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Success of rotavirus vaccination in Finland, a register based study measuring impact beyond overall effectiveness

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ABSTRACT

Introduction: Even with vaccines available since 2006, rotavirus continues to be a major cause of acute gastroenteritis globally in children under 5 years old. Finland introduced the rotavirus vaccine to its national vaccination programme in 2009. Since then hospitalizations due to gastroenteritis caused by rotavirus (RVGE) and of all causes (AGE) have been reduced significantly in young children.
Methods: We performed a retrospective analysis of data from register databases consisting of over 200 000 children aged 0.5–2 years. Children born before rotavirus vaccines were available (2002, 2003) and after the implementation of rotavirus vaccination programme (2014, 2015) were followed for episodes of acute infectious gastroenteritis. We calculated the incidences of hospital outpatient and inpatient episodes and used individual vaccination records to estimate the overall, total, direct and indirect vaccine effect (VE %).
Results: Among children born in 2014 and 2015, there was a 96% reduction in inpatient RVGE episodes and a 78% reduction in episodes of inpatient AGE compared to the pre-vaccination era, comprising the overall VE. Direct effectiveness was 96% and 53% for RVGE and AGE respectively. Herd effect i.e. indirect protection was estimated to be 67% against inpatient RVGE and 56% against inpatient AGE. Protection acquired by the vaccinated children when compared to pre vaccination era i.e. the total VE was 99% for inpatient RVGE and 79% for inpatient AGE.
Conclusions: Although overall incidences for every disease type studied were reduced, rotavirus is still circulating with seasonality and there is a slight shift of disease towards the older age groups. Together with changes observed in the distribution of rotavirus genotypes, our results indicate that continuous monitoring is still necessary.

Rotavirus gastroenteritis (RVGE) is the leading cause of diarrhea related morbidity and mortality globally among children younger than 5 years [1]. Severe cases of RVGE lead to dehydration, which in infants and toddlers generally results in the need of hospitalization. Vaccines against RVGE have been available since 2006. However, still in 2016 rotavirus was estimated to be responsible for more than 285 000 000 cases and over 128 000 deaths in children under 5 years globally [1].

In Finland, the rotavirus vaccine (RotaTeq) was introduced to the national vaccination programme in 2009. By 2014, rotavirus vaccination had reduced hospitalisations due to RVGE by nearly 93% and saved 2.2 million euros in healthcare costs [2]. This reduction corresponds to the overall effect or impact of the vaccination programme, including both direct and indirect protection gained as vaccinated cohorts were compared with cohorts without vaccination.

Rotavirus is transmitted also by the older individuals in the population, although it is mainly the disease of the very young. It is therefore of interest to study if the vaccination among the young cohorts is enough to cause major indirect effects seen as herd protection. The indirect effect on its own is seen when the unvaccinated during the vaccination programme are compared to the cohorts prior to the programme [3]. The largest effect a vaccination programme can produce, however, is the total effect i.e. the difference when the individuals in the population without vaccinations are compared to the vaccinated individuals in the population with high vaccination coverage [3].

In this study we assessed the impact of rotavirus vaccination programme by focusing on the age group with the highest rotavirus incidence and morbidity; children aged 0.5–2 years [4]. Incidences of both rotavirus gastroenteritis (RVGE) and acute

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infectious gastroenteritis (AGE) of any cause were estimated together with information on the severity of the cases i.e. whether the patient was admitted to the hospital (inpatient) or not (outpatient). We estimated the overall effect of the vaccination programme (VE) by comparing birth cohorts before and after vaccination programme implementation. In addition, we estimated total, direct and indirect VE by using the national vaccination register.

1. Methods

1.1. Study setting

In this study children born in 2002, 2003, 2014 and 2015 were followed from the age of 6 months until their 2nd birthday for episodes of acute infectious gastroenteritis. Children born in 2014 and 2015 comprised the post-vaccination cohort and children born in 2002 and 2003 the pre-vaccination era cohort. Years 2002 and 2003 were chosen since they comprise the last birth cohorts rotavirus vaccine had no effect on as from 2006 to 2009 rotavirus vaccines were available at parents' own expense. Birth years 2014 and 2015 were chosen due to 2017 being the most recent year for which all decisive data was available electronically, as of June 2019.

1.2. Data sources

Data used in this study was obtained from the Finnish national healthcare registers. Information on children's inpatient and outpatient visits due to acute gastroenteritis was obtained from the Care Register for Health Care (Hilmo). Hilmo is a secondary healthcare register that contains nationwide data of hospital visits in Finland. Therefore this study includes only visits to Finnish hospitals and not to primary healthcare centres. We selected children born in Finland in 2002, 2003, 2014 and 2015 and extracted their birthdays and the dates of death, date and the type of visits and primary diagnosis codes for these visits. By using encrypted unique personal identity codes we extracted the dates of rotavirus vaccinations from the National Vaccination Register for each child.

1.3. Data categorization

From the Care Register for Health Care, visits coded with A00-A09 (intestinal infectious diseases) in International Classification of Diseases, 10th revision (ICD-10) were selected. Visits were divided into two categories by primary diagnostic codes. All visits coded ICD-10 A00-A09 were categorised as AGE. Visits with ICD-10 A08.0 (rotaviral enteritis) as a primary diagnosis comprised the RVGE category. The AGE category included also all A08.0 coded visits; hence the RVGE acts as a definite subgroup of AGE. AGE and RVGE were each further divided depending on the type of visit (i.e. whether the visit was inpatient or outpatient). Consequently, the data was analysed in four distinct groups: inpatient RVGE, outpatient RVGE, inpatient AGE and outpatient AGE.

Cases were analysed as episodes rather than single visits. All subsequent visits within 21 days of the last visit formed a single episode. Episodes containing multiple codes for primary diagnosis or type of visit were categorised by the most severe and specific coding. Thus all episodes with at least one visit due to A08.0 were classified as RVGE and if an episode included even a single inpatient visit, the whole episode was categorised as inpatient. Episodes were divided into three age groups (6–11 months, 12–17 months and 18–23 months) with the first visit of the episode determining the age group it was categorised in. In the post-vaccination group, children were categorised as vaccinated if they had received at least one dose of rotavirus vaccine.

1.4. Excluded groups

Approximately 18 000 children born abroad or in unknown locations were excluded from the study, primarily because we were not able to assess their vaccination status. 207 children who lacked information of birth date and personal identity code were excluded because they could not be connected to vaccination information or categorised into age groups. 237 children who died within their follow up period (at less than 730 days of age) were also excluded.

1.5. Statistical analysis

Data was acquired from the registers through Stata, and all statistical analyses were performed with R-studio (under R version 3.5.1). Person-time was calculated from the sizes of birth cohorts with exclusions mentioned earlier. Incidences for inpatient and outpatient RVGE and AGE were calculated by dividing the number of episodes by person-years (pyrs). Pyrs were calculated separately

Table 1
Formulas used to calculate vaccine effectiveness (VE) from incidences.

$VE_{overall} = (1 - \frac{2}{1A}) \times 100$	$VE_{total} = (1 - \frac{2B}{1A}) \times 100$
$VE_{direct} = (1 - \frac{2B}{2A}) \times 100$	$VE_{indirect} = (1 - \frac{2A}{1A}) \times 100$

1A = incidence in completely unvaccinated population during 2002–2005, 2 = incidence after introduction of vaccine (i.e. during 2014–2017), 2A = incidence among unvaccinated population during 2014–2017, 2B = incidence among vaccinated population during 2014–2017.

Table 2
Incidence of rotavirus– and acute gastroenteritis in Finnish children born in 2002 and 2003.

Birth year	Age in months [A]	Person-years	Rotavirus gastroenteritis incidence [B,C]		Acute gastroenteritis incidence [B,D]	
			Inpatient	Outpatient	Inpatient	Outpatient
2002	6	27406	10.51 (288)	0.66 (18)	36.82 (1009)	30.72 (842)
	12	27406	6.28 (172)	0.40 (11)	21.86 (599)	19.63 (538)
	18	27406	3.28 (90)	0.22 (6)	10.73 (294)	9.49 (260)
2003	6	27970	7.58 (212)	0.64 (18)	21.88 (612)	20.99 (587)
	12	27970	5.58 (156)	0.36 (10)	20.06 (561)	20.74 (580)
	18	27970	5.65 (158)	0.25 (7)	17.84 (499)	16.41 (459)
Combined		166128	6.48 (1076)	0.42 (70)	21.51 (3574)	19.66 (3266)

[A] = Cohorts were divided into three age-groups; "6″ includes episodes from 6 to 11 months, "12" from 12 to 17 months and "18" from 18 to 23 months.
[B] = (Number of cases) in parentheses.
[C] = Incidence of episodes [per 1000 person-years] with at least one visit due to A08.0 (ICD-10).
[D] = Incidence of episodes [per 1000 person-years] with visits due to A00-A09 (ICD-10).

Table 3
Incidence of inpatient and outpatient rotavirus– and acute gastroenteritis in children born in 2014 and 2015. Children were followed from 6 to 23 months of age and differentiated according to their vaccination status.

Birth year	Vaccination status	Age in months [A]	Person-years	Rotavirus gastroenteritis incidence [B,C]		Acute gastroenteritis incidence [B,D]	
				Inpatient	Outpatient	Inpatient	Outpatient
2014	+	6	26399	0.15 (4)	0.00 (0)	5.42 (143)	18.26 (482)
		12	26399	0.11 (3)	0.00 (0)	4.28 (113)	17.31 (457)
		18	26399	0.08 (2)	0.08 (2)	3.03 (80)	12.92 (341)
	–	6	2260.5	2.65 (6)	0.00 (0)	9.29 (27)	17.25 (39)
		12	2260.5	2.65 (6)	0.00 (0)	8.41 (25)	11.50 (26)
		18	2260.5	2.65 (6)	0.44 (1)	4.42 (16)	16.81 (39)
2015	+	6	25556.5	0.16 (4)	0.00 (0)	5.44 (143)	19.72 (504)
		12	25556.5	0.00 (0)	0.12 (3)	4.19 (107)	18.51 (476)
		18	25556.5	0.08 (2)	0.04 (1)	4.03 (105)	13.73 (352)
	–	6	2043.5	0.49 (1)	0.00 (0)	9.30 (20)	16.64 (34)
		12	2043.5	1.47 (3)	0.00 (0)	4.40 (12)	24.96 (51)
		18	2043.5	2.94 (6)	0.00 (0)	7.34 (21)	18.60 (38)
All vaccinated children (+)			155866.5	0.10 (15)	0.04 (6)	4.43 (691)	16.76 (2612)
All unvaccinated children (-)			12912.0	2.17 (28)	0.08 (1)	9.37 (121)	17.58 (227)
All children (+ & -)			168778.5	0.25 (43)	0.04 (7)	4.81 (812)	16.82 (2839)

+ = Children who have received at least one vaccine dose.
– = Children who have not received any vaccine doses.
[A] = Cohorts were divided into three age-groups; "6" includes episodes from 6 to 11 months, "12" from 12 to 17 months and "18" from 18 to 23 months.
[B] = (Number of cases) in parentheses.
[C] = Incidence of episodes [per 1000 person-years] with at least one visit due to A08.0 (ICD-10).
[D] = Incidence of episodes [per 1000 person-years] with visits due to A00-A09 (ICD-10).

Table 4
Vaccine effect (VE) types for inpatient and outpatient rotavirus gastroenteritis (RVGE) and acute infectious gastroenteritis (AGE).

		VE (%)*			
		Inpatient RVGE	Outpatient RVGE	Inpatient AGE	Outpatient AGE
VE type	Overall	96.1 (95.7–96.4)	90.2 (90.0–90.3)	77.6 (76.8–78.5)	14.4 (13.5–15.4)
	Total	98.5 (98.4–98.6)	90.9 (90.7–91.0)	79.4 (78.5–80.3)	14.8 (13.8–15.8)
	Direct	95.6 (95.4–95.7)	50.3 (50.1–50.5)	52.7 (51.8–53.6)	4.7 (3.7–5.7)
	Indirect	66.5 (65.9–67.2)	81.6 (81.6–81.7)	56.4 (55.6–57.3)	10.6 (9.6–11.6)

For VE calculation formulas, see Table 1.
* = Numbers in parentheses represent 95% confidence intervals.

for each birth year and further divided into three equal-sized age groups. All three age groups per year had the same amount of pyrs because children who died within their follow up period were excluded from the data.

Incidences were used to calculate overall, total, direct and indirect VE. The formulas used in calculations are derived from a paper by Halloran et al. (1997) [3] (Table 1.). Briefly, overall VE was calculated by dividing the incidence in the post-vaccination era by incidence in the pre-vaccination era. This entity is normally reported in impact studies. Total VE was calculated by comparison of incidences between vaccinated individuals in the post-vaccination era and all individuals in the pre-vaccination era. Direct VE was calculated by comparing incidences among the vaccinated and unvaccinated in the post-vaccination era, corresponding to usually reported effectiveness. Indirect VE was calculated by comparing incidences among unvaccinated individuals in the post-vaccination era to incidences in the pre-vaccination era (Table 1.).

2. Results

2.1. Overall reductions in acute gastroenteritis

2.1.1. Inpatient RVGE and AGE

During the pre-vaccination era (i.e. 2002–2005) 1076 episodes of RVGE were registered in Finnish hospitals for children aged 0.5–2 years. This comes down to an incidence of 6.48 per 1000 pyrs (Table 2.). In the post-vaccination era (i.e. 2014–2017) there were a total of 43 episodes of RVGE in children aged 0.5–2 years. Incidence in the whole post-vaccination group for RVGE was 0.25 per 1000 pyrs (Table 3.). Overall VE regarding inpatient RVGE was therefore 96.1% (95% confidence interval being 95.7%–96.4%) (Table 4.). In other words, after the implementation of the rotavirus vaccination programme, the number of RVGE episodes has been reduced by an estimated 96.1%. This corresponds to over 25-fold reduction in incidence and an estimated 1051 (1049.8–1051.8) prevented episodes among the two birth cohorts followed from 6 to 23 months of age.

In the pre-vaccination era, there were 3574 recorded episodes of inpatient AGE with an incidence of 21.51 per 1000 pyrs (Table 2.) For the post-vaccination era, the incidence of inpatient AGE was 4.81 with 812 episodes in total (Table 3.). Hence there were 4.5 times less episodes in the post-vaccination era than there were in the pre-vaccination era. Overall VE for inpatient AGE was 77.6% (76.8%–78.5%) (Table 4.). Among the two birth cohorts followed from 6 to 23 months of age, this corresponds to an estimated 2818 (2817.5–2819.6) prevented episodes.

2.1.2. Secondary care outpatient RVGE and AGE

Outpatient RVGE among the children less than 2 years of age has been rare in Finland with only 70 episodes and an incidence of 0.42 per 1000 pyrs in the pre-vaccination era follow-up period and 7 episodes and an incidence of 0.04 per 1000 pyrs in the

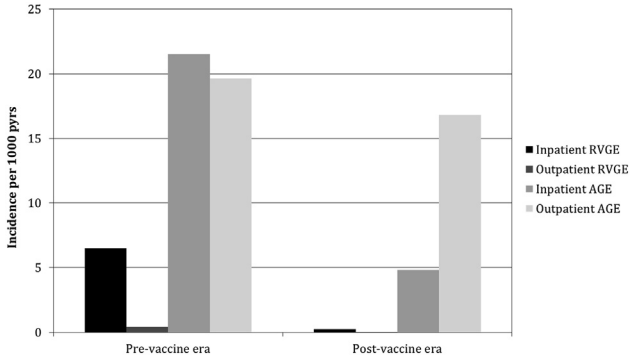

Fig. 1. Incidence of acute gastroenteritis in pre- and post-vaccination era among children aged 0,5–2 years. RVGE = Rotavirus gastroenteritis; episodes with primary diagnosis A08.0 (ICD-10). AGE = Acute infectious gastroenteritis; episodes with primary diagnosis A00-A09 (ICD-10).

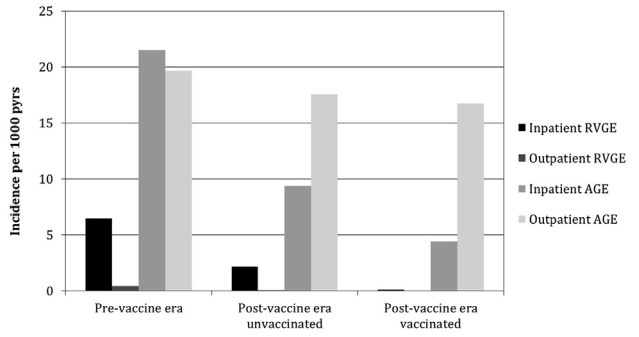

Fig. 2. Incidence of acute gastroenteritis between vaccinated and unvaccinated children aged 0,5–2 years. RVGE = Rotavirus gastroenteritis; episodes with primary diagnosis A08.0 (ICD-10). AGE = Acute infectious gastroenteritis; episodes with primary diagnosis A00-A09 (ICD-10).

post-vaccination era follow up period (Table 2.). Although outpatient RVGE is relatively rare, it's noteworthy that there was a 10-fold decrease in its incidence with overall VE being 90.2% (90.0%–90.3%) (Table 4.).

Because RVGE rarely manifests as outpatient visits in healthcare, major reductions in incidences of outpatient AGE were not expected. In the pre-vaccination era follow-up period, outpatient AGE had an estimated incidence of 19.66 per 1000 pyrs (Table 2.). In the post-vaccination era, the incidence was 16.82 per 1000 pyrs (Table 3.). Although there was a reduction in incidence, it was relatively small (Fig. 1.). This can also be seen in the overall and total VE which were 14.4% (13.5%–15.4%) and 14.8% (13.8%–15.8%), respectively (Table 4.). Hence, as expected, the rotavirus vaccination programme has not been profoundly reducing the burden of secondary care outpatient AGE in Finland (Fig. 1. and Fig 2.).

Different effects of the vaccination programme between vaccinated and unvaccinated children

2.2. Inpatient RVGE

After the implementation of the national rotavirus vaccination programme, inpatient RVGE episodes have practically vanished among the vaccinated with only 15 episodes occurring in the two birth cohorts followed from 6 to 24 months of age during years 2014–2017 (Table 3.). However, rotavirus continues to cause disease to the unvaccinated that had over 20 times higher risk for having inpatient RVGE compared to vaccinated children (Fig. 3.) as incidences were 0.10 and 2.17 per 1000 pyrs for vaccinated and unvaccinated children, respectively (Table 3.). Direct VE was consequently estimated to be 95.6% (95.4%–95.7%) for inpatient RVGE (Table 4.). Total VE (i.e. the maximum effect of vaccination programme) was 98.5% (98.4%–98.6%). Indirect VE is a measure of indirect protection gained by unvaccinated individuals in a population where vaccine coverage is high. In children born in 2014 and 2015, the indirect VE was 66.5% (65.9%–67.2%) for inpatient RVGE (Table 4.). That is, during the post-vaccination era follow-up period, there were 66.5% less episodes among the unvaccinated than during the pre-vaccination era as a result of herd effect. Converted into episodes, herd effect was responsible for preventing an estimated 56 (55.1–57.3) inpatient RVGE episodes among the unvaccinated during the follow-up from 6 to 23 months. It is noteworthy that less than 10% of children in Finland are left unvaccinated against rotavirus and thus solely depend on the indirect protection.

2.3. Inpatient AGE

Since the rotavirus vaccine was added to the national vaccination programme, there has been a major drop in the incidence of inpatient AGE (Fig. 1.). When comparing pre-vaccination incidences to vaccinated children in the post-vaccination era, the reduction in incidence was approximately 4.9-fold (Fig. 2.) and total VE was 79.4% (78.5%–80.3%)(Table 4.). In the unvaccinated the effect was smaller; there was approximately a 2.3-fold reduction in incidence (Fig. 2.). Indirect VE corresponding to the herd effect for inpatient AGE was 56.4% (55.6%–57.3%) and direct VE was 52.7% (51.8%–53.6%) (Table 4.). Herd effect was responsible for preventing an estimated 157 (156.1–158.4) episodes of inpatient AGE among the unvaccinated during the follow-up period.

Age-specific changes in incidence of acute gastroenteritis

In the pre-vaccination era, 6–11-month-old children had the most episodes in every category analysed in this study (Figs. 3 and 4.). Among the unvaccinated children during the post-vaccination era, disease burden had shifted to older children as there were more episodes of RVGE at the age of 18–23 months (Fig. 3, Table 5.). In addition, during the vaccination era, the AGE incidence did not decrease as steeply with increasing age as it had done prior to the vaccination programme (Fig. 4.). Incidences of inpatient RVGE and AGE have become more balanced between the three age groups (Table 5.) during the post-vaccination era. Furthermore, in both vaccinated and unvaccinated children approaching 2 years, incidences for outpatient AGE were slightly higher than in the pre-vaccination era (Table 5, Fig. 4.), even though there was a decrease in outpatient AGE episodes overall.

3. Discussion

The national rotavirus vaccination programme has managed to reduce not only specific RVGE but also additional inpatient AGE cases not diagnosed as rotavirus disease. A typical case of RVGE leads to hospitalization of the child. In our study, we report that cases of inpatient RVGE have been reduced by 96% from 2002 to 2005 to 2014–2017 among children aged 6–23 months. The national vaccination programme has had a widespread impact beyond visits coded as RVGE, as cases of inpatient AGE have also been reduced by approximately 78%. Converted into number of cases, an estimated 2818 cases of inpatient gastroenteritis were prevented. Of this, 1051 were coded specifically as RVGE.

A recent *meta*-analysis reports that rotavirus vaccinations by RV5 (i.e. Rotateq) have reduced hospitalisations of RVGE by 94% in countries of low child mortality [5]. Another systematic review described a decrease of 94% in RVGE and 78% in AGE related hospitalisations in developed countries [6]. In a case-control study

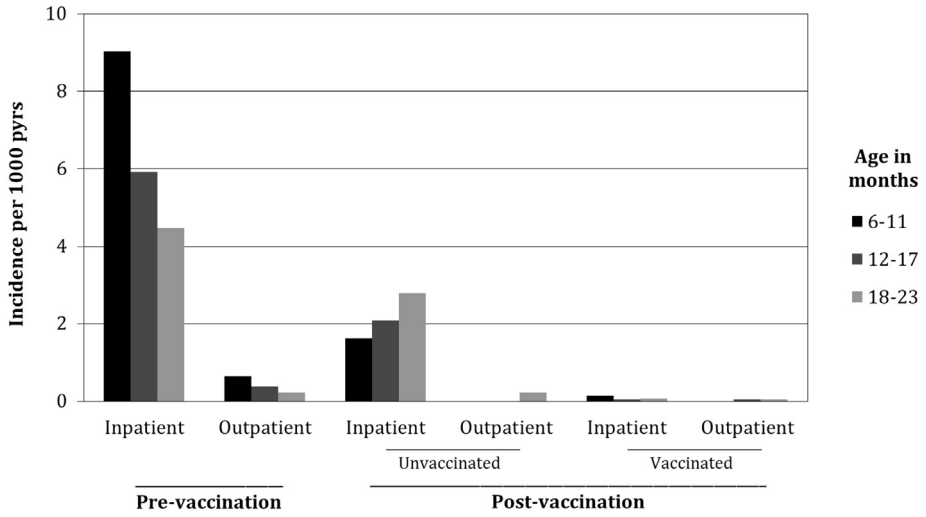

Fig. 3. RVGE incidence by age-group in pre- and post-vaccination periods, vaccinated and unvaccinated children separated. RVGE = Rotavirus gastroenteritis; episodes with primary diagnosis A08.0 (ICD-10).

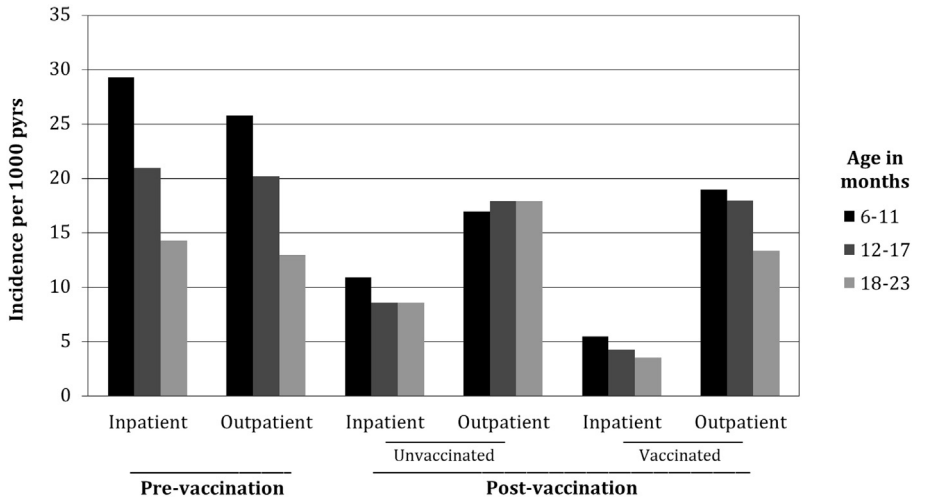

Fig. 4. AGE incidence by age-group in pre- and post-vaccination periods, vaccinated and unvaccinated children separated. AGE = acute infectious gastroenteritis; episodes with primary diagnosis A00-A09 (ICD-10).

including Portuguese children, the reduction in RVGE visits was 96% for inpatient and 83% for outpatient visits [7]. These results are very much within the same range with our observed 96% reduction in cases of inpatient RVGE. In addition, the reductions seen in inpatient AGE by Lamberti *et al.*, (2016) were same as ours [6].

In previous studies conducted on Finnish children, observed reductions in inpatient AGE and RVGE have been corresponding to ours. A study based on a comparison of years 2012–2014 to 2006–2008 in Tampere University Hospital reported a 90% reduction in both inpatient and outpatient RVGE visits and a 59% reduction in all AGE cases [8]. In another Finnish study comparing years 2010–2014 to 1999–2005, the reductions seen in 0–1-year-old children were 92–94% for inpatient RVGE [2]. In addition, a 74% reduction in inpatient AGE was observed among 1-year old children [2]. These results are in line with ours. Understandably, the impact seen by us is slightly larger, for at the time of our study the vaccination programme had been running for longer. Over 50 000 children are being vaccinated against rotavirus every year in Finland, and as the years pass, the total amount of the vaccinated rises and transmission of rotavirus decreases. Our study doesn't strive to represent the average impact of the whole vaccination programme but rather to estimate its impact on children born after 2013.

Determining the baseline incidence is crucial for assessing the impact of any vaccination programme. In this study children born in 2002 and 2003 were chosen to represent the pre-vaccination era. 2003 was a year of relatively high incidences of both inpatient RVGE and AGE, but on the other hand year 2004 was the lowest year of RVGE through 1999–2006 [9]. In our results, this can be observed as children born in 2002 generally having higher incidences of gastroenteritis than children born in 2003. Even though these birth cohorts included notable seasonal variation, we assessed that when summed, these years represent a realistic average of the pre-vaccination era of the early 2000 s. We believe that choosing these years did not steer our results significantly in one way or the other. In the post-vaccination group, there was no notable seasonal variation in gastroenteritis between children born in 2014 and 2015.

Rotavirus is rarely marked as the primary cause of gastroenteritis for children as it is not routinely tested. This stems from the fact that generally, a more precise diagnosis would not change the

Table 5
Incidences of acute gastroenteritis before and after implementation of rotavirus vaccination programme in Finland.

Time-period [A]	Vaccination status	Age in months [B]	Person-years	Rotavirus gastroenteritis incidence [C]		Acute gastroenteritis incidence [D]	
				Inpatient	Outpatient	Inpatient	Outpatient
Pre-vaccination	–	6	55376	9.03	0.65	29.27	25.81
		12	55376	5.92	0.38	20.95	20.19
		18	55376	4.48	0.23	14.32	12.98
	All children		166128	6.48	0.42	21.51	19.66
Post-vaccination	+	6	51955.5	0.15	0.00	5.50	18.98
		12	51955.5	0.06	0.06	4.23	17.96
		18	51955.5	0.08	0.06	3.56	13.34
	All vaccinated children		155866.5	0.10	0.04	4.43	16.76
	–	6	4304	1.63	0.00	10.92	16.96
		12	4304	2.09	0.00	8.60	17.89
		18	4304	2.79	0.23	8.60	17.89
	All unvaccinated children		12912	2.17	0.08	9.37	17.58
	+&–	6	56259.5	0.27	0.00	5.92	18.82
		12	56259.5	0.21	0.05	4.57	17.95
		18	56259.5	0.28	0.07	3.95	13.69
	All children		168778.5	0.25	0.04	4.81	16.82

+ = Children who have received at least one vaccine dose
– = Children who have not received any vaccine doses. Vaccine was not available in pre-vaccination period.
[A] = Pre-vaccination time-period consists of children born in 2002 and 2003 and post-vaccination of children born in 2014 and 2015.
[B] = Cohorts were divided into three age-groups; "6″ includes episodes from 6 to 11 months, "12" from 12 to 17 months and "18" from 18 to 23 months.
[C] = Incidence of episodes (per 1000 person-years) with at least one visit due to A08.0
[D] = Incidence of episodes (per 1000 person-years) with visits due to A00-A09

course of treatment. In Finland too, RVGE is often undetected and health care visits are coded with a more ambiguous code. Hence, analysing only cases of rotavirus gastroenteritis would not represent the real impact of the national vaccination programme. In pursuit of more robust estimation, the AGE-category was incorporated to the analysis. Containing diagnostic codes with similar symptoms to RVGE, it catches the majority of undiagnosed RVGE cases but contains also cases of other intestinal infectious diseases. In addition, by analysing incidences between the vaccinated and unvaccinated in the post-vaccination era, the effectiveness of the vaccination programme could be evaluated in the real-world setting.

When measuring total, direct and indirect VE outside vaccine licensure studies, estimations are commonly made without information on individual children's vaccination status. Generally, herd effect for RVGE have been described either on older children born before programme implementation [10,11] or as estimations based on vaccination coverage [12]. Here, we presented a more precise estimation of herd effect by calculating indirect VE using individual vaccination data. Of the 2818 prevented cases of inpatient AGE, herd effect was responsible for preventing 157 cases. Of this, the number of prevented inpatient RVGE cases was estimated to be 56. The high percentage of vaccinated children (92.9% of children born in 2014–2015) has prevented an estimated 66.5% of inpatient RVGE and 56.4% of inpatient AGE cases among the unvaccinated. In a US study based on individual vaccination records, indirect VE against RVGE on privately insured children rose from 14% at 2007 to 82% in 2010 with very limited rotavirus circulation [13]. For AGE indirect VE rose from –8 at 2007 to 45% in 2010.

As rotavirus rarely caused outpatient gastroenteritis among the very young in Finland [2], the effect of the vaccination programme was not expected to reduce the number of outpatient AGE cases in this study. Recently, Leino *et al.* (2017) reported an increase in the number of outpatient AGE cases among children under 5 during 2010–2014 [2]. Although we saw a slight reduction in the overall incidence of outpatient AGE, there was an increase in cases occurring among children aged 18–23 months. While results from the 2017 study by Leino et al. are not directly comparable to ours, a similar trend can be seen. That is, the burden of acute gastroenteritis among children in Finland is shifting from inpatient burden towards children experiencing more cases of outpatient AGE.

A widely reported consequence of implementing a new vaccination programme is that while the rate of transmission decreases, people fall ill later in life. This has also been associated with rotavirus vaccinations globally [11,14], including in Finland [8,16]. Although our study focused solely on the very young, a shift of incidence amongst the age groups studied could be observed. In the pre-vaccination era, 6–11-month-old children had the most cases of gastroenteritis in all categories analysed in this study. In the post-vaccination era, unvaccinated children aged 12–17 and 18–23 months had higher incidences of inpatient RVGE than children aged 6–11 months. The explanation could well be that due to the high vaccination coverage, virus circulation is somewhat limited and virus is therefore merely acquired later. For a vaccine containing live virus, waning of the immunity during the first 1.5 years post-vaccination is not very likely.

Although the vaccination programme demonstrates a strong impact on reducing disease burden measured as hospital inpatient and outpatient episodes among the very young, it has not been able to prevent rotavirus from circulating in the population. Rotavirus has kept its seasonality in Finland [8,15,17,18]. Furthermore, it seems that new genotypes have arisen to replace the genotypes that were dominant in the pre-vaccination era [8,16,17,18]. Similar observations have been described in multiple countries [19,20]. Together with changes observed in the distribution of rotavirus genotypes [8,16,17,18], our results indicate that continuous monitoring of rotavirus is still necessary.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [THL has performed contract research on pneumococcal vaccines for GSK and is presently doing so on influenza vaccines for Sanofi Pasteur. AS, JO and TL do not have personal conflicts of interest.].

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