firstly, this thesis describes the burden of RVGE before the rotavirus vaccine was introduced in the Norwegian childhood immunization program in 2014; both the incidence of severe episodes requiring hospital care, and cases treated in primary care. Rotavirus remained, just before vaccine introduction, the primary cause of severe AGE in children <5 years of age in Norway. The results of our study indicate that also in a high-income setting like Norway, deaths due to rotavirus infection do occur, but rarely. Intussusception, a potential adverse event of the rotavirus vaccine, was confirmed to be a rare disease among Norwegian children before vaccine introduction, and no deaths was registered in our data. Rotavirus vaccine was introduced under strict age limits to reduce the risk of this adverse event, and we estimated that 1,360 rotavirus hospitalizations would be averted for each intussusception case associated with the vaccine under the current situation, and that administering vaccines beyond the age limits would result in a marginal increase in intussusception cases. Since Norway achieved high vaccination coverage already during the first year after introduction, there were few rotavirus positive cases to include in the case-control study for estimation of the vaccine effectiveness. Still, our results indicate relatively high effectiveness. When we analysed the population-based national hospital registry, there was no doubt that routine vaccination of

Norwegian children has successfully reduced the incidence of severe AGE requiring hospital care, in the target group.

When this study was conducted, the decision on vaccine introduction in Norway was already made, but still today two thirds of European countries have not introduced the vaccine in their national immunization programs. Barriers to the introduction include low awareness of disease burden, perception of unfavourable cost-effectiveness, and potential safety concerns (35, 134). Introduction of rotavirus vaccination in Norway was an opportunity to generate solid scientific evidence on the baseline burden of rotavirus disease, and the benefits and risk of vaccine introduction, in a high-income European country.

Yet, in addition to scientific evidence, there are several other issues to consider in the decision-making process around vaccine introduction (see section 1.3). One important issue is how parents perceive potential benefits and risks of vaccinating their child. This perception could be totally different from how one would prioritize from a public health point of view. The potential for negative consequences of vaccine hesitancy on the vaccination coverage, not only for rotavirus vaccines, is large. Today, the vaccination coverage in the childhood immunization program in Norway is high for all vaccines, however there is a declining trend in many European countries, and we need to be aware of the vulnerable situation.

5.3.2 Implications

This work underscores the importance of continuous surveillance of the benefits and risks of rotavirus vaccination. Because the assessment of vaccine safety signals for intussusception after vaccine introduction are based on comparisons of observed versus expected incidence of events, accurate baseline incidence estimates are crucial. Our study will hopefully form an important basis of safety evaluation of the rotavirus vaccine in the immunization program in Norway, and may provide reassurance for the benefit of the vaccine introduction. As we see from the age distribution in our baseline data, intussusception episodes will occur following vaccine administration in some children, and may or may not be caused by the immunization. Parents need to be aware of the symptoms of this potentially severe adverse event, and seek immediately medical help if symptoms occur. The results of this study could support an extension of the age window for vaccine administration in Norway.

5.3.3 Future perspectives

High vaccination coverage will contribute to a continuous protection of the youngest and most vulnerable children. Further monitoring is vital to identify possible indirect effects beyond the protection of vaccinated children during their first five years of life. The burden of rotavirus disease among elderly is uncertain. In high-income countries like Norway, where the population is getting older and the use of biologic therapy with immunosuppressive effect is increasing, it is of interest to understand better the role rotavirus plays in the aetiology of AGE in adults. More research is also needed to draw conclusions on how socioeconomic factors may influence the impact of rotavirus vaccination, and Norway with its population-based registries is a well-suited setting for such evaluations. The greatest disease burden is however in low- and middle-income countries, and in these settings the currently licensed rotavirus vaccines demonstrate a lower effectiveness than in Norway and other high-income countries. Even if the impact is large because of the much higher baseline disease burden, these countries have a potential of substantial additional reductions in the incidence of severe RVGE. The major challenge in the future is how to expedite the development of rotavirus vaccines for use in countries where the morbidity and mortality of rotavirus disease greatly exceeds that in Norway. Of interest is the increasing evidence that histo-blood group antigen (HBGA) expression has a role in susceptibility to rotavirus disease, leading to interest in their role in vaccine response (6). Recent findings suggest that HBGAs affect the incidence of several entero-pathogens, and that studies measuring the impact of disease control interventions should adjust for the distribution of HBGA status in both the children and their mothers (269, 270). Differences in HBGA expression may be responsible for some of the differences in the level of protection for rotavirus vaccines in low-income versus high-income settings (271, 272). It is also important to study differences in susceptibility to infection versus susceptibility to clinical disease, and whether differences in intestinal microbiome composition can explain some of the differences in clinical presentation across populations based on HBGAs (270). Finally, further studies are needed to address how rotavirus infection contributes to non-gastrointestinal conditions such as type 1 diabetes mellitus and coeliac disease.

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Appendix I

TARMINVAGINASJON

1. Dagens dato

2. Pasientnr

3. Fødselsdato

4. Kjønn

○ mann ○ kvinne

5. Postnummer

6. Sykehus

7. Er barnet tidligere utredet for tarminvaginasjon?

Hvis ja, dato 1:

Dato 2:

8. Innsykningsdato

9. Innskrivningsdato

10. Død

○ nei ○ ja ○ vet ikke

Død dato

11. Utskrivningsdato

Diagnoser

12. ICD - 10 koder

13. NCMP koder

14. NCSP koder

15. Andre relevante diagnoser

Tarminvaginasjon

16. Tarminvaginasjonsdiagnose

○ nei ○ ja ○ vet ikke

17. Lokalisasjon av tarminvaginasjon (f.eks. colon ascend)

18. Type tarminvaginasjon (f.eks. ileocoecal)

Røntgen abdomen

18. Tarminvaginasjon bekreftet ved røntgen colon m/luft

○ nei ○ ja ○ ikke utført ○ vet ikke

19. Tarminvaginasjon bekreftet ved røntgen colon m/væske

○ nei ○ ja ○ ikke utført ○ vet ikke

20. Røntgen abdomen med synlig tarminvaginasjon eller bløtvevsmasse

○ nei ○ ja ○ ikke utført ○ vet ikke

21. Røntgen abdomen med væskenivåer og dilaterte tarmslynger

○ nei ○ ja ○ ikke utført ○ vet ikke

22. Røntgen abdomen med unormale uspesifikke tegn på tarmluft

○ nei ○ ja ○ ikke utført ○ vet ikke

CT

23. CT abdomen med synlig tarminvaginsjon eller bløtvevsmasse

○ nei ○ ja ○ ikke utført ○ vet ikke

Ultralyd abdomen

24. Ultralyd abdomen med synlig tarminvaginasjon eller bløtvevsmasse

○ nei ○ ja ○ ikke utført ○ vet ikke

25. Intraabdominal masse med karakteristiske tegn, bekreftet ved ultralyd abdomen, som reduseres etter hydrostatisk klyster

○ nei ○ ja ○ ikke utført ○ vet ikke

Kirurgi

26. Tarminvaginajson bekreftet v/kirurgi

○ nei ○ ja ○ ikke utført ○ vet ikke

Obduksjon

27. Tarminvaginasjon bekreftet ved obduksjon

○ nei ○ ja ○ ikke utført ○ vet ikke

Klinisk undersøkelse

28. Abdominal masse

○ nei ○ ja ○ ikke utført ○ vet ikke

29. Rektalmasse

○ nei ○ ja ○ ikke utført ○ vet ikke

30. Tarmprolaps

○ nei ○ ja ○ ikke utført ○ vet ikke

31. Blod ved rektaleksplorasjon

○ nei ○ ja ○ ikke utført ○ vet ikke

32. Akutt forstørret abdomen

○ nei ○ ja ○ ikke utført ○ vet ikke

32. Unormale / fraværende tarmlyder

○ nei ○ ja ○ ikke utført ○ vet ikke

Symptomer siste uke før sykehuskontakt

33. Rektalblødning

○ nei ○ ja ○ vet ikke

34. Ripsgelèliknende avføring

○ nei ○ ja ○ vet ikke

35. Magesmerter

○ nei ○ ja ○ vet ikke

36. Oppkast

○ nei ○ ja ○ vet ikke

37. Gallefarget oppkast

○ nei ○ ja ○ vet ikke

38. Slapphet / asteni

○ nei ○ ja ○ vet ikke

39. Hypovolemisk sjokk

○ nei ○ ja ○ vet ikke

40. Blekhet

○ nei ○ ja ○ vet ikke

Avføringsprøveresultat

41. Avføringsprøveresultat

42. Avføringsprøvemetode

Behandling

43. Luft/hydrostatisk klyster

○ nei ○ ja ○ vet ikke

Kommentar klyster

44. Kirurgi

○ nei ○ ja ○ vet ikke

Kommentar kirurgi

45. Annet

○ nei ○ ja ○ vet ikke

Kommentar annet

46. Helbredende behandling

○ spontan ○ kirurgisk ○ klyster ○ vet ikke

47. Merknad

Forekomst av rotavirusinfeksjon i Norge og beskyttende virkning av vaksinasjon

SPØRRESKJEMA (fylles ut av sykehuspersonell)

Del 1: Fylles ut ved innleggelse

PLASS TIL BARKODE Navn: Fødsels- og personnummer:	**Kjønn:** ☐ **M** ☐ **K** **Er samtykkeerklæring fylt ut?** ☐ **Ja**

Innleggelsesdato : ____/____/____ **dd mm åå**	**Dato for utfylling av skjemaet:** ____/____/____ **dd mm åå**

Symptomer

Sett ett kryss for hvert spørsmål. Dette skal brukes for å beregne *Vesikari score* for å vurdere alvorlighetsgrad av gastroenteritt

Varighet av diaré	☐ **ingen diaré** ☐ **1 – 4 dager** ☐ **5 dager** ☐ **6 dager eller mer** ☐ **vet ikke**
Maksimalt antall diaré-episoder i løpet av ett døgn i sykdomsforløpet	☐ **ingen diaré** ☐ **1 - 3** ☐ **4 - 5** ☐ **6 eller mer** ☐ **vet ikke**
Varighet av oppkast	☐ **ingen oppkast** ☐ **1 dag** ☐ **2 dager** ☐ **3 dager eller mer** ☐ **vet ikke**
Maksimalt antall oppkastepisoder i løpet av ett døgn i sykdomsforløpet	☐ **ingen oppkast** ☐ **1** ☐ **2-4** ☐ **5 eller mer** ☐ **vet ikke**
Temperatur ved ankomst (skriv den eksakte temperaturen som er målt, og sett ett kryss for hvor den er målt)	**Temperatur:** _____°C ☐ **rektalt** ☐ **axillært** ☐ **øret**
Dehydrering	☐ **ingen** ☐ **moderat (1-5 % vekttap)** ☐ **alvorlig (6% eller mer vekttap)**

OBS: 2 sider

Andre forhold

Sett ett kryss for hvert spørsmål

Har barnet noen gang blitt ammet?	☐ **ja** ☐ **nei** ☐ **ukjent**
Barnets ammestatus per i dag: *Fullammet:* får kun morsmelk og evt. vann/saft/juice/kosttilskudd *Delvis ammet*: får morsmelkerstatning og/eller fast føde i tillegg til morsmelken. *Ikke ammet:* får ikke morsmelk	☐ **fullammet** ☐ **delvis ammet** ☐ **ikke ammet**
Hvor passes barnet på dagtid?	☐ **hjemme med mor/far/annet familiemedlem** ☐ **hjemme med dagmamma/praktikant** ☐ **hos dagmamma** ☐ **familiebarnehage** ☐ **barnehage**
Har barnet nedsatt motstandskraft mot infeksjoner?	☐ **nei** ☐ **ja** **Hvis ja, velg faktorer som påvirker barnets immunforsvar:** ☐ **medfødt immunsvikt** ☐ **kreft** ☐ **immunsupprimerende behandling** ☐ **annet, beskriv**_____

Del 2: Fylles ut ved utskrivelse

Utskrivningsdato: ____/_____/_____ **dd mm åå**	
Er noen form for rehydrering gitt under sykehusoppholdet: (p.o./i.v./sonde)?	☐ **ja** ☐ **nei**
Utfall av sykehusopphold	☐ **restituert** ☐ **overflyttet til annen avdeling eller sykehus** ☐ **død** **Dato for dødsfall (dd/mm/åå):** ____/_____/_____
Var barnet innlagt på intensivavdeling under dette sykehusoppholdet?	☐ **nei** ☐ **ja** **Antall dager/timer på intensiv avdeling:** _____**dager** _____**timer** ☐ **ukjent**

Paper II

Vaccine 37 (2019) 5717–5723

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Intussusception among Norwegian children: What to expect after introduction of rotavirus vaccination?

Tone Bruun *, Sara Sofie Viksmoen Watle, Ingun Heiene Tveteraas, Elmira Flem

Norwegian Institute of Public Health, PO Box 222 Skøyen, N-0213 Oslo, Norway

ARTICLE INFO

Article history:
Received 31 March 2019
Received in revised form 14 June 2019
Accepted 18 June 2019
Available online 26 June 2019

Keywords:
Rotavirus vaccines
Intussusception
Vaccine safety

ABSTRACT

Background: To reduce the risk of vaccine-associated intussusception, rotavirus vaccination in Norway was implemented under strict age limits (the first dose given by 12 weeks of age and the second dose by 16 weeks of age) in 2014. We estimated the incidence of intussusception in children <2 years old before vaccine introduction and the number of vaccine-associated cases under current and extended age limits for vaccine administration in Norway.

Methods: To estimate the baseline incidence, we validated all diagnoses in children <2 years old registered in the national hospital registry during the pre-vaccine period of 2008–2013. Using national vaccine coverage data and international estimates of intussusception risk after rotavirus vaccination, we calculated the numbers of expected vaccine-associated intussusception cases to compare with the estimated numbers of averted rotavirus cases. Uncertainty was accounted for by several scenario analyses using current and extended age limits for vaccine administration.

Results: The pre-vaccine incidence of intussusception was 26.7 (95% CI 23.1–30.6) cases/year per 100,000 children <2 years old and 37.1 (95% CI 31.2–43.8) cases/year per 100,000 children <1 year old. In the 2016 birth cohort (approx. 60,000) vaccinated under the current age limits, 1.3 (95% CI 0.7–2.0) vaccine-associated intussusception cases were expected to occur. If age limits were extended to 16 weeks for the first vaccine dose and 24 weeks for the second dose, leading to more children vaccinated at an older age, 2.2 (95% CI 1.2–3.5) excess cases would be expected in the same cohort. Simultaneously, an estimated 1768 rotavirus hospitalizations/year in children <5 years old would be averted under current age limits, with 98 additional rotavirus hospitalizations averted under extended age limits.

Conclusions: Administering rotavirus vaccines beyond current age limits in Norway would lead to a marginal increase in the number of intussusception cases, which would be offset by the benefits of vaccination.

1. Introduction

Intussusception is the most common cause of bowel obstruction in infants and young children; without treatment it can disrupt the bowel's vascular supply and cause ischemia, perforation, and ultimately death. The background incidence of intussusception varies largely by country. Overall, many industrialized countries report a baseline incidence of under 60 cases per 100,000 person-years among children <1 year of age, with a peak incidence around 5–7 months of age [1–5]. Currently licensed rotavirus vaccines are associated with a small risk of intussusception of 1–5 cases per 100,000 vaccinees [1,6–8]. The vaccine-attributable risk seems to be highest in the first week following the first dose [9]. A previous rotavirus vaccine, Rotashield®, was withdrawn from the market due to a higher risk of intussusception (approximately 10 cases per 100,000 vaccinees) [10–12]; the risk was highest in infants who received their first dose after 3 months of age. Because the vaccine-attributable risk of intussusception seems to be age-dependent, the first dose of rotavirus vaccine is recommended in Europe between 6 and 12 weeks of age, with a full schedule (2 doses for Rotarix® and 3 doses for RotaTeq®) completed by 6 months of age [13].

Universal rotavirus vaccination programs are currently implemented only in one third of European countries [14]. Vaccine safety concerns have been considered a barrier to the introduction [15]. For example, French health authorities withdrew their vaccine recommendations in 2015 after two intussusception deaths temporally related to rotavirus vaccination [16]. Rotarix® and

* Corresponding author at: Department of Vaccine Preventable Diseases, Norwegian Institute of Public Health, PO Box 222 Skøyen, N-0213 Oslo, Norway.
E-mail address: tone.bruun@fhi.no (T. Bruun).

https://doi.org/10.1016/j.vaccine.2019.06.058
0264-410X/

RotaTeq®, have been available for purchase on the Norwegian market since 2006 and 2010, respectively, with a minimal uptake prior to introduction in the national program. In 2014, Norway introduced rotavirus vaccination in the national immunization program using Rotarix® (GSK, Belgium). To minimize the risk of intussusception, Norway adopted strict age limits for vaccine administration despite a probability of negatively affecting vaccine uptake. The first dose is recommended at 6 weeks of age with a maximum age limit of 12 weeks, and the second dose is recommended at 12 weeks with a maximum limit of 16 weeks. An interval of at least 28 days is advised between doses. Norway rapidly achieved high national coverage and excellent adherence to the recommended vaccine schedule during the first year of introduction [17]. The national coverage for rotavirus vaccine was 91% for one dose among children aged 12 weeks and 86% for two doses among children aged 16 weeks in December 2017; 88% were vaccinated within the recommended age limits. However, the rotavirus vaccine coverage is still below the routine coverage of 96% for other pediatric vaccines in Norway.

The World Health Organization recommends post-licensure surveillance to detect rare adverse events, including intussusception, in countries with routine rotavirus vaccination [18]. Country-specific incidence estimates of intussusception are a prerequisite for detecting safety signals post-licensure. We estimated the baseline incidence of intussusception among children <2 years of age in Norway before vaccine introduction, and the expected numbers of vaccine-associated intussusception cases post-vaccination, under current and extended age limits for vaccine administration. We also performed a benefit–risk analysis by comparing the numbers of expected vaccine-associated intussusception cases with the estimated numbers of averted rotavirus cases in the post-vaccine birth cohorts.

2. Patients and methods

2.1. Pre-vaccine incidence of intussusception

We used data from the Norwegian Patient Registry, which contains information about nearly all hospitalizations in public and private hospitals in Norway [19]. We extracted data on hospital contacts with 10th Revision of the International Classification of Diseases (ICD-10) code K56.1 for intussusception in children <2 years of age occurring from January 1999 to December 2017. Data reported before 2008 did not contain the individual personal identification number, whereas data reported from 2008 onwards were person-identifiable, allowing us to link the registry data to patients' medical records to validate the intussusception diagnoses. Information extracted from medical records included admission dates, symptoms, treatments, and outcomes. Medical chart review and data extraction were conducted using a standardized form by three study investigators (physicians) from the Norwegian Institute of Public Health (NIPH) with support from a local pediatrician at each hospital. Two NIPH investigators reviewed each record to reduce observer bias. In case of doubt, the medical record was discussed until consensus was reached.

We classified intussusception cases for the period 2008–2013 as definite, probable, and possible using the Brighton Collaboration Clinical Case Definition [20]. To calculate the incidence among children <2 years of age, we included only the first episode of definite (confirmed by surgery, air or liquid-contrast enema, or ultrasound) intussusception occurring in each child during the study period. The annual numbers of children <2 years of age provided by Statistics Norway was used as denominator, assuming a constant birth-rate throughout the year [21]. We used a Poisson regression model fitted to weekly data on reported intussusception cases using a restricted cubic spline with 6 degrees of freedom to model the non-linear age association and predict the weekly intussusception rates before vaccine introduction.

2.2. Vaccine-associated intussusception

The size of the Norwegian birth cohort (approx. 60,000) does not allow a sufficient statistical power to estimate the country-specific risk of vaccine-associated intussusception after rotavirus vaccination. We therefore applied pooled estimates of intussusception risk for the monovalent rotavirus vaccine obtained in a meta-analysis for industrialized settings (relative risk 2.35 (95% CI 1.45–3.80) during days 1–21 after dose one, and 1.77 (95% CI 1.29–2.43) during days 1–21 after dose two) [8]. Using the predicted baseline incidence of intussusception, the weekly numbers of vaccinated children by age in weeks in 2016 and population data estimates from Statistics Norway for the period 2016–2019 [21], we estimated the mean number of vaccine-associated intussusception cases occurring in each birth cohort during 2016–2019 vaccinated under the current age limits. The Norwegian Immunization Registry SYSVAK provided data on age at rotavirus vaccination among children vaccinated in 2016 [22].

2.3. Scenarios

Furthermore, we estimated the mean number of intussusception cases that would occur if current age limits were extended to 16 weeks of age for the first dose and 24 weeks for the second dose. We used several scenarios to test the impact of different assumptions about the vaccine uptake and distribution of age at vaccination under extended age limits. The main scenario assumed that extended age limits would increase the coverage for one dose to 96% (based on the highest proportion of Norwegian children vaccinated with other routine vaccines at 2 years of age) and 91% for two doses (based on the difference between current coverage for one and two rotavirus doses). Currently, 95% of Norwegian children receive the first rotavirus dose within 3–4 weeks of the lowest recommended age limit of 6 weeks. If age limits were extended, we expect that the age distribution of vaccinated children would largely remain left-skewed but a shift to the right may occur with some children being vaccinated later compared to the present situation. Hence, in the main scenario, we assumed that age at vaccination would be uniformly distributed over the time window allowed for each dose, suggesting that equal proportions of children will be immunized each week. Because the baseline incidence of intussusception in Norway increases by age with a peak incidence at 6–7 months (Fig. 2), this scenario is considered to be least favorable with regard to the vaccine program. In addition we evaluated four other scenarios: (1) extending age restrictions under a uniform distribution of age at vaccination but without increasing the current coverage; (2) increasing the coverage under the current age restrictions with the same distribution of vaccination age as at present; (3) increasing the vaccine-associated intussusception risk to the upper bound of the confidence interval for the RR estimates; and (4) decreasing the vaccine-associated intussusception risk to the lower bound of the confidence interval. The confidence intervals for our intussusception estimates were generated by simulating 1000 datasets from the estimated error associated with our regression models and risk ratios, making estimates for each of the 1000 datasets, and then taking the 2.5th, 50th, and 97.5th percentiles.

2.4. Rotavirus episodes averted

Lastly, we compared the number of vaccine-associated intussusception cases with the number of rotavirus-related outcomes

that would be averted by vaccination under both extended and current age limits. Rotavirus-related outcomes (hospital and primary care contacts, homecare episodes and deaths) were estimated by using a previously published dynamic rotavirus transmission model [23,24] fitted to the Norwegian data. The model was updated with 2015–2017 birth cohort data and projections from Statistics Norway [21].

2.5. Statistical analyses and ethics

Analyses were performed using Stata version 13 (StataCorp., College Station, TX) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Regional Committee for Medical and Health Research Ethics.

3. Results

3.1. Pre-vaccine incidence and epidemiology of intussusception

A total of 1512 admissions (annual mean 80, range 42–134) with the intussusception code in children <2 years of age were registered in Norway during 1999–2017. Overall during the 19-year study period, there was a decrease in the annual number of cases, with 134 in 1999 and 42 in 2017 (Fig. 1).

Of 447 intussusception-coded admissions registered during 2008–2013, 431 (96%) were linked to medical records. Linkage was not possible due to missing personal identifiers in 14 cases and missing medical records in two patients. The 431 admissions represented 274 disease episodes in 267 children <2 years of age (157 admissions were duplicate records of patients transferred between hospitals or readmitted in connection with the same episode). Seven intussusception episodes were excluded because they were the second or third episode in the same patient during the study period. Of 267 cases included in the analysis, 195 were defined as intussusception level 1 (definite) according to the Brighton Collaboration Clinical Case Definition, whereas 18 were level 2 (probable) and four were level 3 (possible). In 50 cases (18.7%), the intussusception diagnosis was ruled out during admission or the Brighton criteria were not met.

Over the 6-year study period from 2008 to 2013, the mean incidence of definite intussusception among children <2 years of age was 26.7 (95% CI 23.1–30.6) cases/year per 100,000 among children <2 years and 37.1 (95% CI 31.2–43.8) cases/year per 100,000 among children <1 year of age (Table 1).

The median age of patients <2 years of age with definite intussusception was 9.3 (IQR: 5.6–15.1) months (40.3 weeks) with a peak at 6–7 months (26–30 weeks) of age (Fig. 2). Children aged <12 months accounted for 69% of cases, and only four were <2 months old.

3.2. Vaccine-associated intussusception cases after rotavirus introduction

Under current age restrictions for rotavirus vaccination in Norway, 1.1 (95% CI 0.5–2.1) vaccine-associated intussusception cases per 100,000 vaccinees are expected to occur in the 2016 birth cohort after the first dose, and 1.3 (95% CI 0.5–2.4) cases per 100,000 are expected to occur after the second dose. This corresponds to a combined estimate of 1.3 (95% CI 0.7–2.0) intussusception cases in the entire cohort (Table 2). Simultaneously, rotavirus immunization program would avert a mean of 8534 rotavirus-related primary care consultations and 1768 hospitalizations (inpatient and outpatient contacts) in the same cohort during their first five years of life (Table 2), corresponding to 1360 rotavirus hospitalizations being averted for each intussusception hospitalization.

If the age limits for vaccine administration were extended to 16 weeks of age for the first dose and 24 weeks for the second dose with a uniform distribution of age at vaccination, 2.2 (95% CI 1.2–3.5) vaccine-associated intussusception cases are estimated to occur in the 2016 cohort, resulting in less than one additional vaccine-associated intussusception case compared to the present situation (Table 2). Considering an increase in vaccine coverage under this scenario, rotavirus immunization program would avert an additional 598 rotavirus primary care visits and 98 rotavirus hospitalizations in the same cohort (Table 2). Additional scenario analyses demonstrated that the estimates of vaccine-associated intussusception cases after rotavirus vaccination were more sensitive to the increase in the age at vaccination compared with an

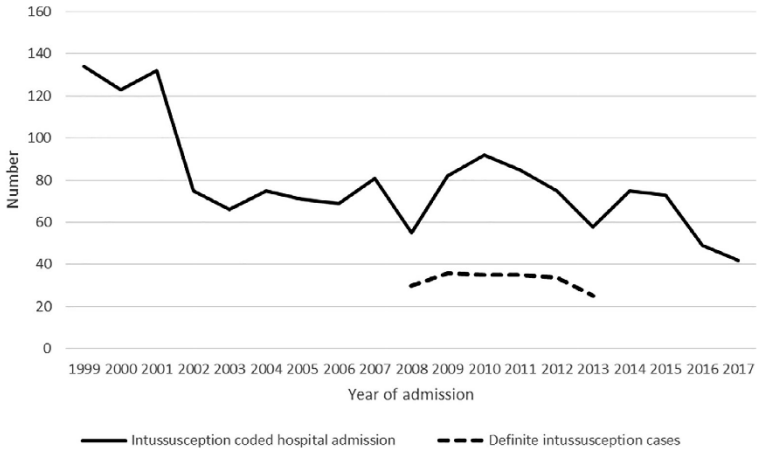

Fig. 1. Number of intussusception-coded hospital admissions (1999–2017) and definite intussusception cases (2008–2013) by year among Norwegian children <2 years of age.

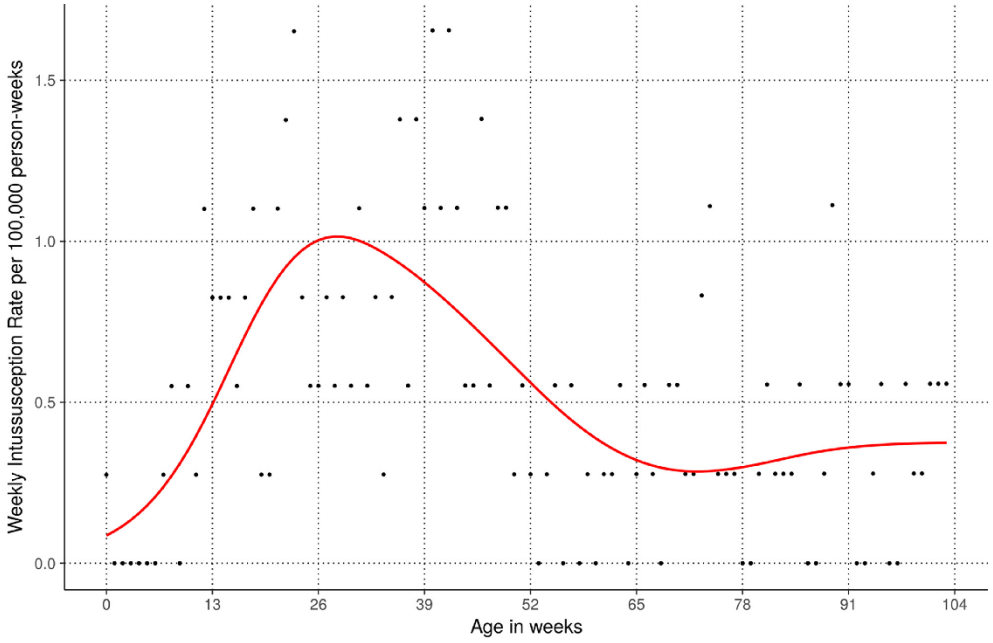

Fig. 2. Observed and predicted weekly intussusception rates per 100,000 person-weeks for definite cases <2 years of age hospitalized in Norway, 2008–2013.

Table 1
Pre-vaccine incidence of definite intussusception in hospitalized children <2 years of age in Norway, 2008–2013.

Year	No. cases <2 y	Incidence per 100,000 infants <2 y	95% confidence interval	No. cases <1 y	Incidence per 100,000 infants <1 y	95% confidence interval
2008	30	25.4	17.1–36.2	22	37.5	23.5–56.8
2009	36	30.0	21.0–41.5	26	42.9	28.0–62.8
2010	35	28.3	19.7–39.4	22	35.4	22.2–53.7
2011	35	28.1	19.6–39.1	26	42.2	27.6–61.8
2012	34	27.7	19.2–38.6	25	41.3	26.8–61.0
2013	25	20.5	13.3–30.3	14	23.1	12.7–38.8
Total	195			135		

increased vaccination coverage (Table 3). Nevertheless, in all our scenario analyses, only a marginal increase in the numbers of vaccine-associated intussusception cases was observed.

4. Discussion

This study confirms that childhood intussusception is a rare disease, with an estimated pre-vaccine rate of 27 cases annually per 100,000 children <2 years of age in Norway. Following introduction of rotavirus vaccination under the current age limits, between 1.2 and 1.3 vaccine-associated cases of intussusception were estimated to occur annually during 2016–2019. These estimates are based on the calculation of intussusception risk obtained in other industrialised settings outside Norway and represent a marginal increase compared with the pre-vaccine levels. The increase in intussusception would be offset by the number of rotavirus cases averted by vaccination. If age limits were extended and more children were vaccinated at an older age, roughly one additional intussusception case would occur annually in the vaccinated cohort, which would also be offset by the benefits of the vaccination program. Our scenario analysis demonstrated that the age at rotavirus vaccination is the key determinant in defining the expected number of vaccine-associated intussusception cases. However, we believe that despite extended age limits, most Norwegian infants will still be vaccinated closer to the lowest recommended age given a high compliance with existing recommendations, thereby minimizing the number of vaccine-associated intussusception cases.

A risk-benefit analysis from England reported that vaccination would prevent 375 rotavirus hospitalizations for each additional intussusception admission caused by the vaccine [25]. A study in the United States estimated the prevention of 1093 rotavirus admissions for each additional intussusception admission [26], closer to our estimate of 1360 averted rotavirus hospitalizations per excess intussusception case under the current age restrictions. In France, it was reported that for every intussusception hospitalization and every intussusception death caused by vaccination, 1624 rotavirus hospitalizations and 743 deaths were prevented by vaccination, respectively [27]. The recommended dosing schedule for Rotashield® in the United States resulted in many infants being vaccinated between three and seven months of age, a peak period for naturally occurring intussusception. Restricting vaccination to

Table 2
Estimated annual risks and benefits of the rotavirus vaccination in Norway under current and extended age limits for vaccine administration.

Current age restrictions and 91% coverage for first dose						
Birth cohort	Annual average vaccine-attributable intussusception cases (95% CI)	Annual average avoided rotavirus episodes in children < 5 y (95% CI)				
		Homecare episodes	Primary care visits	Inpatient hospital contacts	Outpatient hospital contacts	Deaths
2016	1.26 (0.71–1.96)	30,525 (30,515–30,534)	8,534 (8,525–8,543)	1,128 (1,123–1,133)	640 (638–641)	0.48 (0.45–0.51)
2017	1.24 (0.68–2.00)	19,184 (19,153–19,214)	6,034 (6,024–6,044)	903 (899–907)	512 (511–514)	0.41 (0.38–0.44)
2018	1.18 (0.65–1.97)	32,500 (32,490–32,509)	9,117 (9,108–9,125)	1,188 (1,183–1,194)	674 (672–676)	0.49 (0.46–0.52)
2019	1.19 (0.69–1.98)	18,520 (18,442–18,599)	7,104 (7,088–7,121)	979 (975–983)	555 (554–557)	0.42 (0.39–0.45)
Extended age restrictions and 96% coverage for first dose						
Birth cohort	Annual average vaccine-attributable intussusception cases (95% CI)	Annual average avoided rotavirus episodes in children <5 y (95% CI)				
		Homecare episodes	Primary care visits	Inpatient hospital contacts	Outpatient hospital contacts	Deaths
2016	2.17 (1.19–3.50)	32,929 (32,920–32,938)	9,132 (9,123–9,140)	1,191 (1,186–1,196)	675 (674–677)	0.50 (0.47–0.54)
2017	2.19 (1.20–3.57)	21,511 (21,479–21,542)	6,687 (6,677–6,698)	981 (977–985)	556 (555–558)	0.44 (0.41–0.47)
2018	2.06 (1.15–3.34)	30,525 (30,509–30,541)	8,806 (8,797–8,815)	1,162 (1,157–1,167)	659 (657–661)	0.48 (0.45–0.51)
2019	2.22 (1.23–3.42)	22,463 (22,399–22,528)	7,910 (7,896–7,925)	1,064 (1,059–1,069)	603 (602–605)	0.46 (0.43–0.49)

Table 3
Estimated number of vaccine-associated intussusception cases in the 2016 cohort, under different scenarios.

Scenario	No. (95% CI)
Current situation	1.26 (0.71–1.96)
Extended age restrictions with increased vaccine coverage and uniform distribution of age at vaccination	2.17 (1.19–3.50)
Extended age restrictions, current vaccine coverage and uniform distribution of age at vaccination	2.09 (1.16–3.30)
Current age restrictions, increased coverage and current distribution of age at vaccination	1.31 (0.70–2.09)
Upper bound of 95% CI of intussusception risk[^], current age restrictions, current vaccination coverage and current distribution of age at vaccination	2.43 (1.53–3.72)
Lower bound of 95% CI of intussusception risk[↓], current age restrictions, current vaccination coverage and current distribution of age at vaccination	0.45 (0.09–0.93)

[^] Increasing RR to the higher confidence limit for the risk estimates (3.80 for dose 1 and 2.43 for dose 2).
[↓] Lowering RR to the lower confidence limit for the risk estimates (1.45 for dose 1 and 1.29 for dose 2).

those younger than 3 months old would probably have reduced the risk [28]. Several studies suggest that adherence to upper age limits for vaccine administration may reduce the likelihood of vaccine-related intussusception. Data from Australia demonstrated a weaker association between Rotarix® and intussusception when cases of vaccination at an age beyond the upper limits (24 weeks) were excluded [29]. Estimates from Singapore showed that the risk of intussusception would be the lowest if both first and second vaccine dose were given at under three months of age [30]. Whether the risk of vaccine-associated intussusception relative to the baseline rates increases with age is not fully understood. Limited previous data have demonstrated no such effect modification by age [31], which is in line with a previous assessment of intussusception associated with Rotashield® [10].

It has been questioned whether rotavirus vaccines may trigger intussusception to occur earlier in some children with no overall long-term increase in the incidence [29]. This assumption is supported by Simonsen et al., who found no evidence of an increased rate of intussusception admissions during the Rotashield® period, but observed an increase in admissions at 2–4 months of age that was offset by a decrease among older infants during the Rotashield® period compared to the previous data period [32]. Several other studies also suggest that rotavirus vaccine does not increase the overall risk of intussusception [33–35].

The baseline incidence rates of intussusception were lower in our study than in neighboring Denmark (85 cases per 100,000 person-years among children <5 years of age) in 2000 [36], though we studied another age group (children <2 years of age). However, there has been a decreasing trend in both countries, and the difference may be partly explained by the different study periods. Earlier European studies conducted during 1995–2005 reported higher incidence rates [37]. In Finland, however, during the pre-vaccine years of 1999–2005, the mean incidence (12 cases per 100,000 person-years in children <1 year of age) was even lower than our rate (1). Our estimate of 37 cases per 100,000 children <1 year of age is nevertheless comparable to reports from Switzerland (4), the United Kingdom (2), the Netherlands [4], Australia [38] and the United States (5). A multi-country study from Latin America reported an incidence of definite intussusception ranging from 2 per 100,000 person-years in Brazil to 62 in Argentina for children <2 years of age, and from 4 per 100,000 person-years in Brazil to 105 cases in Argentina for children <1 year of age [39]. A literature review from 2014 reported a mean intussusception incidence of 74 per 100,000 (range: 9–328) infant years across studies from all regions of the world [40]. Differences in the reported rates may be true differences in the background rate of intussusception in the population or related to variations in health care utilization patterns, diagnostic and reporting practices. Study populations also differed substantially including only definite cases [1,2,38], probable cases [4,8] or all cases coded as intussusception in the hospital discharge database [5,36]. Several studies excluded cases with underlying pathology such as Meckel's diverticulum and other possible lead points [38,41]. We found a decrease in the rates of intussusception-coded hospital admissions from 1999 to 2017,

which is consistent with results from Denmark, the UK, and Ireland [2,36]. Coding and reporting differences might explain some of the decrease, however the reason for the observed decrease is unknown. Studies in other countries have found stable or increasing trends [5,41].

Children <12 months old in our study accounted for 69% of all cases aged <2 years of age, in line with data from Australia and Denmark [36,38]. Our model shows a peak in intussusception immediately after the sixth month of life, which is comparable to the peak incidence at 5–7 months of age noted in other studies [2,4,36,40,41]. Notably, this peak is well above the upper age limit for the second dose of rotavirus vaccination in Norway. Few of the patients were in the age group targeted by vaccination, only 6% were between 6 and 12 weeks of age which are the current age limits for the first dose in Norway.

Similar to reports from other high-income countries [41], zero mortality from intussusception was recorded in this study. However, children may die before reaching the hospital, without their death being registered in the medical record, leading to an underestimation of the true mortality.

The strength of this study is the use of data from a nationwide, population-based patient registry with personal identifier allowing us to validate the intussusception diagnoses through a review of the medical records. Because of the organization of the Norwegian healthcare system, nearly all hospital contacts are captured in the registry. We were able to identify all hospital contacts linked to one episode of intussusception and avoid counting all encounters as unique cases. If we used registry-based data alone without linking to medical records, the incidence could have been overestimated by almost one-third because 27% of the patients with intussusception-coded admissions did not meet the Brighton Collaboration criteria for definite intussusception [42]. Furthermore, using real-life data about weekly numbers of rotavirus vaccinations and the age at vaccination from a population-based vaccination registry enabled us to better estimate the number of vaccine-associated intussusception cases [22].

Even though we used comprehensive registry data, data validity should be considered. Because non-specific ICD codes are widely used by clinicians, the intussusception rates derived from hospital-based data may be underestimated. A study from the US demonstrated that intussusception rates derived on the basis of hospital discharge statistics alone underestimate the true incidence, whereas a study from Australia did not identify any additional intussusception cases during a search for associated conditions that may have been miscoded [38,43]. Moreover, we were unable to directly measure the vaccine-associated intussusception risk in Norway, which may have impacted our findings as the estimates of vaccine-associated risk were derived from countries with broader age limits for vaccine administration than Norway. This could possibly overestimate the numbers of expected cases post-vaccination. Lastly, the intussuception risk was estimated only during the three weeks after vaccination, and thus no possible compensatory reduction in the risk later in infancy was accounted for.

The benefits of rotavirus vaccination and risk of intussusception are not directly comparable. When estimating averted rotavirus cases, we did not take into consideration the expected herd protection, which may increase the benefits of vaccine program. Before vaccine introduction, rotavirus was estimated to cause one death every second year among Norwegian children <5 years of age [44], whereas no intussusception deaths were identified in our data. However, we did not further compare in detail the clinical severity and complications of rotavirus disease and intussusception. Besides, an adverse event caused by an intervention such as vaccination may be perceived more negatively than the condition caused by a failure to intervene.

5. Conclusion

Defining the acceptable risk for a vaccination program and how to manage and mitigate such risk remains a challenge. Childhood intussusception is rare in Norway, and administering rotavirus vaccines beyond the current strict age limits was estimated to result in a marginal increase in the number of vaccine-associated intussusception cases. The exact intussusception risk in Norway is yet to be determined, and because it is unclear whether an increased intussusception risk after vaccination implies an increase in the overall childhood risk, it is important to continue monitoring intussusception trends after vaccine introduction.

Funding source

The study was fully funded by the Norwegian Institute of Public Health.

Declaration of Competing Interest

All authors have indicated they have no potential conflicts of interest to disclose.

Acknowledgements

We thank the staff at the study hospitals for their assistance and support during the medical chart reviews. We would also like to acknowledge our colleagues at the Norwegian Institute of Public Health: Terese Bekkevold for coordinating the data collection, Richard Aubrey White for setting up the intussusception risk model, Birgitte Freiesleben de Blasio for updating and running the rotavirus transmission model and Beatriz Valcarcel Salamanca and Liliana Vazquez Fernandez for assistance with the models and statistical analysis.

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Paper III

Impact of the rotavirus vaccination program in Norway after four years with high coverage

Tone Bruun, MD[1], Beatriz Valcarcel Salamanca, MSc, PhD[2], Terese Bekkevold, MPhil2, Henrik Døllner, MD, PhD[3,4], Moustafa Gibory, MSc[5], Ann Marit Gilje, MD[6], Elisebet Haarr, MD[7], Anne-Marte Bakken Kran, MD, PhD[8]*, Truls M. Leegaard, MD, PhD[9,10], Britt Nakstad, MD, PhD[10], Svein Arne Nordbø, MD[4,11], Astrid Rojahn, MD[12], Ketil Størdal, MD, PhD[13] and Elmira Flem, MD, PhD[2]**, for the Norwegian Enhanced Pediatric Immunisation Surveillance (NorEPIS) Network

[1]Department of Infection Control and Vaccines, Norwegian Institute of Public Health, Oslo, Norway

[2]Department of Infectious Disease Epidemiology and Modelling, Norwegian Institute of Public Health, Oslo, Norway

[3]Children's Department, St. Olavs University Hospital, Trondheim, Norway

[4]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[5]Department of Virology, Norwegian Institute of Public Health, Oslo, Norway

[6]Department of Pediatrics, Stavanger University Hospital, Stavanger, Norway

[7]Department of Medical Microbiology, Stavanger University Hospital, Stavanger, Norway

[8]Department of Microbiology, Oslo University Hospital, Oslo, Norway

[9]Department of Microbiology and Infection Control, Akershus University Hospital, Lørenskog, Norway

[10]Institute of Clinical Medicine - Campus Ahus, Division of Medicine and Laboratory Sciences, University of Oslo, Norway

[11]Department of Medical Microbiology, St. Olavs University Hospital, Trondheim, Norway

[12]Department of Pediatrics, Oslo University Hospital, Oslo, Norway

[13]Department of Pediatrics, Østfold Hospital Trust, Fredrikstad, Norway

*Current affiliation: Department of Infectious Disease Registries, Norwegian Institute of Public Health, Oslo, Norway

**Current affiliation: MSD Norway, Drammen, Norway

ABSTRACT

Background: Use of rotavirus vaccines worldwide since 2006, has led to significant impact on the burden of rotavirus disease. However, only a third of European countries have introduced rotavirus vaccination in their immunization programs. In October 2014, rotavirus vaccination was introduced for Norwegian infants under strict age restrictions. Exclusive use of Rotarix® and high vaccination coverage from the beginning enabled evaluation of the impact of this vaccine during the first four years after introduction.

Methods: Prospective laboratory-based surveillance among children aged <5 years hospitalized for acute gastroenteritis at five Norwegian hospitals was used to assess the vaccine effectiveness of two vaccine doses against rotavirus hospitalization in a case-control study. We used community controls selected from the national population-based immunization registry, and test-negative controls recruited through hospital surveillance. We also assessed the vaccine impact by using time series analysis of retrospectively collected registry data on acute gastroenteritis in primary and hospital care during 2009-2018.

Results: Vaccine effectiveness against rotavirus-confirmed hospitalization was 76% (95% CI: 34-91%) using test-negative controls, and 75% (95% CI: 44-88%) using community controls. In the post-vaccine period, acute gastroenteritis hospitalizations in children <5 years were reduced by 45% compared with the pre-vaccine years (IRRa 0.55; 95% CI: 0.49-0.61). Reduction in hospitalizations was also seen in cohorts not eligible for vaccination, suggesting herd effects. Rates in primary care decreased to a lesser degree.

Conclusions: Four years after introduction of rotavirus vaccination in the national childhood immunization program, we recorded a substantial reduction in the number of children hospitalized for acute gastroenteritis in Norway, attributable to a high vaccine effectiveness.

INTRODUCTION

Rotavirus is the leading cause of severe acute gastroenteritis (AGE) among children <5 years of age globally (1, 2). In 2006, two rotavirus vaccines were licensed internationally, following large trials on efficacy and safety (3, 4): the monovalent (RV1) vaccine Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and the pentavalent (RV5) vaccine RotaTeq® (Merck & Co., Inc., Kenilworth, NJ, USA). In 2009, the World Health Organization (WHO) recommended that all countries introduce rotavirus vaccination into their national immunization programs (5). As of August 2018, universal rotavirus vaccination was in place in 98 countries. Two thirds of European countries have not yet implemented universal vaccination (6).

Prior to vaccine introduction, rotavirus gastroenteritis (RVGE) was the primary cause of severe AGE in Norwegian children (7). In October 2014, Norway introduced rotavirus vaccination in the national immunization program using RV1. To minimize the intussusception risk, Norway adopted strict age limits for vaccine administration (first dose given by maximum 12 weeks of age and second dose by 16 weeks of age). High national coverage and adherence to the recommended vaccine schedule were achieved during the first year of introduction (8). In December 2018, the national coverage for rotavirus vaccine was 95% for one dose and 93% for two doses measured at the age of two years, being among the highest across countries in Europe and globally (9-11).

Although several studies provide evidence for effective rotavirus immunization programs in many countries, the coverage and impact vary, also within Europe (9, 12). The exclusive use of RV1 and a high vaccination coverage from the start, together with the Norwegian population-based registries, provides a valuable opportunity to evaluate the impact of this vaccine in a low-mortality setting. We aimed to assess the effectiveness and impact of rotavirus vaccination among Norwegian children aged <5 years during a four year follow-up period after vaccine introduction.

METHODS

We performed a case-control study to estimate vaccine effectiveness (VE) against hospital admission, and a time-series analysis to estimate the impact of the vaccination program.

Case-control study of vaccine effectiveness

The study was based on a previously established (7) rotavirus sentinel surveillance network of the Norwegian Institute of Public Health (NIPH) and five hospitals: Oslo University Hospital Ullevål, Stavanger University Hospital, St. Olavs University Hospital in Trondheim, Østfold Hospital and (from December 2015) Akershus University Hospital, covering approximately 40% of all Norwegian children. Surveillance was going on from February 1st 2014 until May 31st 2018. Children aged <5

years admitted to hospital with AGE within 10 days of illness onset were enrolled. AGE was defined as diarrhea (at least 3 loose stools in 24 hours) or vomiting (at least 1 episode in 24 hours). Children were not enrolled if they were hospitalized within 48 hours before illness onset, to exclude nosocomial transmitted infections. Health data and stool samples were collected within 48 hours of admission. Samples were screened for rotavirus at the hospital laboratory and then transferred to the national rotavirus reference laboratory at the NIPH for further testing.

Cases

For this study, we included as cases consecutive children from the sentinel surveillance who fulfilled these three criteria: 1) born after September 1st 2014, 2) aged ≥56 days when admitted to hospital (to ensure eligibility to have received at least one vaccine dose at least 14 days before admission), and 3) a fecal specimen obtained within 48 hours after admission tested positive for rotavirus by both enzyme immunoassay (EIA) (RIDASCREEN® Rotavirus, R-Biopharm, Darmstadt, Germany) and RT-PCR (RIDA®GENE, R-Biopharm, Darmstadt, Germany; Seegene, Seoul, South Korea). Positive samples were genotyped by a multiplex semi-nested RT-PCR (13, 14), and samples with genotype G1P[8], were tested by Rotarix qRT-PCR for the presence of vaccine virus strain, using previously described protocols with adjustments (15). Those who tested positive for the vaccine strain were excluded from the study.

Controls

Two control groups were included: test-negative controls and community controls. Test-negative controls were children enrolled in the sentinel surveillance that fulfilled the same criteria as cases, except tested negative for rotavirus by EIA and RT-PCR. Community controls were children born after September 1st 2014 that were registered in the National Vaccination Registry (SYSVAK) (16) on August 25th 2018 when immunization data were extracted from SYSVAK, lived in the catchment area of the study hospitals and were ≥56 days of age at the extraction date. Use of population-based immunization registries for selection of community controls has been shown to produce valid results in other VE studies (17, 18).

Immunization data

Rotavirus vaccination status (number and dates of doses received) of cases and controls was ascertained through linkage with SYSVAK. Registration in SYSVAK is mandatory for all vaccines included in the childhood immunization program (16).

A vaccine dose was considered valid if given at least 14 days before admission for cases and test-negative controls. Matched community controls were considered vaccinated if they were immunized at least 14 days before the admission of the corresponding case.

Analysis of vaccine effectiveness

Characteristics of cases and controls were compared by two-sided Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

We estimated the VE against hospital admission for RVGE after two doses using the following formula: VE = (1-Odds Ratio)×100%.

Using test-negative controls, we calculated odds ratios (OR) (odds of being vaccinated among cases versus the odds of being vaccinated among controls) and 95% confidence intervals (CI) by using unconditional logistic regression, adjusting for age and date of hospital admission. In addition, we conducted conditional logistic regression, matching each case to one or two (if possible) test-negative controls by age (±60 days) and date of hospital admission (±60 days), also adjusting for age and admission date. Using community controls, we calculated OR and 95% CI for vaccination by using unconditional logistic regression, adjusting for age, and using conditional logistic regression, matching each case to five community controls by age (±60 days), also adjusting for age. The matched controls were randomly selected 1,000 times, the VE calculated for each set of cases and controls, and the mean value of the VE is reported.

Time-series analysis of impact of the vaccination program

We used national population-based registry data for health care encounters associated with AGE during the years 2009-2018. Two or more encounters registered within 10 days in one patient were considered the same AGE episode.

Hospital admissions

We used data from the Norwegian Patient Registry (NPR) (19), which holds information about hospital treatment in all public and private hospitals in Norway. We selected all contacts (outpatients and inpatients) <5 years of age with International Classification of Diseases (ICD-10) codes corresponding to AGE as the main discharge diagnosis: A080 (Rotavirus), A081 (Norovirus), A082 (Adenovirus), A083-A084 (Other or unspecified viral infection), A000-A059 (Bacterial), A060-A079 (Parasitic) and A085; A090; A099 (Other, specified or unspecified infection). We also selected contacts with the dehydration code E86 as the main discharge diagnosis in combination with one of the AGE codes as secondary discharge diagnosis.

Primary care consultations

We used data from the National Health Economics Administration Database (KUHR) (20), which contains reimbursement claims from all general practitioners (GP) and emergency primary care (EPC) providers. We selected all consultations in children <5 years of age during the years 2009–2018 with the International Classification of Primary Care (ICPC-2) codes corresponding to AGE on the main diagnosis: D10 (Vomiting), D11 (Diarrhea), D70 (Bowel infection) and D73 (Gastroenteritis, presumed infectious).

Population data

Population data by year and age group provided by Statistics Norway were used to calculate AGE rates (21).

Analysis

We analyzed the data by rotavirus epidemiological year, defined as July through June. As vaccination was introduced in mid-October 2014, we defined a pre-vaccine period from July 2009 through June 2015 (assuming that the impact of vaccination before June 2015 were negligible) and a post-vaccine period from July 2015 through June 2018. Using a similar approach as Thomas et al. (22), we estimated the vaccine impact using age-stratified time series analysis of monthly counts of AGE cases using negative binomial regression, accounting for age-specific population size per month. We controlled for long-term trends by adding epidemiological year as a linear term, and for seasonal patterns by using month as an indicator variable. An indicator variable that distinguished pre- and post-vaccine periods was included in the model to obtain adjusted incidence rate ratios (IRRa). To control for autocorrelation, we included an autoregressive term up to one month in the model. The model was built in a stepwise fashion by first constructing the long-term trend, seasonality model and then the pre-/post-vaccine indicator variable. The results of the final model were expressed as IRRa compared to the pre-vaccine period. We evaluated plots of model residuals, predicted and observed time-series plots and partial autocorrelation function of the residuals to ensure the adequate fit of the data.

Statistical analyses and ethics

Analyses were performed using Stata version 13 (StataCorp., College Station TX) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). The Regional Committee for Medical and Health Research Ethics approved this study.

RESULTS

Rotavirus vaccine effectiveness

Characteristics of cases and controls

Overall, we enrolled 39 rotavirus-positive cases and 266 rotavirus-negative AGE controls for the case-control study (Figure 1, Table 1). Rotavirus cases were older than the test-negative controls (median age of 17.6 versus 7.6 months, Table 1) and had more severe disease, with 96% being classified as severe compared with 53% among rotavirus-negative controls (Table 1). The majority (69%) of rotavirus cases were admitted to hospital during a typical season between December and May, which was not significantly different from the test-negative controls (Table 1).

Vaccine effectiveness assessment

Using test-negative controls, we estimated the VE of full immunization with two doses against hospital admission for RVGE among vaccine-eligible children to be 76% (95% CI: 34-91%), whereas restricting the analysis to those admitted during the rotavirus seasons (defined as the period from December until May) resulted in VE of 79% (95% CI: 29-94 %) (Table 2). The VE in children <18 months of age was 83% (95% CI: 35-96%). Similar VE estimates of 78% (95% CI: 20-94%) were demonstrated in the matched analysis. Using community controls, the overall VE of two doses was estimated at 75% (95% CI: 44-88%), with similar results in the matched analysis.

Impact of rotavirus vaccination on acute gastroenteritis

In the pre-vaccine period from July 2009 to June 2015, 20,786 AGE episodes during 1,852,177 person-years in children <5 years of age were treated in hospital (average 3,464 episodes per epidemiological year (range: 2,825-3,841)). Of these, 52% were inpatients and 48% were outpatients. In the post-vaccine period from July 2015 to June 2018, 5,007 AGE episodes were seen in hospital during 912,977 person-years of follow-up (average 1,669 episodes per epidemiological year (range: 1,608-1,739)); 49% inpatients and 51% outpatients. The median age of AGE cases admitted to hospital prior to vaccine introduction were 17 (IQR: 10-27) months, similar to the median age of those admitted post-vaccination (16 (IQR: 9-30) months) (p=0.14).

A total of 222,035 AGE episodes were registered in primary care during the six-year pre-vaccine period (average 37,006 episodes per epidemiological year (range: 32,528-39,847)) and 90,002 cases during the three years post-vaccine (average 30,001 episodes (range: 29,049-30,608)). The median age for AGE cases treated during pre- and post-vaccine periods was 19 months (IQR: 12-32) and 20 (IQR: 11-34), respectively (p=0.21). We observed a marked winter seasonality in both hospital and

primary care during the study period (Figure 2). 14% of the hospital cases had a rotavirus-specific code on the main discharge diagnosis before vaccine introduction, compared with 8% post-vaccination (Figure 3).

In the time series analysis, we found that the rates of AGE-associated hospital episodes among children aged <5 years decreased by 45% in the post-vaccine period compared with the pre-vaccine years (IRRa 0.55; 95% CI: 0.49-0.61) overall (Table 3 a). The reduction among children <1 year of age was 40%, and among children 1-3 years of age 40%-52%. Among children between 4 and 5 years of age who were not eligible for vaccination, the incidence decreased by 37% (IRRa 0.63; 95% CI: 0.52-0.78). We found only modest reductions in the rates of AGE episodes in primary care (Table 3b). The overall reduction in the post-vaccine period compared with the pre-vaccine period was 10% (IRRa 0.90; 95% CI: 0.85-0.96), whereas rates decreased by 13% during the first post-vaccine epidemiological year 2015-2016 (IRRa 0.87; 95% CI: 0.82-0.93; $p<0.05$), with significant reductions in all age groups.

There was a marked seasonality with higher AGE rates during the winter months also after vaccine introduction (Figure 2).

DISCUSSION

Four years after introduction of RV1 in the Norwegian childhood immunization program, AGE-associated hospitalizations have declined substantially, attributable to a high effectiveness of the vaccine against rotavirus hospitalizations, as established in this study.

The impact of vaccination has been significant worldwide (2, 6, 23), manifesting as early as during the first year after introduction (24, 25). Our VE estimates are comparable with results from studies in other high-income settings. In high-income European countries, VE against rotavirus hospital admissions are estimated to be between 80% and 98% (12, 26-29), while in middle-income European countries, the estimates are lower (30, 31). In a review from the US, the pooled VE of full series RV5 and RV1 against rotavirus-associated hospitalizations and emergency department visits were 84% (32). Both with test-negative and community controls we found a VE against hospital admission for RVGE among vaccine-eligible children after two vaccine doses to be around 75%, with wide confidence intervals. Other studies show that VE decreases with age, suggesting waning vaccine-induced protection (27, 33), but significant VE was documented up to the fifth year of life in a German study (27) and the seventh year in a US study (33). High VE is demonstrated through the first two years of life (17, 26), which is of importance since the risk of rotavirus hospitalizations is high during this period (34, 35). Our study was too small to demonstrate significant differences between

age groups. We plan future studies in Norway to provide more evidence on the duration of protection.

We found a 40%-52% decline in AGE-hospitalizations overall in the post-vaccine years compared with pre-vaccine years in vaccine-eligible cohorts, and even significant reductions in vaccine-ineligible cohorts, indicating a herd effect. A Finnish study of children aged <5 years, found a 69% reduction in AGE inpatient hospitalizations in the post-vaccination period (2010–2014) compared with the pre-vaccination period (1999–2005) (36); in Belgium the mean incidence of all-cause AGE hospitalizations was found to decrease by 27% between the pre- and post-vaccination period (37); a review of 10 US studies with impact data from 2006-2017 found that the median reduction of AGE hospitalization rates was 38.5% (IQR: 33.3, 46.5) (32). Protection of unvaccinated age groups is suggested in several studies (32, 38-40).

There was a lower vaccine impact in the primary care data. The small reductions are likely caused by the inclusion of episodes caused by a wide range of microbiological agents, many giving milder disease that do not require hospital care. Also, the effectiveness of the vaccine is presumably lower against mild rotavirus disease (41). Low impact was reported in pediatric outpatient care in a Swedish study (42), among Finnish outpatient AGE cases (24, 36), and in primary care in a study from England (39). Interestingly, there was a declining trend in the immediate pre-vaccine years in our data, without any obvious explanation.

Strengths of our study are the comprehensive national registries complemented with prospective hospital surveillance, and the personal ID numbers allowing us to link cases and controls in the VE study to the national immunization registry and obtain reliable information about vaccination status, including accurate dates for vaccine administration. The use of rotavirus test-negative controls can reduce confounding from healthcare-seeking behavior, and has been shown to be an efficient approach to estimate rotavirus VE (43, 44). Also, the use of immunization registries as source of controls is believed to produce valid results in rotavirus VE studies (17, 18). SYSVAK is a suitable source for selection of controls because it captures 98% of the Norwegian child population (45). A strength of the impact study is that we used pre-vaccine data over six epidemiological years, allowing us to control for underlying trends in AGE incidence. A minimal uptake of rotavirus vaccines in Norway prior to introduction of routine vaccination in 2014, and the high coverage already during the first year, makes an ideal setting for studying the impact of vaccination.

Our estimates of VE should be interpreted in lights of several limitations of the case-control analysis. Firstly, the exact recruitment rate is not known and this may affect the representativeness of the study participants. Also, 150 samples were not available for supplemental EIA testing by the

reference laboratory, and thereby excluded from the study. However, we do not believe that inclusion differs between cases and controls and affect the results much. Secondly, high vaccine coverage was achieved rapidly after the program start in Norway, resulting in a small sample size after vaccine introduction and limited study power. Case-control studies are more efficient to assess VE in settings with vaccine coverage under 80%, and there is a stronger potential for confounding if the coverage is very high or low (46). The study was underpowered to estimate VE by genotypes, age groups or incomplete vaccination. Finally, test-negative AGE controls can potentially be misclassified, although the risk is reduced by requiring two different assays to be negative. The impact studies have the limitations of being descriptive and ecological, and therefore the measured effects could be due to other factors than vaccination only. Testing and diagnostic practices could have changed during the study period, diagnostic coding is often inaccurate and unspecific, and coding practices can also change over time. Some of the observed reductions can be due to natural variations in the rotavirus burden.

In conclusion, four years after the introduction of rotavirus vaccine in the Norwegian childhood immunization program, the vaccine has been shown to be effective against RVGE treated in hospital and has reduced the burden of AGE substantially among children <5 years of age in Norway, and also to some degree among children not eligible for vaccination. High vaccine coverage will contribute to a continuous protection of the youngest and most vulnerable children. Further monitoring is vital to measure the duration of protection and identify possible indirect effects in non-vaccinated individuals.

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Figure 1. Inclusion of rotavirus positive cases and test-negative controls in the case-control study, Norway 2014-2018

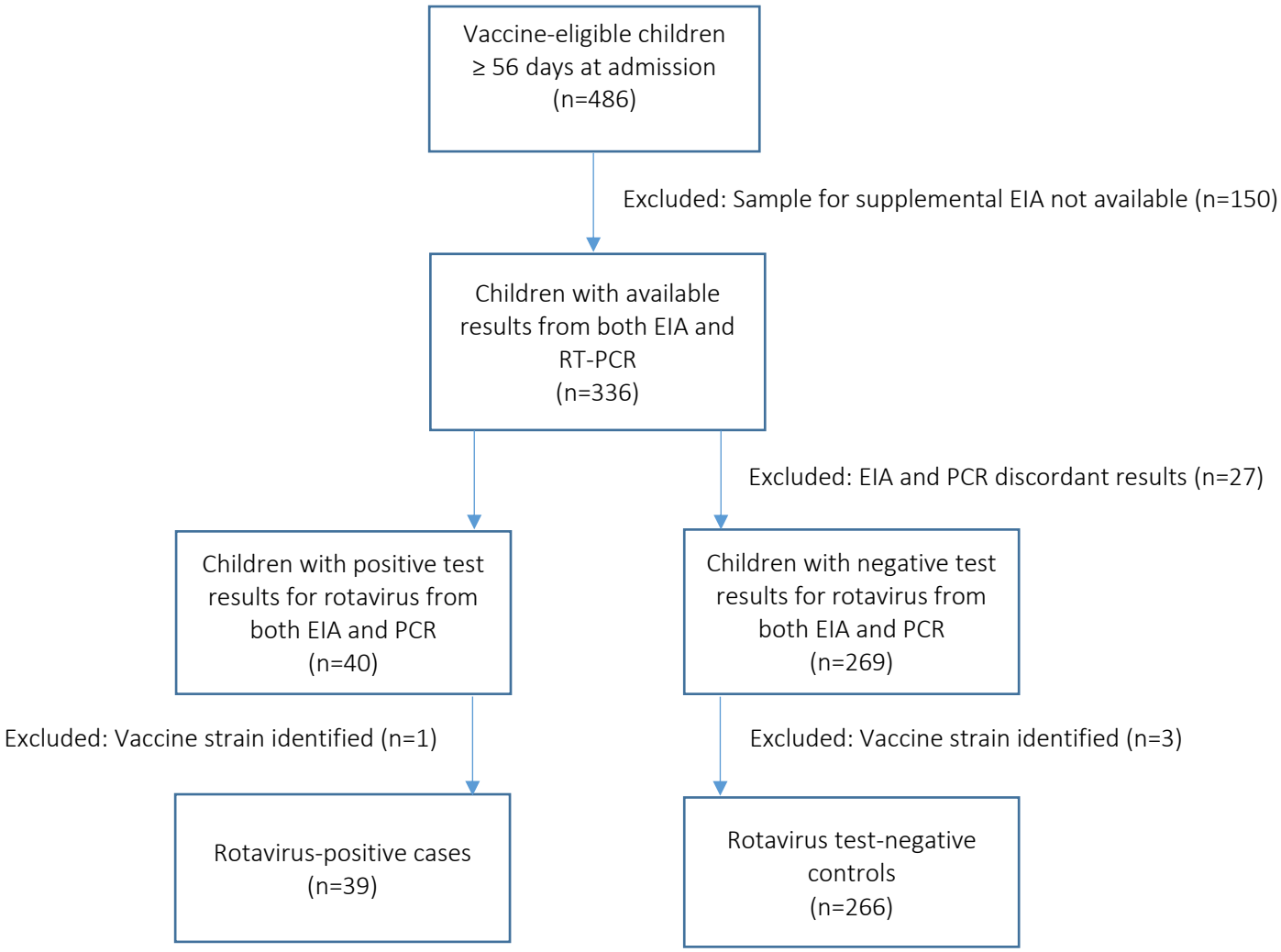
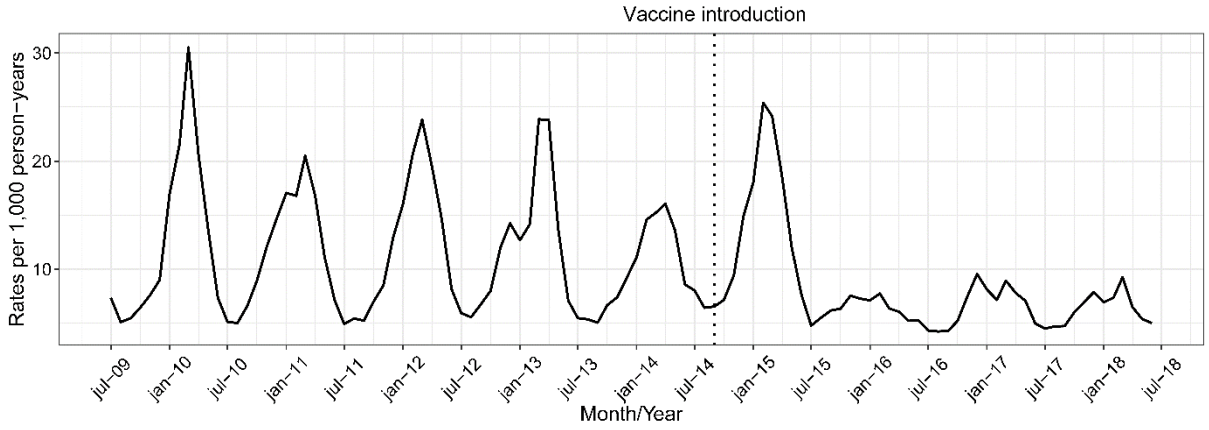


Figure 2. Incidence of AGE cases in a) hospital and b) primary care per 1,000 person-years, Norway July 2009-June 2018

a)



b)

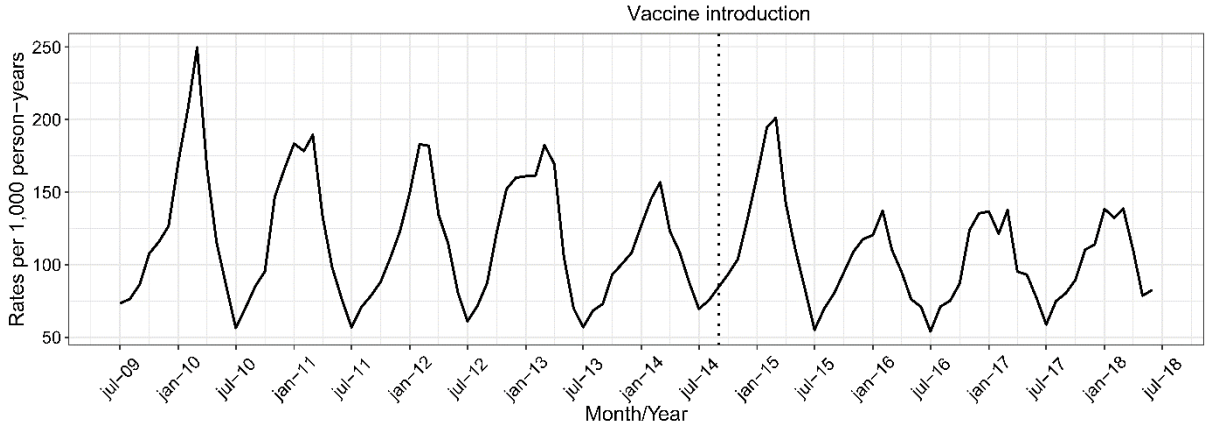


Figure 3. Incidence of AGE episodes in children <5 years of age in hospital, stratified by etiology, Norway July 2009-June 2018

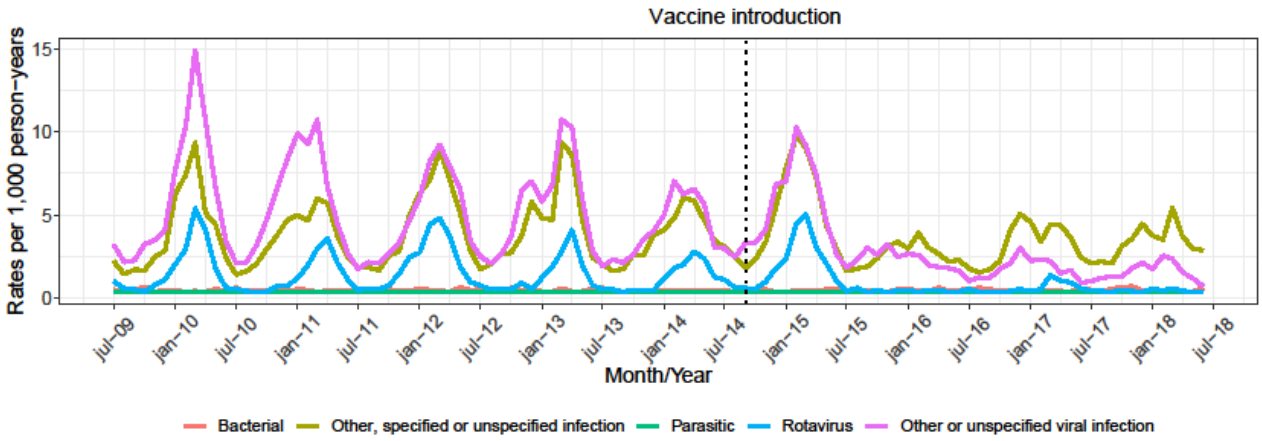


Table 1: Characteristics of rotavirus positive cases, test-negative controls and community controls, Norway 2014-2018

Characteristics		Cases (n =39)	Test-negative controls (n = 266)	p	Community controls (n =113,429)	p
Age in months, median (IQR)		17.6 (12.1-22.8)	7.6 (4.5-12.9)	<0.001	–	–
Age Groups	<6 months	3 (8%)	101 (38%)	<0.001	–	–
	6-12 months	7 (18%)	90 (34%)	–	–	–
	12-18 months	10 (26%)	46 (17%)	–	–	–
	18-24 months	10 (26%)	16 (6%)	–	–	–
	>24 months	9 (23%)	13 (5%)	–	–	–
Sex	Female	15 (38%)	125 (47%)	0.320	54928 (48%)	0.210
	Male	24 (62%)	141 (53%)	–	58501 (52%)	–
Vaccination*	Fully Vaccinated	29 (74%)	196 (74%)	0.007	99769 (88%)	<0.001
	Partially Vaccinated	1 (3%)	44 (17%)	–	7755 (7%)	–
	Non Vaccinated	9 (23%)	26 (10%)	–	5905 (5%)	–
Type of hospital contact	Inpatient	33 (87%)	165 (62%)	0.003	–	–
	Outpatient	5 (13%)	100 (38%)	–	–	–
Vesikari Score**	Severe	24 (96%)	109 (53%)	<0.001	–	–
	Mild	0 (0%)	22 (11%)	–	–	–
	Moderate	1 (4%)	76 (37%)	–	–	–
Admission during rotavirus season***	No	12 (31%)	101 (38%)	0.380	–	–
	Yes	27 (69%)	165 (62%)	–	–	–

**Fully vaccinated means two doses and partially vaccinated means one dose*

***Information on severity was incomplete for 14 cases and 59 test-negative controls*

****December-May*

Table 2. Rotavirus vaccine effectiveness* for two doses against hospital admission for rotavirus gastroenteritis among vaccine-eligible children, Norway 2014-2018

	No. of rotavirus positive cases	No. of test-negative controls	VE	95% CI
Overall	38	222	76%	34-91%
<18 months of age at admission	19	193	83%	35-96%
Inpatients	32	135	85%	51-95%
Admitted during rotavirus season	26	142	79%	29-94%

** OR calculated by unconditional logistic regression using test-negative controls, adjusting for age and date of hospital admission*

Table 3. AGE incidence rates among Norwegian children <5 years of age, seen in a) hospital and b) primary care, and change (incidence rate ratio) in the post-vaccine era 2015-2018 compared to the pre-vaccine era 2009-2015*

a)

	Incidence rate per 1000 person-years (95% CI)				Incidence rate ratio** (95% CI)							
	Pre-vaccine (Mean)	Post-vaccine**										
Age (years)	2009-2015	2015-2016	2016-2017	2017-2018	2015-2016	p	2016-2017	p	2017-2018	p	2015-2018	p
0	6.0 (4.0-7.7)	4.9 (4.3-5.5)	4.9 (4.3-5.5)	4.9 (4.4-5.5)	0.63 (0.54-0.73)	<0.05	0.59 (0.50-0.69)	<0.05	0.55 (0.46-0.66)	<0.05	0.60 (0.53-0.69)	<0.05
1	21.3 (17.1-24.4)	10.2 (9.4-11.1)	9.5 (8.7-10.3)	9.5 (8.7-10.3)	0.55 (0.47-0.64)	<0.05	0.47 (0.40-0.55)	<0.05	0.49 (0.41-0.59)	<0.05	0.52 (0.45-0.59)	<0.05
2	16.5 (11.3-19.8)	**6.3 (5.7-7.0)**	6.6 (6.0-7.3)	5.9 (5.3-6.6)	**0.47 (0.40-0.56)**	**<0.05**	0.51 (0.42-0.61)	<0.05	0.43 (0.35-0.52)	<0.05	0.48 (0.41-0.57)	<0.05
3	8.1 (5.1-10.7)	**3.5 (3.0-4.0)**	**5.0 (4.5-5.6)**	3.5 (3.0-4.0)	**0.53 (0.43-0.67)**	**<0.05**	**0.70 (0.56-0.87)**	**<0.05**	0.53 (0.41-0.69)	<0.05	0.60 (0.49-0.73)	<0.05
4	4.2 (3.0-5.7)	**2.4 (2.1-2.8)**	**2.7 (2.3-3.1)**	**3.0 (2.6-3.5)**	**0.61 (0.48-0.78)**	**<0.05**	**0.65 (0.50-0.83)**	**<0.05**	**0.70 (0.53-0.92)**	**<0.05**	**0.63 (0.52-0.78)**	**<0.05**
Total	11.2 (8.7-12.8)	5.4 (5.2-5.7)	5.7 (5.5-6.0)	5.3 (5.1-5.6)	0.56 (0.49-0.63)	<0.05	0.55 (0.48-0.63)	<0.05	0.52 (0.45-0.61)	<0.05	0.55 (0.49-0.61)	<0.05

b)

	Incidence rate* per 1000 person-years (95% CI)				Incidence rate ratio* (95% CI)							
	Pre-vaccine (Mean)	Post-vaccine**										
Age (years)	2009-2015	2015-2016	2016-2017	2017-2018	2015-2016	p	2016-2017	p	2017-2018	p	2015-2018	p
0	159.0 (143.0-172.3)	141.0 (138.0-144.1)	147.0 (143.9-150.1)	146.0 (142.9-149.1)	0.94 (0.88-1.00)	<0.05	0.98 (0.91-1.00)	0.5	1.00 (0.92-1.10)	0.94	0.95 (0.90-1.00)	0.13
1	210.5 (174.7-243.9)	151.0 (147.9-154.1)	154.0 (150.9-157.2)	155.0 (151.9-158.2)	0.81 (0.75-0.88)	<0.05	0.85 (0.78-0.93)	<0.05	0.88 (0.80-0.97)	<0.05	0.83 (0.77-0.90)	<0.05
2	114.9 (97.2-130.8)	**87.1 (84.8-89.5)**	95.9 (93.5-98.4)	92.0 (89.6-94.5)	**0.81 (0.75-0.89)**	**<0.05**	0.89 (0.81-0.98)	<0.05	0.86 (0.77-0.95)	<0.05	0.84 (0.78-0.91)	<0.05
3	68.2 (56.6-77.6)	**57.1 (55.3-59.0)**	**62.9 (61.0-64.9)**	66.2 (64.2-68.3)	**0.89 (0.82-0.96)**	**<0.05**	**0.99 (0.91-1.10)**	**0.77**	1.10 (0.96-1.20)	0.24	0.94 (0.87-1.00)	0.1
4	48.7 (42.4-53.0)	**42.4 (40.8-44.0)**	**47.3 (45.6-49.0)**	**47.5 (45.8-49.3)**	**0.89 (0.81-0.98)**	**<0.05**	**0.98 (0.89-1.10)**	**0.77**	**1.00 (0.89-1.10)**	**0.96**	**0.93 (0.86-1.00)**	**0.12**
Total	119.8 (102.9-133.3)	94.6 (93.5- 95.7)	100.5 (99.4-101.6)	100.6 (99.5-101.7)	0.87 (0.82-0.93)	<0.05	0.93 (0.87-1.00)	0.07	0.96 (0.89-1.00)	0.34	0.90 (0.85-0.96)	0.12

*estimates in bold are results for vaccine-ineligible age groups
**compared to the pre- vaccination period, adjusted for month and rotavirus epidemiological year (July-June)