Impact of the Rotavirus Vaccination Program in Norway After Four Years With High Coverage

Tone Bruun, MD, Beatriz Valcarcel Salamanca, MSc, PhD,† Terese Bekkevold, MPhil,† Henrik Døllner, MD, PhD,‡§ Moustafa Gibory, MSc,¶ Ann Marit Gilje, MD,‖ Elisebet Haarr, MD,** Anne-Marte Bakken Kran, MD, PhD,†† Truls M. Leegaard, MD, PhD,‡‡§§ Britt Nakstad, MD, PhD,§§ Svein Arne Nordbø, MD,§¶¶ Astrid Rojahn, MD,‖‖ Ketil Størdal, MD, PhD,*** and Elmira Flem, MD, PhD,† for the Norwegian Enhanced Pediatric Immunisation Surveillance (NorEPIS) Network*

Background: Use of rotavirus vaccines worldwide since 2006 has led to a 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 the monovalent rotavirus vaccine (RV1) and high vaccination coverage from the beginning enabled evaluation of the impact of this vaccine during the first 4 years after introduction.

Methods: Prospective laboratory-based surveillance among children <5 years of age hospitalized for acute gastroenteritis at 5 Norwegian hospitals was used to assess the vaccine effectiveness of 2 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% confidence interval [CI]: 34%–91%) using test-negative controls, and 75% (95% CI: 44%–88%) using community controls. In the postvaccine period, acute gastroenteritis hospitalizations in children <5 years were reduced by 45% compared with the prevaccine years (adjusted incidence rate ratios 0.55; 95% CI: 0.49–0.61). Reduction in hospitalizations was also seen in cohorts not eligible for vaccination. 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.

Key Words: rotavirus, gastroenteritis, vaccine effectiveness, epidemiology

(*Pediatr Infect Dis J* 2020;XX:00–00)

Rotavirus is the leading cause of severe acute gastroenteritis (AGE) among children <5 years of age globally.[1,2] In 2006, 2 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). In 2009, the World Health Organization recommended that all countries introduce rotavirus vaccination into their national immunization programs.[5] As of October 2018, universal rotavirus vaccination was in place in 98 countries. Two thirds of European countries had not yet implemented universal vaccination.[6]

Rotavirus gastroenteritis (RVGE) used to be the primary cause of severe AGE in Norwegian children.[7] In October 2014, Norway introduced rotavirus vaccination in the national immunization program using RV1 with first dose offered at 6 weeks of age and the second dose at 12 weeks of age.[8] To minimize the intussusception risk, Norway adopted strict age limits for vaccine administration: the first dose is recommended to be given by maximum 12 weeks of age and the second dose before 16 weeks of age.[9] High national coverage was achieved during the first year: 89% for the first dose and 82% for the second dose.[10] Nearly 95% of vaccinated children receive their first vaccine dose before 8 weeks of age. Vaccine coverage increased gradually and measured 95% for 1 dose and 93% for 2 doses at the age of 2 years in 2018, being among the highest across countries in Europe and globally.[11–14]

Although several studies provide real-world evidence about the effectiveness of rotavirus immunization programs, the coverage and vaccine impact vary across countries, also within the high-income European settings.[11,14,15] The exclusive use of RV1 and a high vaccination coverage from the start, together with the use of Norwegian population-based registries, provided a valuable opportunity to evaluate the impact of rotavirus vaccination in a low-mortality setting. We aimed to assess the effectiveness and impact of the rotavirus immunization program during a 4-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.

Accepted for publication November 1, 2020

From the Departments of *Infection Control and Vaccines; †Infectious Disease Epidemiology and Modelling, Norwegian Institute of Public Health, Oslo; ‡Children's Department, St. Olavs University Hospital; §Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim; ¶Department of Virology, Norwegian Institute of Public Health, Oslo; Departments of ‖Pediatrics; **Medical Microbiology, Stavanger University Hospital, Stavanger; ††Department of Microbiology, Oslo University Hospital, Oslo; ‡‡Department of Microbiology and Infection Control, Akershus University Hospital, Lørenskog; §§Institute of Clinical Medicine—Campus Ahus, Division of Medicine and Laboratory Sciences, University of Oslo, Oslo; ¶¶Department of Medical Microbiology, St. Olavs University Hospital, Trondheim; ‖‖Department of Pediatrics, Oslo University Hospital, Oslo; and ***Department of Pediatrics, Østfold Hospital Trust, Fredrikstad, Norway. Anne-Marte Bakken Kran, MD, PhD, is currently at the Department of Infectious Disease Registries, Norwegian Institute of Public Health, Oslo, Norway. Elmira Flem, MD, PhD, is currently at MSD Norway, Drammen, Norway.

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

E.F. is an employee of MSD Norway. The current work was performed by Dr. Flem while affiliated with the Norwegian Institute of Public Health. The other authors have no conflicts of interest to disclose.

Address for correspondence: Tone Bruun, MD, Norwegian Institute of Public Health, PO Box 222, N-0213 Oslo, Norway. E-mail: tone.bruun@fhi.no.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/20/XXXX-0000

DOI: 10.1097/INF.0000000000003020

Case-control Study of VE

The study was based on a previously established[7] rotavirus sentinel surveillance network of the Norwegian Institute of Public Health and 5 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 implemented from February 1, 2014 until May 31, 2018. Children <5 years of age admitted to hospital with AGE within 10 days of illness onset were enrolled if their parents provided written informed consent. 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 nosocomially 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 Norwegian Institute of Public Health for further testing. We applied the Vesikari severity scale[16] to classify cases as severe (score of ≥11), moderate[(7–10)] or mild (<7).

Cases

We included as cases consecutive children from the sentinel surveillance who fulfilled the following criteria: (1) birth after September 1, 2014; (2) age ≥56 days when admitted to hospital (to ensure eligibility to have received at least 1 vaccine dose from age 6 weeks (42 days) 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-polymerase chain reaction (PCR) (RIDAGENE, R-Biopharm, Darmstadt, Germany; Seegene, Seoul, South Korea). Testing positive both by EIA and RT-PCR was required to avoid false positive results. We used Jaccard similarity index to test for similarity between EIA and RT-PCR results, and found the correlation between the tests to be 0.84. Positive samples were genotyped by a multiplex seminested RT-PCR,[17,18] 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.[19] 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 testing negative for rotavirus by EIA and RT-PCR. Community controls were children born after September 1, 2014 who were registered in the National Immunization Registry[20] on August 25, 2018 when immunization data were extracted from the registry, 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.[21,22]

Immunization Data

Rotavirus vaccination status (the number and dates of doses received) of cases and controls was ascertained through linkage with the National Immunization Registry. Registration is mandatory for all vaccines included in the childhood immunization program.[20]

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 VE

Characteristics of cases and controls were compared by the two-sided Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables.

We estimated the VE against hospital admission for RVGE after 2 doses using the following formula: VE = (1 − Odds Ratio [OR]) × 100%.

Using test-negative controls, we calculated ORs (odds of being vaccinated among cases versus the odds of being vaccinated among controls) and 95% confidence intervals (CIs) by using unconditional logistic regression, adjusting for date of birth and date of hospital admission. In addition, we conducted conditional logistic regression, matching each case to 1 or 2 (if possible) test-negative controls by date of birth (±60 days) and date of hospital admission (±60 days), also adjusting for date of birth and admission date. Using community controls, we calculated OR and 95% CI for vaccination by using unconditional logistic regression, adjusting for date of birth and using conditional logistic regression, matching each case to 5 community controls by date of birth (±60 days), also adjusting for date of birth. The matched controls were resampled with replacement from the original dataset (by bootstrapping). The VE was calculated for each set of cases and controls with the mean value being reported.[23]

Time-series Analysis of Impact of the Vaccination Program

We used national population-based registry data for healthcare encounters associated with AGE during the years 2009–2018. Two or more encounters registered within 10 days in 1 patient were considered the same AGE episode.

Hospital Admissions

We used data from the Norwegian Patient Registry,[24] 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),[25] which contains reimbursement claims from all general practitioners and emergency primary care 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.[26]

Analysis

We analyzed the data by rotavirus epidemiologic year, defined as July through June. As vaccination was introduced in mid-October 2014, we defined a prevaccine period from July 2009 through June 2015 (when vaccine coverage was low and the impact of the program was negligible), and a postvaccine period from July 2015 through June 2018. Using a similar approach as Thomas et al,[27] 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 epidemiologic year as a linear term, and for seasonal patterns by using month as an indicator variable. An indicator variable that distinguished prevaccine and postvaccine periods was included in the model to obtain adjusted incidence rate ratios (IRRa). To control for autocorrelation, we included an autoregressive term up to 1 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/postvaccine indicator variable. The results of the final model were expressed as IRRa compared with the prevaccine 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 (Application number 2013/2038).

RESULTS

Rotavirus VE

Characteristics of Cases and Controls

Overall, we enrolled 39 rotavirus-positive cases and 266 rotavirus-negative AGE controls (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E261; Table 1). Rotavirus cases were older than test-negative controls (median age of 17.6 vs. 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 controls (Table 1). Breakthrough infections occurred in 29 fully vaccinated children (age range 4–37 months).

VE Assessment

Using test-negative controls, we estimated the VE of full immunization with 2 doses against hospital admission for RVGE to be 76% (95% CI: 34%–91%). Restricting the analysis to those admitted during the rotavirus seasons 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 were demonstrated in the matched analysis, with an overall 2-dose VE of 78% (95% CI: 20%–94%). Using community controls, the overall VE of 2 doses was 75% (95% CI: 44%–88%), with similar results in the matched analysis.

Impact of Rotavirus Vaccination on Acute Gastroenteritis

In the prevaccine 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 3464 episodes per epidemiologic year [range: 2825–3841]). Of these, 52% were inpatients and 48% were outpatients. In the postvaccine period from July 2015 to June 2018, 5007 AGE episodes were seen in the hospital during 912,977 person-years of follow-up (average 1669 episodes per epidemiologic year [range: 1608–1739]); 49% inpatients and 51% outpatients. The median age of AGE cases admitted to hospital before vaccine introduction were 17 (IQR: 10–27) months, similar to the median age of those admitted postvaccination (16 [IQR: 9–30] months).

A total of 222,035 AGE episodes were registered in primary care during the 6-year prevaccine period (average 37,006 episodes per epidemiologic year [range: 32,528–39,847]) and 90,002 cases during the 3 postvaccine years (average 30,001 episodes [range: 29,049–30,608]). The median age for AGE cases treated during pre and postvaccine periods was 19 months (IQR: 12–32) and 20 (IQR: 11–34), respectively. We observed a marked winter seasonality in both hospital and primary care during the study period (Fig. 1). Fourteen percent of the hospital cases had a rotavirus-specific code on the main discharge diagnosis before vaccine introduction, compared with 8% postintroduction (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E262).

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 (mo)	<6	3 (8%)	101 (38%)	<0.001	—	—
	6–12	7 (18%)	90 (34%)		—	—
	12–18	10 (26%)	46 (17%)		—	—
	18–24	10 (26%)	16 (6%)		—	—
	>24	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%)	
	Nonvaccinated	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 2 doses and partially vaccinated means 1 dose.
†Information on severity was incomplete for 14 cases and 59 test-negative controls.
‡December–May.

TABLE 2. Rotavirus Vaccine Effectiveness* for 2 Doses Against Hospital Admission for Rotavirus Gastroenteritis Among Vaccine-eligible Children, Norway 2014–2018

	No. Rotavirus-positive Cases	No. Test-negative Controls	VE (%)	95% CI
Overall	38	222	76	34%–91%
<18 mo 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.

The time-series analysis demonstrated a 45% decrease in the rates of AGE-associated hospital episodes among children <5 years of age in the postvaccine period compared with the prevaccine years (IRRa 0.55; 95% CI: 0.49–0.61) overall (Table 3). The reduction among children <1 year of age was 40%, and among children 1–3 years of age 40%–52%. There was also a 37% decrease among children between 4 and 5 years of age who were not eligible for vaccination (IRRa 0.63; 95% CI: 0.52–0.78). We found modest reductions in the rates of AGE episodes in primary care (Table 3). The overall reduction in the postvaccine period compared with the prevaccine period was 10% (IRRa 0.90; 95% CI: 0.85–0.96), whereas rates decreased by 13% during the first postvaccine epidemiologic year 2015–2016 (IRRa 0.87; 95% CI: 0.82–0.93), with significant reductions across all age groups.

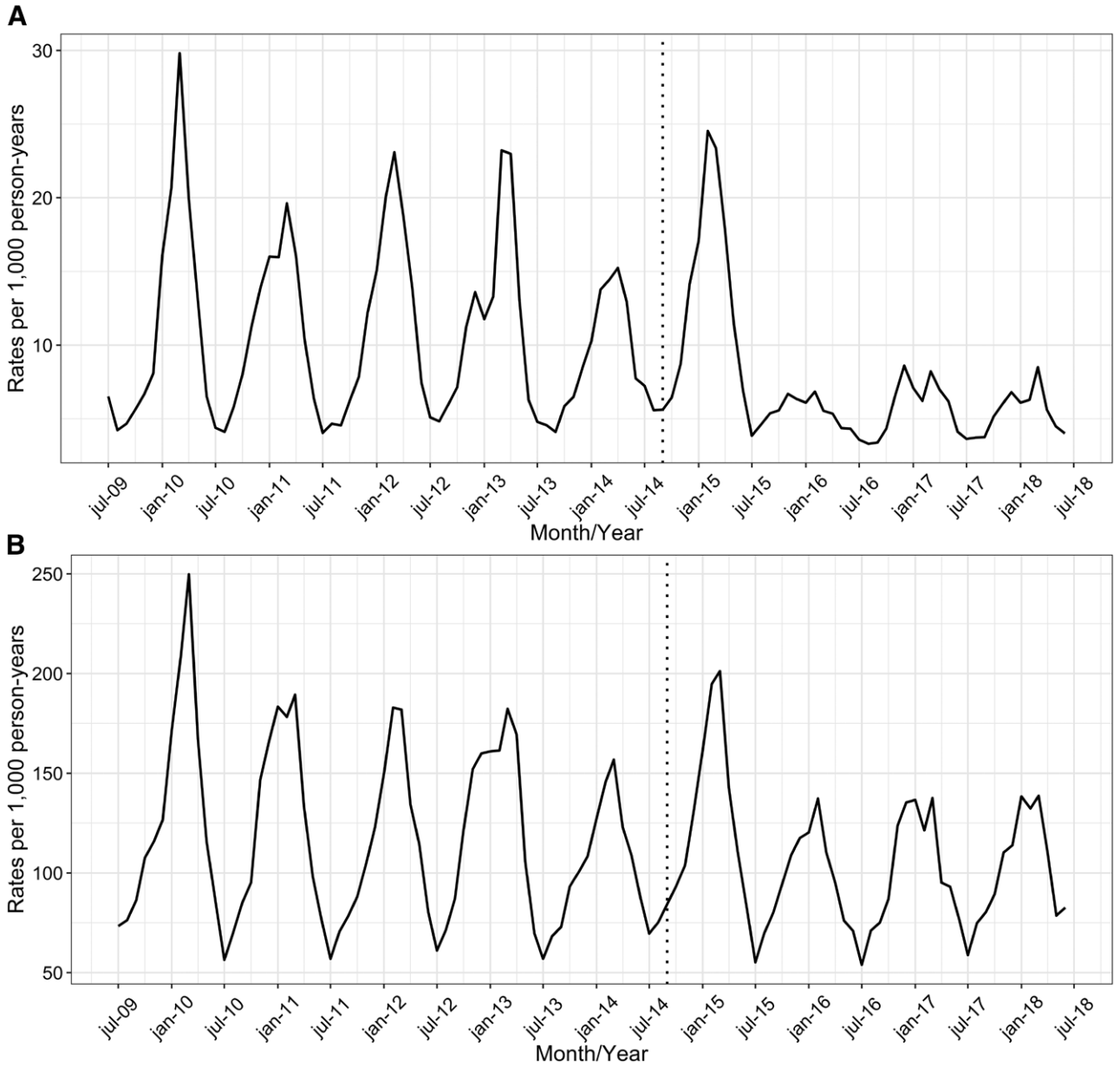

FIGURE 1. AGE incidence among Norwegian children <5 years of age 2009–2018. Incidence of AGE cases in (A) hospital and (B) primary care per 1000 person-years, Norway July 2009–June 2018.

There was a marked seasonality with higher AGE rates observed during the winter months also after vaccine introduction (Fig. 1).

DISCUSSION

Four years after the 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,[2,6,28] manifesting as early as during the first year after introduction.[29,30] The benefits of rotavirus vaccination were estimated to largely exceed the increased risk of vaccine-associated intussusception also in Norway, as estimated in a recent modeling study.[9] Our VE estimates are comparable with results from studies in other high-income settings. In high-income European countries, VE against rotavirus hospital admissions were estimated to be between 80% and 98%,[14,15,31–34] while in middle-income European countries, the estimates are lower.[35,36] In a review from the United States, the pooled VE of full series RV5 and RV1 against rotavirus-associated hospitalizations and emergency department visits were 84%.[37] Both with test-negative and community controls, we found a VE against hospital admission for RVGE among vaccine-eligible children after 2 vaccine doses to be around 75%, with wide CIs. Other studies show that VE decreases with age, suggesting waning vaccine-induced protection,[32,38] but significant VE was documented up to the fifth year of life in a German study[32] and the seventh year in a US study.[38] High VE is demonstrated through the first 2 years of life,[21,31] which is of importance because the risk of rotavirus hospitalizations is high during this period.[39,40] The current study was not powered to demonstrate significant differences in VE by age, but future studies in Norway are planned to provide more evidence on the durability of vaccine protection.

We found a 40%–52% decline in AGE hospitalizations overall in the postvaccine years compared with pre-vaccine years in vaccine-eligible cohorts, and even significant reductions in vaccine-ineligible cohorts, indicating a herd effect. Finland reported a 69% reduction in AGE inpatient hospitalizations among children <5 years of age in the postvaccination period (2010–2014) compared with the prevaccination period (1999–2005)[41] and in Belgium, the mean incidence of all-cause AGE hospitalizations was found to decrease by 27% between the pre and postvaccination period.[42] A review of 10 US studies with impact data from 2006 to 2017 found that the median reduction of AGE hospitalization rates was 38.5% (IQR: 33.3–46.5).[37] Protection of unvaccinated age groups was suggested in several studies.[14,37,43–45]

Few studies have assessed the impact of vaccination on utilization of primary care. The program-impact in the primary care was lower in Norway, likely because the VE is presumably lower against mild rotavirus disease.[45] The smaller observed reductions in the incidence of AGE in primary care can be also related to the inclusion of gastroenteritis episodes caused by a wide range of microbiologic agents, many giving milder disease that do not require hospital care. A lower impact of rotavirus vaccination in pediatric outpatient care was also reported in Sweden,[46] Finland[29,41] and England.[47] Interestingly, there was a declining trend in rotavirus consultations in the years immediately before vaccine introduction in our primary care data, which may be related to secular trends. Similar observations were reported in the Netherlands and Belgium but a decrease in rotavirus cases in those countries was observed only during the 2013/2014 season without any obvious explanation.[42,48]

Strengths of our study are the use of comprehensive national registries complemented with prospective hospital surveillance, which allowed data linkage with the national immunization registry to obtain reliable information about vaccination status, including accurate dates for vaccine administration. The use of test-negative controls can reduce confounding from healthcare-seeking behavior, and has been shown to be an efficient approach to estimate VE against rotavirus, influenza and other diseases.[49,50] Also, the use of immunization registries as source of controls is believed to produce valid results in rotavirus VE studies.[21,22] The National Immunization Registry in Norway is a suitable source for selection of controls because it captures 98% of the Norwegian pediatric population.[51] In addition, we could distinguish wild-type infection from excreted vaccine virus and exclude cases with the vaccine strain. A further strength is the use of long observation period of over 6 epidemiologic years before vaccine introduction, which allowed to control for underlying trends in the AGE incidence. A minimal uptake of rotavirus vaccines in Norway before the introduction of routine vaccination in 2014, and the high coverage provided an ideal setting for studying the impact of vaccination.

TABLE 3. Change in AGE Incidence (Incidence Rate Ratios) Among NORWEGIAN Children <5 Years of Age, Seen in Hospital and Primary Care in the Postvaccine Era 2015–2018 Compared With the Prevaccine Era 2009–2015*

	Incidence Rate Ratio† (95% CI)							
	Hospital Care							
Age (y)	2015–2016	*P*	2016–2017	*P*	2017–2018	*P*	2015–2018	*P*
0	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	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	**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	**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	**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	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
				Primary Care				
0	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	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	**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	**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	**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	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

*Compared with the prevaccination period, adjusted for month and rotavirus epidemiologic year (July–June).
†Estimates in bold are results for vaccine-ineligible age groups.

Our estimates of VE should be interpreted in light of several limitations. First, the exact recruitment rate is not known and this may affect the representativeness of the study participants. Also, the 150 samples were not available for supplemental EIA testing due to loss or low sample volume, and thereby were excluded from the study. However, we do not believe that inclusion differed between cases and controls and affected the results. Second, high vaccine coverage was achieved rapidly after the program start in Norway, resulting in a small study sample and a limited 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.[52] Thus, our study was underpowered to estimate VE by genotypes, age groups or number of doses. Finally, misclassification of test-negative AGE controls could occur, although we reduced this risk by requiring 2 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 evolve over time. Some of the observed reductions can be due to secular trends in the virus circulation.

In conclusion, 4 years after the introduction of rotavirus vaccination in the Norwegian childhood immunization program, the vaccine program has been shown to be effective against RVGE treated in the hospital thereby reducing the burden of AGE 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 durability of protection and identify possible indirect effects in nonvaccinated individuals.

ACKNOWLEDGMENTS

We would like to acknowledge staff at the study hospitals for their assistance during the study, particularly: Olaug Aarseth, Ine Bjørndal, Eli Dahl, Sara Debes, Magnhild Owesen Eidem, Hanne Holm-Gabler, Anja Dyresen Guleng, Kirsti Jakobsen, Anita Kanestrøm, Anette Lunde, Barbro Marie Medås, Siv Anita Myhre, Dianne Carlyn Ditlevsen Nordstoga, Ann Cathrin Pettersen, Ida Helen Simonstad and Heidi Christin Sivertsen. We thank Liliana Vazquez Fernandez at the Norwegian Institute of Public Health for assistance with the models and statistical analysis, and all enrolled children and their families for valuable contribution to this study.

REFERENCES

1. Tate JE, Burton AH, Boschi-Pinto C, et al; World Health Organization-Coordinated Global Rotavirus Surveillance Network. Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000-2013. *Clin Infect Dis*. 2016;62(suppl 2):S96–S105.
2. Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. *JAMA Pediatr.* 2018;172:958–965.
3. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med.* 2006;354:11–22.
4. Vesikari T, Matson DO, Dennehy P, et al; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med.* 2006;354:23–33.
5. World Health Organization. Rotavirus vaccines: an update. *Wkly Epidemiol Rec*. 2009;84:533–540.
6. The ROTA Council. Global Introduction Status 2018. Available at: http://rotacouncil.org/vaccine-introduction/global-introduction-status/. Accessed September 2019.
7. Bruun T, Salamanca BV, Bekkevold T, et al; Norwegian Enhanced Pediatric Immunisation Surveillance (NorEPIS) Network. Burden of rotavirus disease in Norway: using national registries for public health research. *Pediatr Infect Dis J.* 2016;35:396–400.
8. Norwegian Institute of Public Health. Vaksine mot rotavirus. 2018. Available at: https://www.fhi.no/sv/vaksine/barnevaksinasjonsprogrammet/vaksinene-i-barnevaksinasjonsprogrammet/vaksine-mot-rotavirussykdom/. Accessed October 2020.
9. Bruun T, Watle SSV, Tveteraas IH, et al. Intussusception among Norwegian children: what to expect after introduction of rotavirus vaccination? *Vaccine.* 2019;37:5717–5723.
10. Valcarcel Salamanca B, Hagerup-Jenssen ME, Flem E. Uptake and timeliness of rotavirus vaccination in Norway: the first year post-introduction. *Vaccine.* 2016;34:4684–4689.
11. Abou-Nader AJ, Sauer MA, Steele AD, et al. Global rotavirus vaccine introductions and coverage: 2006 - 2016. *Hum Vaccin Immunother.* 2018;14:2281–2296.
12. Braeckman T, Theeten H, Lernout T, et al. Rotavirus vaccination coverage and adherence to recommended age among infants in Flanders (Belgium) in 2012. *Euro Surveill*. 2014;19:20806.
13. Lo Vecchio A, Liguoro I, Dias JA, et al. Rotavirus immunization: global coverage and local barriers for implementation. *Vaccine.* 2017;35:1637–1644.
14. European Centre for Disease Prevention and Control. *Expert Opinion on Rotavirus Vaccination in Infancy*. European Centre for Disease Prevention and Control; 2017.
15. Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006-2014. *Vaccine.* 2015;33:2097–2107.
16. Lewis K. Vesikari Clinical Severity Scoring System Manual. PATH website. 2011. Available at: http://www.path.org/publications/files/VAD_vesikari_scoring_manual.pdf. Accessed January 2020.
17. Banerjee I, Ramani S, Primrose B, et al. Modification of rotavirus multiplex RT-PCR for the detection of G12 strains based on characterization of emerging G12 rotavirus strains from South India. *J Med Virol.* 2007;79:1413–1421.
18. Iturriza-Gómara M, Kang G, Gray J. Rotavirus genotyping: keeping up with an evolving population of human rotaviruses. *J Clin Virol.* 2004;31:259–265.
19. Gautam R, Esona MD, Mijatovic-Rustempasic S, et al. Real-time RT-PCR assays to differentiate wild-type group A rotavirus strains from Rotarix(®) and RotaTeq(®) vaccine strains in stool samples. *Hum Vaccin Immunother.* 2014;10:767–777.
20. Trogstad L, Ung G, Hagerup-Jenssen M, et al. The Norwegian immunisation register--SYSVAK. *Euro Surveill*. 2012;17:19.
21. Cortese MM, Immergluck LC, Held M, et al. Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics.* 2013;132:e25–e33.
22. Cortese MM, Leblanc J, White KE, et al. Leveraging state immunization information systems to measure the effectiveness of rotavirus vaccine. *Pediatrics.* 2011;128:e1474–e1481.
23. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. Chapman & Hall/CRC Monographs on Statistics and Applied Probability; 1994:456.
24. The Directorate of Health. The Norwegian Patient Registry. Available at: https://helsedirektoratet.no/norsk-pasientregister-npr. Accessed September 2020.
25. The Norwegian Health Economics Administration. The Norwegian Health Economics Administration Database. Available at: https://helfo.no/english/about-helfo. Accessed September 2020.
26. Statistics Norway. Available at: https://www.ssb.no/en. Accessed September 2020.
27. Thomas SL, Walker JL, Fenty J, et al. Impact of the national rotavirus vaccination programme on acute gastroenteritis in England and associated costs averted. *Vaccine*. 2016;19:19.
28. Burnett E, Jonesteller CL, Tate JE, et al. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. *J Infect Dis.* 2017;215:1666–1672.
29. Leino T, Ollgren J, Salo H, et al. First year experience of rotavirus immunisation programme in Finland. *Vaccine.* 2012;31:176–182.
30. Marlow RD, Muir P, Vipond I, et al. Assessing the impacts from the first year of rotavirus vaccination in the UK. *Arch Dis Child*. 2015;100:A30.
31. Braeckman T, Van Herck K, Meyer N, et al; RotaBel Study Group. Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *BMJ.* 2012;345:e4752.
32. Pietsch C, Liebert UG. Rotavirus vaccine effectiveness in preventing hospitalizations due to gastroenteritis: a descriptive epidemiological study from Germany. *Clin Microbiol Infect.* 2019;25:102–106.

33. Hemming-Harlo M, Vesikari T, Uhari M, et al. Sustained high effectiveness of RotaTeq on hospitalizations attributable to rotavirus-associated gastroenteritis during 4 years in Finland. *J Pediatric Infect Dis Soc.* 2017;6:317–323.
34. Martinón-Torres F, Bouzón Alejandro M, Redondo Collazo L, et al; ROTACOST Research Team. Effectiveness of rotavirus vaccination in Spain. *Hum Vaccin.* 2011;7:757–761.
35. Sahakyan G, Grigoryan S, Wasley A, et al. Impact and effectiveness of monovalent rotavirus vaccine in Armenian children. *Clin Infect Dis.* 2016;62(suppl 2):S147–S154.
36. Gheorghita S, Birca L, Donos A, et al. Impact of rotavirus vaccine introduction and vaccine effectiveness in the Republic of Moldova. *Clin Infect Dis.* 2016;62(suppl 2):S140–S146.
37. Pindyck T, Tate JE, Parashar UD. A decade of experience with rotavirus vaccination in the United States - vaccine uptake, effectiveness, and impact. *Expert Rev Vaccines.* 2018;17:593–606.
38. Payne DC, Selvarangan R, Azimi PH, et al. Long-term consistency in rotavirus vaccine protection: RV5 and RV1 vaccine effectiveness in US children, 2012-2013. *Clin Infect Dis.* 2015;61:1792–1799.
39. Hasso-Agopsowicz M, Ladva CN, Lopman B, et al; Global Rotavirus Surveillance Network and Rotavirus Age Study Collaborators. Global review of the age distribution of rotavirus disease in children aged <5 years before the introduction of rotavirus vaccination. *Clin Infect Dis.* 2019;69:1071–1078.
40. Giaquinto C, van Damme P; REVEAL Study Group. Age distribution of paediatric rotavirus gastroenteritis cases in Europe: the REVEAL study. *Scand J Infect Dis.* 2010;42:142–147.
41. Leino T, Baum U, Scott P, et al. Impact of five years of rotavirus vaccination in Finland - and the associated cost savings in secondary healthcare. *Vaccine.* 2017;35:5611–5617.
42. Sabbe M, Berger N, Blommaert A, et al. Sustained low rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014. *Euro Surveill*. 2016;21:07.
43. Lopman BA, Payne DC, Tate JE, et al. Post-licensure experience with rotavirus vaccination in high and middle income countries; 2006 to 2011. *Curr Opin Virol.* 2012;2:434–442.
44. Clarke MF, Davidson GP, Gold MS, et al. Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisations in South Australian children following the introduction of rotavirus vaccination. *Vaccine.* 2011;29:4663–4667.
45. Hungerford D, Smith K, Tucker A, et al. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. *BMC Infect Dis.* 2017;17:569.
46. Ask LS, Liu C, Gauffin K, et al. The effect of rotavirus vaccine on socioeconomic differentials of paediatric care due to gastroenteritis in Swedish infants. *Int J Environ Res Public Health*. 2019;16:27.
47. Hungerford D, Vivancos R, Read JM, et al. Rotavirus vaccine impact and socioeconomic deprivation: an interrupted time-series analysis of gastrointestinal disease outcomes across primary and secondary care in the UK. *BMC Med.* 2018;16:10.
48. Hahne S, Hooiveld M, Vennema H, et al. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. *Euro Surveill*. 2014;19:20945.
49. Tate JE, Patel MM, Cortese MM, et al. Use of patients with diarrhea who test negative for rotavirus as controls to estimate rotavirus vaccine effectiveness through case-control studies. *Clin Infect Dis.* 2016;62(suppl 2):S106–S114.
50. Doll MK, Morrison KT, Buckeridge DL, et al. Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study. *Clin Infect Dis.* 2016;63:1080–1086.
51. Riise ØR, Laake I, Bergsaker MA, et al. Monitoring of timely and delayed vaccinations: a nation-wide registry-based study of Norwegian children aged<2 years. *BMC Pediatr.* 2015;15:180.
52. Verani JR, Baqui AH, Broome CV, et al. Case-control vaccine effectiveness studies: preparation, design, and enrollment of cases and controls. *Vaccine.* 2017;35:3295–3302.