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Acute gastroenteritis hospitalizations after implementation of universal mass vaccination against rotavirus

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ABSTRACT

Background: Estonia implemented rotavirus universal mass vaccination (RV UMV) in July 2014. We aimed to describe changes in acute gastroenteritis (AGE) hospitalization during RV seasons before (2007–2013) and after (2015–2018) RV UMV and compare patient profile of hospitalized AGE patients aged 0–18 years during first two consecutive RV seasons 2015 vs 2016.

Methods: We described AGE hospitalization patterns pre-and post-vaccine era using Estonian Health Insurance Fund (HIF) database. During a two-year observational multicenter study in seven Estonian hospitals from 01st of February 2015 to 30th August 2016 we assessed patient profile of all patients who met pre-determined AGE criteria.

Results: In post-vaccine era AGE hospitalization rate decreased from 10 to 8 per 1000 population (RR 0.81, 95% CI 0.79–0.83) compared to pre-vaccine era. Decreased RV seasonal activity, 81% (95% CI 77–84) and 55% (95% CI 52–58) reduction of rotavirus gastroenteritis (RVGE) hospitalization among age groups <1 and 1–4, respectively and upsurge of norovirus gastroenteritis (NoVGE) hospitalizations (RR = 1.8; 95% CI 1.6–1.9) was seen.

In the multicenter observational study, among 2249 AGE patients hospitalized median age of RVGE patients increased from 2 to 3 years ($p < 0.01$) and duration of hospital stay decreased among RVGE, NoVGE and other GE patients during two consecutive RV seasons. According to Vesikari Clinical Severity Scoring System statistically significant change of severity score distribution in two RV seasons was seen ($p < 0.001$) with trend towards less severe AGE hospitalizations; 82.5% vs 70.5% severe cases in 2015 vs 2016, respectively.

Conclusion: RV UMV lead to immediate and sustainable reduction of hospitalizations due to RVGE in children aged <4 years and reduction of overall AGE accompanied with the decrease in the severity of hospitalized children.

1. Introduction

Since 2006 World Health Organization has recommended the use of two live-attenuated rotavirus (RV) vaccines: a single-strain G1P[8] human vaccine given as two doses (RV1, Rotarix™, GlaxoSmithKline, Belgium) and pentavalent G1, G2, G3, G4, and P[8] human-bovine WC3 reassortant vaccine given as three doses (RV5 (RotaTeq®, Merck and Co. Inc., USA) for universal mass vaccination (UMV) to prevent severe rotavirus gastroenteritis (RVGE) among children under the age of 5 [1,2]. By the end of 2018, 92 countries had implemented rotavirus vaccines in their national immunization program [3]. Countries with vaccination coverage exceeding 90%, like Austria, Belgium, and Finland, have demonstrated remarkable decline of RVGE after RV UMV implementation [1,4]. In addition, several countries have presented declining trends of overall acute gastroenteritis (AGE) hospitalizations in the target population for the RV vaccine [5–7]. Leino *et al.* demonstrated 53% (95% CI 49.8–57.7) decline of total inpatient AGE burden among children under the age of 1 already within a year of RV UMV in Finland [4,8]. By 2014, when all children under the age of 5 years had been eligible for RV vaccination in Finland, 68.5% (66.6–70.3%) decline of total hospitalized AGE was observed among this age group [9].

According to Estonian Health board estimates prior to rotavirus vaccine introduction in Estonia RVGE disease burden demonstrated seasonality, presenting annually as three month long season lasting generally from week nine to week 22 (2005–2007, 2009–2010, 2012–2014). Exceptions were years 2008, when RV season lasted up to week 27, and 2011, when RVGE season lasted from week 1 to 17 [10].

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During pre-vaccine era RVGE was the leading cause of hospitalization among children under the age of 5 years with a hospitalization rate of 8–15 per 1000 population [11]. According to our previous study, majority of cases (65%) in 2007–2008 occurred in infants aged 7–24 months and were of moderate severity according to Clark severity score (mean score 12.1 (SD 3.2)). The prevailing RV genotype was G2P[4] [12].

In July 2014, RV5 was implemented in the Estonian national immunization program and replaced by RV1 in October 2015 due to national procurement. As a result, infants born from 1st of May 2014 to 1st of August 2015 were eligible for vaccination with RV5 and those born after 1st of August 2015 with RV1. Vaccination coverage of 65.6% and 86.8% was achieved by the end of 2015 and 2016, respectively [13,14].

Taking into account the unique situation in Estonia with G2P[4] strain dominance [12] and consecutive use of two RV vaccines we considered crucial to commence a study evaluating RV UMV immediate effects on AGE hospitalizations and patient profile.

As no comprehensive studies regarding AGE in Estonia have been previously done, we included a 12-year period in our study to better understand the AGE dynamics over longer periods of time.

2. Materials and methods

2.1. Study design and population

We conducted two studies. First, a descriptive study was carried out using the databases of Estonian Health Insurance Fund (HIF) to characterize AGE hospitalization in 2007–2018. HIF is the only health insurance provider in Estonia and their databases include data on demographics and ICD 10 codes of all diagnoses of all patients of the country, including children.

Second, we performed an observational study from 01st of February 2015 to 30th of August 2016 in seven largest hospitals to assess the effect of RV UMV on patient characteristics. Two regional hospitals (Tartu University Hospital, Tallinn Children's Hospital), two central hospitals (West-Tallinn Central Hospital and Pärnu Hospital), and three general hospitals (Ida-Viru Hospital, Kuressaare Hospital, and South-Estonian Hospital) that covered about 80% of pediatric hospitalizations participated in the study (Fig. 1).

We included patients aged 0–18 years admitted with AGE symptoms if AGE diagnostic criteria were met. AGE was defined as three or more loose stools or a single watery stool per day and/or at least one forceful vomiting episode within the last 24 h unexplained by any other medical condition [15]. The maximum allowed duration of symptoms at hospitalization was less than seven days.

2.2. Collection of data

In the descriptive study, data of all hospitalized patients due to AGE (ICD-10 codes A08.0, A08.1, A08.2, A08.3, A08.4, A08.5, A09, A01, A02, A03, A04, R11, K52.8, and K52.9) aged from 0 to 18 years were extracted from the HIF database. Age-specific mid-year population data was obtained from Statistics Estonia (www.stat.ee).

In the observational study, demographic (age, gender, nationality, RV vaccination history) and clinical data (onset of diarrhea and/or vomiting) were recorded at study entry to web-based study database. Two stool samples were collected at the very first opportunity into 30 ml transparent polystyrene fecal containers with an attached spoon and sent to study hospital laboratory for rotavirus, norovirus, and adenovirus 41/42 antigen detection by commercial antigen detection kits according to manufacturer's instructions. The final ICD-10 code and disease outcome was entered from

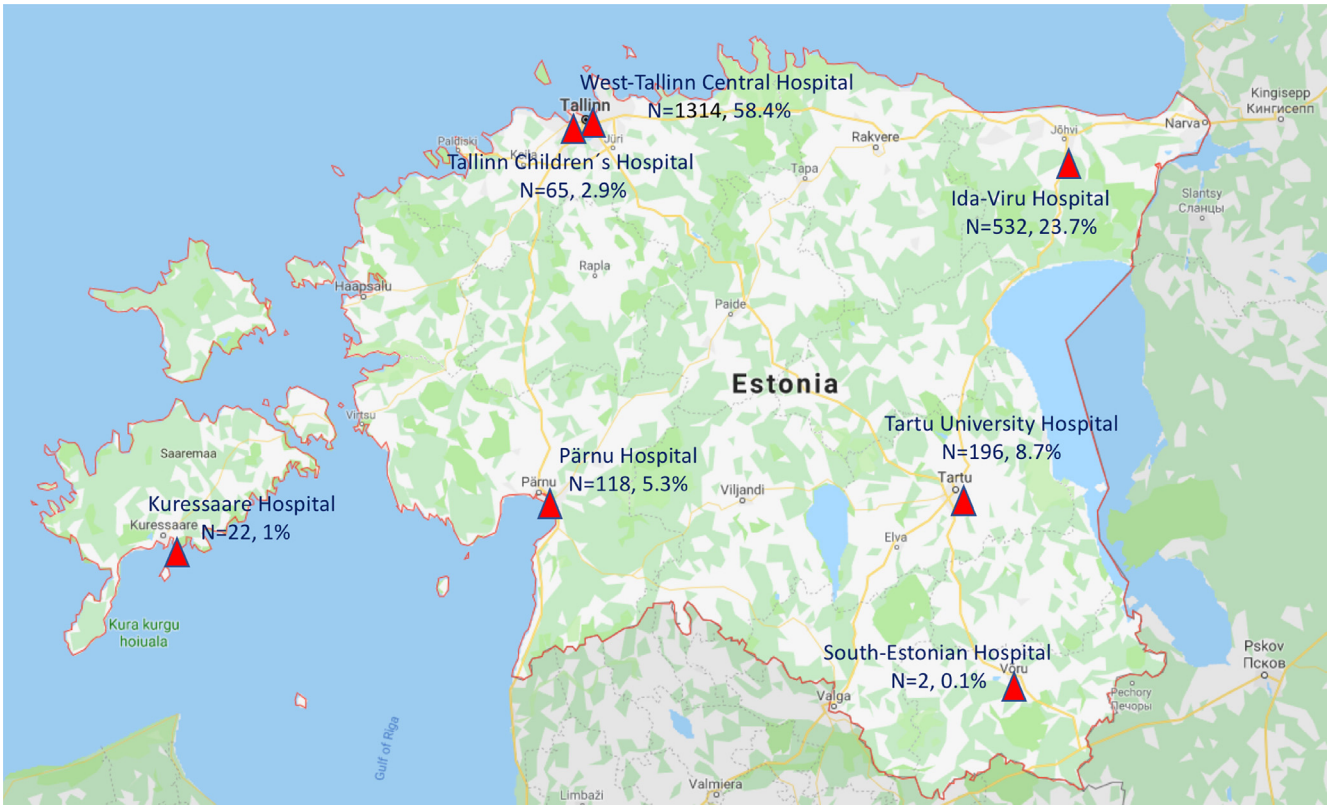

Fig. 1. Number and percentage of patients recruited by study hospitals.

patient records of discharge from the hospital. Disease severity was calculated according to Vesikari Clinical Severity Scoring System (VCSS) and categorized mild <7, moderate 7–10, and severe 11–20 [16].

2.3. Data analysis

The start of RV season was defined according to the ECDC criteria as the first of two consecutive weeks during which the percentage of specimens taken from patients with AGE tested positive for RV exceeded 10%. Seasonal peak was defined as the week with the highest proportion of RV positive test results and the end of RV season as the last of two consecutive weeks during which the percentage of specimens positive for RV was less than 10% [17].

Yearly hospitalization rates for pre-vaccine era (2007–2013) and post-vaccine era (2015–2018) were calculated for age groups < 1, 1–4, 5–9, 10–14, 15–18 years per 1000 population. The year 2014 was excluded as a wash-out period.

Hospitalization reduction by age group for 2016 vs 2015 was calculated using the following formula:

$$1 - \frac{\textit{hospitalized cases in year } 2016/\textit{midyear population in year } 2016}{\textit{hospitalized cases in year } 2015/\textit{midyear population in year } 2015}$$

Patients with AGE were analyzed in following groups: RVGE (A08.0), norovirus gastroenteritis (NoVGE) (A08.1), adenovirus gastroenteritis (HAdVGE) (A08.2). Infectious gastroenteritis and colitis, unspecified (A09), other viral enteritis (A08.3), viral intestinal infection, unspecified (A08.4) were included and further analyzed together and designated as "other GE". Patients with definite or suspected bacterial GE, parasitic GE, non-infectious GE or undefined GE (ICD-10 codes A01, A02, A03, A04, A07, A08.5, K52.8, K52.9, K56.4, and R11) were excluded from further analysis.

Wilcoxon rank-sum test for numerical variables and Fisher's exact test for categorical variables were used to compare patient characteristics and VCSS distributions between RV seasons 2015 and 2016. Mean VCSS scores of RVGE and NoVGE and total AGE by seasons were compared using Student's *t*-test. NoVGE and RVGE patients were included to a further linear regression analyses to assess the differences between mean VCSS scores between RV seasons after adjusting for diagnosis and age group. Diagnosis and age-group interaction was included in the final model.

All statistical analyses were performed with Stata/IC version 14.2.

2.4. Ethical considerations

The Research Ethics Committee of the University of Tartu approved the study protocol. Parents or legal guardians signed informed consent prior to study entry. Consent was also signed by children aged 7–18 years.

3. Results

According to HIF data, 21 037 children were hospitalized due to AGE in 2007–2013 and 10 225 in 2015–2018. During pre-vaccine era RVGE, NoVGE, HAdVGE, and other GE were diagnosed in 7620 (36%), 1 424 (7%), 616 (3%), and 8 828 (42%) cases versus 1938 (19%), 1 441 (14%), 507 (5%), and 4624 (45%) cases post-vaccine era, respectively. Highest number of hospitalized AGE cases was seen similarly in both periods from December to May.

3.1. RV seasons 2007–2018

As shown in Fig. 2, the incidence of RVGE was below the seasonal 10% threshold from 2007 to 2012 only for brief periods

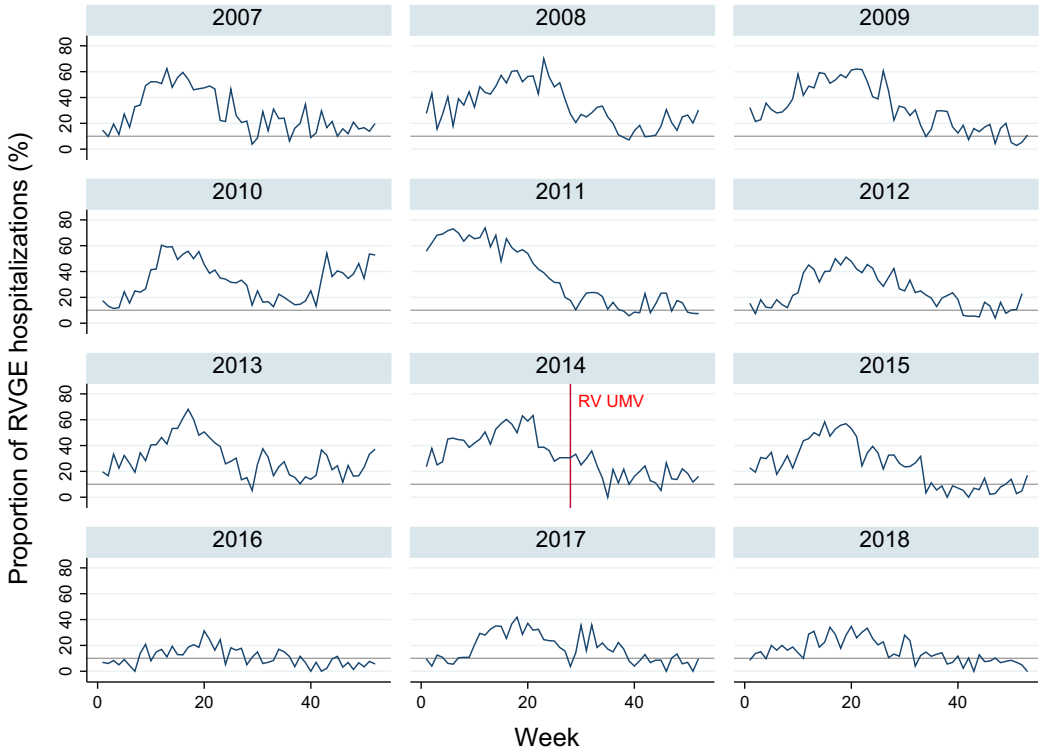

Fig. 2. Rotavirus seasonality in 2007–2018 according to Estonian HIF database. Please note that the 10% seasonal threshold is marked with the horizontal gray line and the vertical red line marks the beginning of RV UMV in July 2014. Presented is proportion of RVGE hospitalizations from all AGE hospitalizations among age group 0–18 years (%). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(2007 weeks 29–30; 2008 weeks 38–39; 2009 weeks 50–52; 2011 weeks 38–41; 2012 weeks 42–45). In 2010, 2013, and 2014 there was no two-week period below the seasonal threshold that would mark the end of RV season. At the beginning of 2015 at week 1 RV season was ongoing, peak occurred at week 15 and season ended at week 37. 2016 RV season started at week 8, peaked at week 20 and ended at week 32. 2016 presented a second wave from week 34 to 40. RV seasons 2017 and 2018 began at week 7 and 2, respectively, and ended at week 39; both retained low seasonal activity, similarly to 2016 RV season.

3.2. AGE hospitalization pre- and post-vaccine era

Before RV UMV implementation in 2007–2013, AGE hospitalization rate by diagnosis varied by year and age group (Fig. 3). Overall AGE hospitalization rate among children aged 0–18 years during pre-vaccine era was 10 per 1000 population being the highest for age groups <1 and 1–4 years; 37.3 and 26.4 per 1000 population, respectively. By diagnosis, the highest hospitalization rate was in RVGE patients aged <1 year (15 per 1000 population) and 1–4 years (13 per 1000 population).

After RV UMV, overall AGE hospitalization rate among children aged 0–18 years decreased to 8 per 1000 population (RR 0.8, 95% CI 0.79–0.83) and to 26 and 20 per 1000 population among children aged <1 (RR 0.7, 95% CI 0.65–0.73) and 1–4 years (RR 0.8, 95% CI 0.73–0.78), respectively.

Compared to pre-vaccine era RVGE hospitalization rate during post-vaccine era dropped to 3 and 6 per 1000 population among children <1 (RR 0.2, 95% CI 0.16–0.23) and 1–4 years (RR 0.5, 95% CI 0.42–0.48) accounting for 81% and 55% decline, respectively (Fig. 3). Overall RVGE hospitalization reduction during post-vaccine era was 55% (95% CI 53–57).

There was a statistically significant increase in hospitalization rate for NoVGE from 0.77 to 1.38 (RR 1.79, 95% CI 1.66–1.92) and HAdVGE from 0.33 to 0.49 (RR 1.45, 95% CI 1.29–1.64) per 1000 population in post-vaccine era compared to pre-vaccine era.

When focusing on the two first consecutive RV seasons after RV UMV implementation, RVGE hospitalization reduction was present in age groups up to 9 years (<1 years 53% (95% CI 25–72), 1–4 years 62% (95% CI 56–68), 5–9 years 55% (95% CI 37–68)). Overall RVGE hospitalization reduction within the first two RV seasons after RV UMV implementation among children aged 0–18 was 61% (95% CI 55.4–66.0). In the second year, hospitalization due to NoVGE and other GE increased 2.2 (95% CI 1.9–2.6) and 1.2 (95% CI 1.1–1.3) times, respectively. Overall AGE hospitalizations rates remained unchanged during the first two years of RV UMV.

3.3. Patient characteristics in a two-year observational study

During the observational study a total of 2249 patients were recruited (Fig. 1).

RVGE seasonality pattern for 2015 and 2016 was largely similar to data collected from HIF (Fig. 2). Based on the clinical study data, RV season was ongoing at the start of the study in 2015 at week 9 with the highest proportion of RV positive test results at week 15 and season end at week 35. The 2016 RV season started at week 9, demonstrated flattened undulating pattern with a period below 10% threshold at weeks 16 and 17 and seasonal peaks at weeks 12 and 20. Due to the end of our study, the end of the 2016 RV season remained undefined, as during the week 36, the last week of our study, the proportion of RV cases still exceeded 10%.

Overall, 1697 patients were hospitalized during RV seasons and 552 during off-season. During 2015, RVGE dominated by being diagnosed in 43.4% of hospitalized cases. Other GE and NoVGE

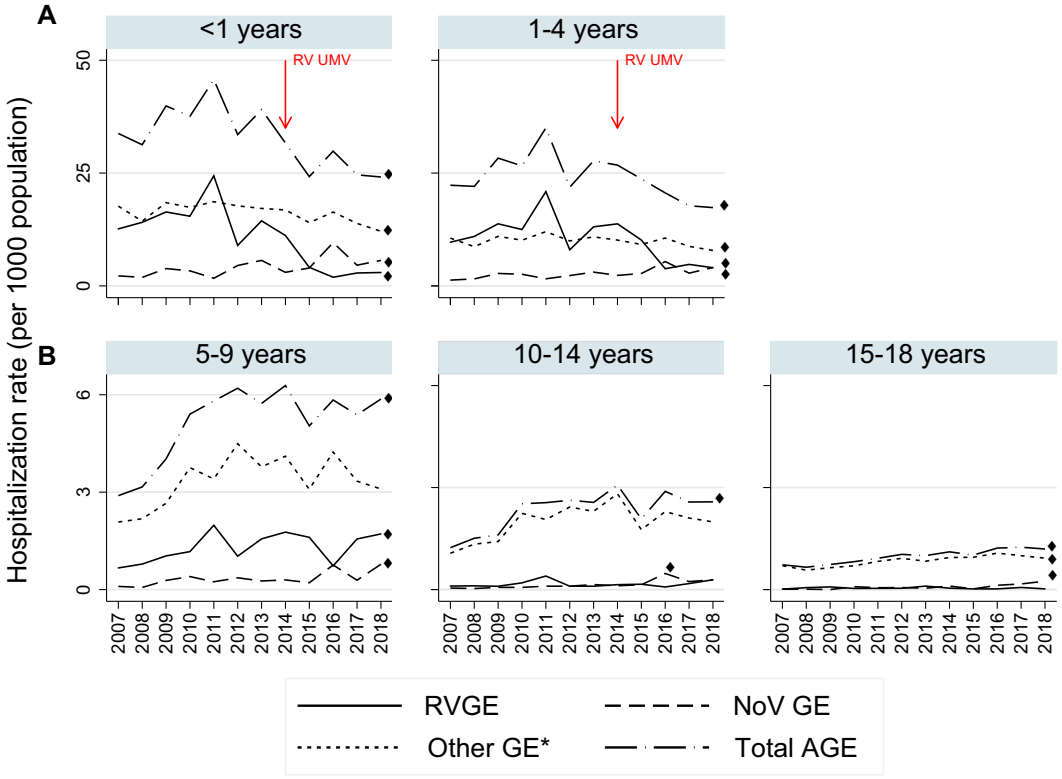

Fig. 3. Hospitalization rate per 1000 population by age group and diagnosis 2007–2018: (A) Age groups <1 years and 1–4 years. (B) Age groups 5–9 years, 10–14 years and 15–18 years. Please note for better visualization the scale is magnified. Diamond sign at the end of the line marks statistically significant differences in hospitalization rate by diagnosis and age group pre-vaccine era (2007–2013) versus post-vaccine era (2015–2018). *Other GE, comprises of the following International Classification of Diseases (ICD-10) diagnoses: A09, (infectious gastroenteritis and colitis, unspecified); A08.3 (other viral enteritis); A08.4 (viral intestinal infection, unspecified).

constituted for 34% and 6% of diagnoses, respectively. In 2016, the leading cause for hospitalization was other GE (49%) followed by NoVGE (20%). Similar pattern was seen during the off-season in 2016 with 56.2% and 20.8% of cases, respectively (Table 1).

Demographic and clinical characteristics of patients with AGE are presented in Table 2. Compared with RV season 2015, in 2016 we observed an increase of median age from 2 to 3 years in patients with RVGE (Fig. 4), higher number of vomiting episodes per day, higher prevalence of fever among patients with other GE, and a decrease in median length of hospital stay among patients with RVGE, NoVGE, and other GE. There was a statistically significant increase in the proportion of hospitalized patients vaccinated against RV in 2015 and 2016, respectively (Table 2).

3.4. Severity of AGE

VCSS was available for 1328 (59%) patients. Of those, 0.8% (n = 5) had mild disease, 16.7% (n = 111) moderate, and 82.5% (n = 547) severe in 2015 compared to 0.8% (n = 5), 28.7% (n = 191), and 70.5% (n = 469) in 2016, respectively. RVGE had the highest proportion of severe cases during both seasons compared to all other groups – 94.6% in 2015 and 93.4% in 2016.

Mean VCSS scores by age group, season and diagnosis are presented in Table 3.

In age group 0–18 years lower total AGE mean VCSS in 2016 RV season was seen compared to 2015 season ($p < 0.001$).

In age group 0–18 years lower NoVGE mean VCSS was seen compared to RVGE mean VCSS ($p < 0.001$).

Compared to RVGE mean VCSS in age group <1 higher RVGE mean VCSS was detected in age groups 1–4 years ($p < 0.001$), 5–9 years ($p < 0.001$) and 10–14 years ($p = 0.03$), when adjusted to season.

Mean VCSS of NoVGE patients aged 1–4 and 5–9 were lower compared to mean VCSS of RVGE patients aged 1–4 ($p < 0.001$) and 5–9 ($p = 0.03$).

Adjusting for RVGE and NoVGE diagnosis and age mean VCSS was not statistically significantly different in 2015 vs 2016 RV season.

4. Discussion

Our study of a 12-year period contributes to the knowledge of RV UMV effects on RVGE and AGE hospitalizations and patient profile among children aged 0–18 years.

We confirm the decrease in AGE hospitalization rate during post-vaccine era and decline of RVGE hospitalization rate as well as changes in hospitalized AGE patient profile in age groups of <5 years shortly after RV UMV implementation [8,9,12,18]. We also demonstrate that the mean age of hospitalized RVGE patients

Table 1
Distribution of patients according to etiologic diagnosis during RV 2015 and 2016 seasons.

Etiology	RV season 2015	RV season 2016	Off-season 2015 and 2016	Total
Rotavirus n (%)	402 (43.4)	125 (16)	40 (7.3)	567 (25.2)
Norovirus n (%)	56 (6)	154 (20)	115 (20.8)	325 (14.5)
Adenovirus n (%)	56 (6)	25 (3.3)	18 (2.3)	99 (4.4)
Other GE* n (%)	315 (34)	377 (49)	310 (56.2)	1002 (44.6)
Bacterial GE n (%)	80 (8.6)	80 (10.4)	55 (10)	215 (9.6)
Parasitic GE n (%)	2 (0.2)	1 (0.1)	1 (0.2)	4 (0.2)
Non-infectious n (%)	4 (0.4)	4 (0.5)	6 (1.1)	14 (0.6)
Unspecified GE n (%)	12 (1.3)	4 (0.5)	7 (1.3)	23 (1)
Total n (%)	927 (1 0 0)	770 (1 0 0)	552 (1 0 0)	2249 (1 0 0)

* Comprises of the following International Classification of Diseases (ICD-10) diagnoses: A09, (infectious gastroenteritis and colitis, unspecified); A08.3 (other viral enteritis); A08.4 (viral intestinal infection, unspecified).

Table 2
Clinical characteristics of AGE patients by diagnosis.

Diagnosis	RV season 2015				RV season 2016			
	RVGE (n = 402)	NoVGE (n = 56)	HAdVGE (n = 56)	Other GE* (n = 315)	RVGE (n = 125)	NoVGE (n = 154)	HAdVGE (n = 25)	Other GE* (n = 377)
Median age in years (IQR)	**2 (1–4)**[2]	1 (0–3)	2 (1–3)	2 (1–5)	**3 (2–4)**	1 (0–3)	1 (0–3)	2 (1–6)
Median time to hospitalization in days (IQR)	1 (0–3)	1 (0–1)	2.5 (2–4)	1 (0–3)	1 (0–2)	0 (0–1)	3 (1–4)	1 (0–3)
Median length of hospital stay in days (IQR)	**3 (2–4)**[1]	**2 (2–3)**[3]	2 (1.5–3)	**2 (1–3)**[1]	**2 (2–3)**	**2 (1–2)**	2 (2–4)	**2 (1–2)**
Number of cases with diarrhea (%)	399 (99.3)	52 (92.9)	56 (100.0)	286 (90.8)	124 (99.2)	146 (94.8)	25 (100.0)	324 (85.9)
Median number of diarrhea episodes per 24 h on admission, (IQR)	5 (3–8)	3 (2–4)	5 (4–7)	3 (2–6)	5 (4–5)	3 (1–5)	6 (4–10)	4 (2–7)
Median duration of diarrhea in days (IQR)	3 (2–4)	2 (1–3)	4 (3–6)	2 (1–4)	3 (3–4)	2 (1–3)	4.5 (4–5.5)	2 (1–4)
Number of cases with vomiting (%)	381 (94.8)	53 (94.6)	49 (87.5)	266 (84.4)	118 (94.4)	152 (98.7)	19 (76.0)	324 (85.9)
Median number of vomiting episodes/day (IQR)	7 (3–10)	7 (4–10)	3 (2–5)	**5 (3–8)**[3]	7 (4–10)	8 (5–10)	2 (1–3)	**6 (3–10)**
Median duration of vomiting in days (IQR)	2 (1–3)	1 (1–2)	2 (1–3)	1 (1–2)	2 (1–3)	1 (1–2)	2 (1–3)	1 (1–2)
Number of cases with temperature ≥37.1°C (%)	397 (99.0)	54 (96.4)	55 (98.2)	**301 (95.6)**[1]	122 (97.6)	151 (98.1)	25 (1 0 0)	**376 (99.7)**
Number of cases with temperature <37.1°C (%)	4 (1.0)	2 (3.6)	1 (1.8)	14 (4.4)	3 (2.4)	3 (1.9)	0 (0)	1 (0.3)
Number of cases with dehydration ≥1% (%)	221 (65.1)	25 (61.0)	25 (59.5)	108 (44.1)	79 (65.3)	66 (44.0)	9 (36.0)	148 (39.6)
Number of cases with dehydration <1% (%)	118 (34.8)	16 (39.0)	17 (40.5)	137 (55.9)	42 (34.7)	84 (56.0)	16 (64.0)	226 (60.4)
Number of cases received intravenous rehydration (%)	394 (98.0)	56 (1 0 0)	53 (94.6)	290 (92.4)	124 (99.2)	150 (98)	24 (1 0 0)	352 (94.4)
Number of cases vaccinated against RV (%)	**17 (4.2)**[3]	16 (28.6)	20 (35.7)	**69 (21.9)**[1]	**15 (12.0)**	61(39.6)	9 (36.0)	**130 (34.5)**

Statistically significant changes are marked in bold.
* Other GE, other gastroenteritis, ICD codes A09, A08.3, and A08.4.
[1] $p < 0.001$ 2015 RV season vs 2016 season.
[2] $p = 0.01$ 2015 RV season vs 2016 season.
[3] $p = 0.003$ 2015 RV season vs 2016 season.

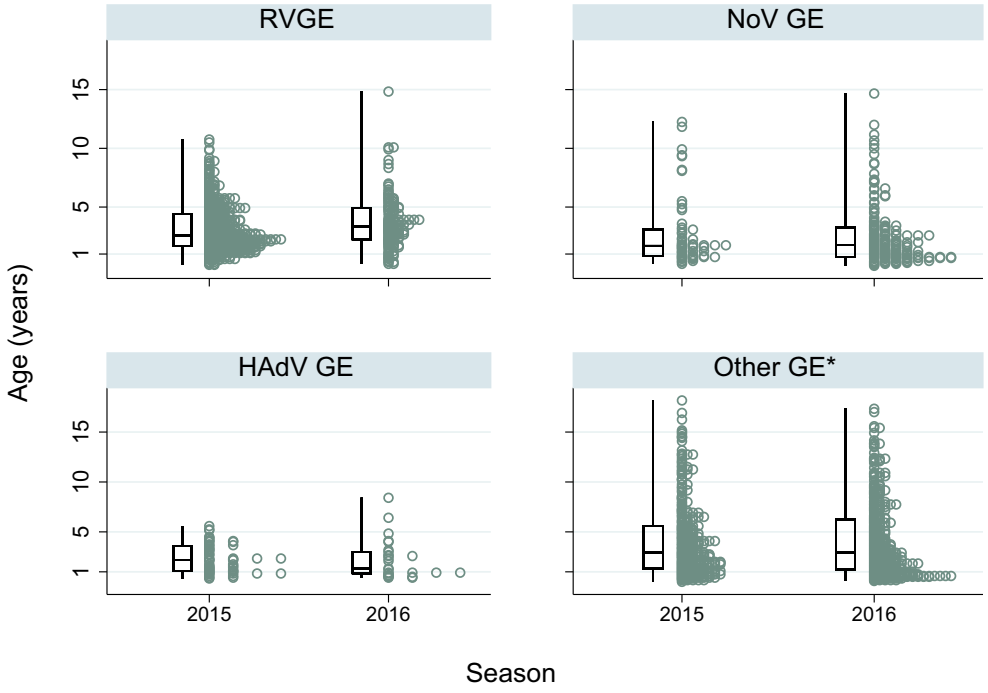

Fig. 4. Age distribution of hospitalized patients according to diagnosis and study year. Y-axis presents age in years and X-axis 2015 and 2016 RV seasons. Each dot represents one patient. On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme parameter values.

Table 3
Mean Vesikari Clinical Severity Score (VCSS) by diagnosis and age in 2015 and 2016 RV seasons.

	RV seasons 2015–2016						Season 2015	Season 2016
Age years	<1	1–4	5–9	10–14	15–18	0–18	0–18	0–18
RVGE mean VCSS	12	14.3	13.6	14.3	NA	14.0	14.0	14.0
SD	2.9	1.9	1.9	3.0		2.1	2.1	2.1
N	36	334	83	4	0	457	336	121
NoVGE, mean VCSS	11.9	11.8	12.1	11.6	NA	11.8	12.2	11.7
SD	2.0	1.9	1.9	1.9		1.9	2.1	1.9
N	56	107	20	7	0	190	41	149
HAdVGE mean VCSS	12.2	12.4	15.8	NA	NA	12.6	12.9	12.1
SD	1.9	2.6	1.6			2.5	2.7	2.2
N	17	44	5	0	0	66	42	24
Other GE mean VCSS	11.1	11.6	11.4	11.3	11.9	11.4	11.7	11.3
SD	2.1	2.6	2.4	2.4	3.1	2.5	2.4	2.4
N	119	308	126	51	11	615	244	371
Total AGE mean VCSS	11.5	12.8	12.3	11.5	11.9	12.4	13.0	11.9
SD	2.2	2.6	2.5	2.4	3.1	2.5	2.5	2.5
N	228	793	234	62	11	1328	663	665

NA, not applicable.

increased by one year and AGE disease was less severe in post-vaccine as compared to pre-vaccine era. Both findings are likely caused by the decline of RVGE as it mainly declined in young children and it is more severe than AGE of other etiology. Unlike reports from U.S. and Finland [19,20] we witnessed statistically significant increase in NoVGE hospitalization rate among all age groups post-vaccine era. The reasons for such increase were not studied as this was out of the scope of our study. We suggest that most likely explanations are the changing norovirus epidemic patterns [21] and previously unmet need for admission [22]. However, we cannot exclude the possibility of changes in circulating NoV genotypes with varying disease severity profile [23]. Further studies with larger sample sizes over longer period of time are crucial to thoroughly understand the topic.

The strengths of our study are involvement of entire country and multifaceted approach; on the one hand we present data on AGE hospitalization rate dynamics over 12 years and on the other hand we provide details of AGE patient characteristics over two years immediately after RV UMV implementation.

Similar to other developed countries with ongoing RV vaccination program we witnessed decreased and sustained RV seasonal activity [15,24].

We observed reduction of RVGE hospitalization among age groups of 0–9 years within first two consecutive RV seasons after RV UMV but did not observe any changes in older age groups. Similar to the results presented by Baker *et al.* [25] RVGE hospitalization rate among children aged 5–9 returned to levels seen prior to vaccine introduction after initial decline in the second year

post-vaccine period whereas among the age group 0–4 hospitalization rates were decreased throughout the post-vaccine period. Previous studies have suggested indirect effect of the RV vaccine among age groups not eligible for vaccination [18,25] but this may not be universal and as shown by a recent study in US indirect effect of the RV vaccine may be observed in some but not in all years [25]. We were not able to demonstrate changes in RVGE hospitalization in age groups 10–18 years. This may be explained by a very low hospitalization rate in these groups.

Our study data supports previous reports demonstrating that the efficacy of rotavirus vaccines does not depend on their genotypic composition and that both RV vaccines are similarly effective in all developed countries [18,26]. In pre-vaccine era, in contrast to other Central or Eastern European countries, where G1P[8] dominated [27], prevailing genotypes in Estonia were G2P[4] in 2007 and G4P[8] in 2008 [12], although due to natural fluctuations dominating genotypes immediately prior to implementation of UMV may have been other. However, UMV in Estonia resulted in reduction of RVGE hospitalization by 55% which is similar to other countries with different genotype distribution before UMV implementation [26].

There is always a worry that reduction of one microorganism may result in an increase of another [19,28]. In line with it we observed a significant increase of NoVGE hospitalization during post-vaccine era but at the same time the severity of AGE and the duration of hospitalization also decreased. We cannot confirm that RV vaccine out selected NoVGE but nevertheless NoVGE is a shorter and less severe disease as demonstrated by us and in a recent meta-analysis of studies conducted in 17 countries [26].

Few limitations should be noted. Firstly, as screening log was not implemented we are unable to ensure that all hospitalized patients were included as requested in the protocol. Secondly, defining RV season based on ECDC criteria may be questioned in our study as we used only hospital based data and may have been missing those treated in ambulatory settings. However, as the included hospitals cover 80% of the pediatric population and the high RVGE hospitalization rate in Estonia was previously known, we believe that the hospitalization curve most likely mimics the RV seasonal curve.

5. Conclusion

RV UMV lead to overall AGE hospitalization reduction among children aged 0–18 years, decreased RV seasonal activity, changes in patient profile towards older age of RVGE patients and less severe disease at hospitalization among all AGE patients already in the second RV vaccination season. Succeeding dominance of norovirus among AGE hospitalizations followed after RV UMV implementation.

Our study data provides further reassurance that rotavirus vaccines are effective in routine use regardless of prevailing rotavirus genotype and vaccine used. Also we provide information for further cost effectiveness analyses.

6. Author's contributions

All authors have read and approved the final manuscript.

CRediT authorship contribution statement

Kadri Kõivumägi: Conceptualization, Methodology, Project administration, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Karolin Toompere:** Formal analysis, Visualization, Data curation, Validation, Writing - review & editing. **Hiie Soeorg:** Formal analysis, Validation, Writing - review & editing. **Eveli Kallas:** Writing - review & editing. **Ene-Ly Jõgeda:** Writing - review & editing. **Kristi Huik:** Writing - review & editing. **Irja Lutsar:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition, Supervision. Rotavirus Study group: Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.01.098. These data include Google maps of the most important areas described in this article.

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