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ORIGINAL PAPER

Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study

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Abstract Rotavirus Efficacy and Safety Trial (REST) enrolled nearly 70,000 infants, of whom more than 23,000 were from Finland. REST determined the efficacy of the pentavalent rotavirus vaccine (RV5) against rotavirus-related hospitalisations and emergency department (ED) visits in the first year after vaccination. Finnish infants initially in REST transitioned into the Finnish Extension Study (FES), where they were followed for rotavirus-related hospitalisations and ED visits through their second year of life and beyond. FES identified 150 (31%) additional rotavirus gastroenteritis (RVGE) cases beyond those identified in REST in the Finnish participants. Overall, RV5 reduced RVGE hospitalisations and ED visits, regardless of the rotavirus serotype, by 93.8% (95% confidence interval [CI]: 90.8–95.9%) for up to 3.1 years following the last vaccine dose. Vaccine efficacy against combined hospitalisations and ED visits between ages 4 months to 11 months, 12 months to 23 months, and 24 months to 35 months was 93.9% (95% CI: 89.1–96.9%), 94.4% (95% CI: 90.2–97.0%), and 85.9% (95% CI: 51.6–97.2%), respectively. The reduction of hospitalisations and ED visits due to any acute gastroenteritis, rotavirus or not, was 62.4% (95% CI: 57.6–66.6%) over the entire follow-up period. The results from FES confirm that RV5 induces high and sustained protection against rotavirus-related hospitalisations and ED visits, and has a very substantial impact on all gastroenteritis-related hospitalisations and ED visits into the third year of life in Finnish children.

Keywords RV5 · Rotavirus vaccine · Gastroenteritis · Efficacy

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Introduction

Finland has a heavy burden of rotavirus disease. Prior to the introduction of rotavirus vaccination in Finland, one child in 33 was hospitalised for rotavirus gastroenteritis (RVGE) [17], which is one of the highest hospitalisation rates in Europe (Pediatric ROTavirus European CommitTee [PROTECT]) [8]. Finland also has a long and distinct rotavirus epidemic season, which starts as early as November or December and lasts until June or July [17]. Over the years, numerous clinical trials evaluating candidate rotavirus vaccines were conducted in Finland [4, 13, 16], and Finland contributed significantly to the Rotavirus Efficacy and Safety Trial (REST), evaluating the pentavalent rotavirus vaccine (RV5), RotaTeq® (Merck & Co., Whitehouse Station, NJ, USA). In REST, Finland enrolled more than 23,000 of the approximately 70,000 infants, and contributed more than one-half of the cases of rotavirus gastroenteritis in the efficacy analysis [15].

In REST, all infants in the large-scale safety study were followed for hospitalisations and emergency department (ED) visits for 365 days after their first vaccination, when children were from 13.5 months to 15 months old, and a subset (clinical-efficacy substudy) was followed for episodes of RVGE for up to 2 years. In Finland, and in Europe

overall [11], the burden of RVGE is greatest during the second year of life, when infants usually attend day-care centres [10]. We have recently shown that among the Finnish infants in the clinical-efficacy cohort of REST, the efficacy of RV5 was 98.3% against severe RVGE and 68.0% against RVGE of any severity, during the first and second rotavirus seasons combined [19]. Additionally, in this cohort, there was a statistically significant shift in the types of health care encounters towards less intensive care settings among vaccine recipients compared to the placebo recipients for the first 2 years following vaccination.Using the large-scale safety cohort of more than 23,000 Finnish infants, the Finnish Extension Study (FES) was carried out to supplement the follow-up period of REST and demonstrate the potential full impact of RV5. In the United States, the majority of RVGE health care encounters occur in the first year of life; thus, continued follow-up after REST was not necessary. In FES, Finnish infants in the large-scale safety study who were followed for 365 days after the first vaccination visit immediately transitioned from REST into FES, where they were followed for episodes of RVGE that required hospitalisation or an ED visit from their second year of life. Here, we present the results of the combined efficacy follow-up of RV5 in the Finnish participants of REST and FES up to 3.1 years of age.

Rotavirus vaccination has been incorporated into the national immunisation programme in Finland since September 2009 [6], based on estimates of high burden of disease and cost-effectiveness of vaccination [3]. RV5 vaccine was chosen for the vaccination programme in Finland [6]. The findings of FES highlight the expected benefits from a universal rotavirus vaccination programme in Finland.

Materials and methods

Study design

The methods used in FES generally conformed to the original REST protocol, the details of which have been published [15]. In brief, REST was a double-blind, placebo-controlled, randomised trial of nearly 70,000 infants. Healthy infants between 6 weeks and 12 weeks of age were eligible for the study. Infants were randomised 1:1 to receive three doses of either RV5 or placebo. REST evaluated the large-scale safety of RV5, primarily with respect to intussusception. The efficacy of RV5 was evaluated mainly for reduction in hospitalisations and ED visits because of acute gastroenteritis (AGE). The efficacy follow-up in the safety cohort lasted for 365 days. In addition, in a subset of infants in Finland and the United States, efficacy was evaluated for all AGE; this follow-up lasted, in some subjects, up to 2 years.

In Finland, infants received RV5 vaccine or placebo at 2, 3, and 4 to 5 months of age. Infants were enrolled from 30 sites located throughout the country. A total of 23,422 Finnish infants were enrolled in REST between 2 February 2001 and 13 August 2003, 2,271 in the clinical efficacy subset and 21,151 in the large-scale safety study that followed infants for RVGE-associated hospitalisations and ED visits for 365 days after the first dose. All the Finnish infants originally enrolled in REST were invited to continue on into FES, with the exception of the 2,271 Finnish infants in the clinical-efficacy substudy. Because the clinical-efficacy cohort did not transition into FES, the severity of rotavirus disease was not determined. The majority (20,732) of the Finnish infants in the large-scale safety study transitioned from REST into FES after they had completed the final 365-day contact in REST, or when they had reached either the study site's prespecified end date or the Finland end-of-study date in REST (31 December 2003), whichever date was earlier. In FES, infants were followed for hospitalisations and ED visits for RVGE or intussusception until 31 May 2004. FES captured additional health care encounters that occurred after the termination of REST in year 1 and year 2 post-vaccination, and allowed for the collection of health care encounters in year 3 post-vaccination. The FES protocol was approved by the Sub-Committee on Medical Research Ethics (TUKIJA) of the National Ethics Committee in Finland, and written informed consent was obtained from the parents of children who continued in FES.

Monitoring for health care encounters in FES followed the same approach that was used to monitor infants in REST [15]. However, in FES, episodes of AGE requiring hospitalisation or an ED visit were collected at prespecified 12-week intervals by automated short message service contacts, sent via mobile phones, or by direct telephone calls for those without access to text messaging, rather than at 6-week intervals as in REST [15, 18]. Case report forms in FES were modelled after the case report forms in REST [15, 18].

Efficacy analysis

For consistency, the case definition of RVGE and the assays used to detect and type rotavirus in the stool samples collected in FES were the same as in REST [15]. RVGE was defined as forceful vomiting and/or three or more watery or looser-than-normal stools within a 24-hour period, along with the detection of rotavirus by enzyme immunoassay [21] in a stool specimen obtained within 14 days after symptom onset. Reverse transcription-polymerase chain reaction assays were used to determine the VP7 and VP4 genotypes [1, 15].

Vaccine efficacy in preventing RVGE hospitalisations and ED visits, regardless of rotavirus serotype, was

examined in the per-protocol and intention-to-treat populations as previously described [18]. The per-protocol population included infants who received all three doses of RV5 or placebo, and for whom there were no protocol violations. The intention-to-treat population included infants who received at least one dose of RV5 or placebo. Measures of efficacy were assessed beginning 14 days after the third dose in the per-protocol population and any time immediately after the first dose in the intention-to-treat population. Because of rolling enrollment in REST, the duration of follow-up differed among subjects in REST and FES. For this reason, rates of hospitalisations and ED visits were expressed as the annual number of encounters per 1,000 person-years. Efficacy was calculated as previously described [18].

Results

Study population

In Finland, the median age of entry in REST was 10 weeks. A total of 21,151 infants were enrolled in the large-scale safety study of REST, 20,732 (~98%) of whom continued in FES. The demographic characteristics of the Finnish infants in the vaccine and placebo groups in the large-scale safety study are shown in Table 1. In addition, 2,271 infants were enrolled in the efficacy subset, with efficacy follow-up for up to 2 years. In FES, subjects were followed for up to 3.1 years after the third vaccine dose, which is equivalent to ~3.5 years of age. Depending on the date of entry in the original REST study, which enrolled infants over a period of 3 years in Finland, the number of children included in the analysis for each year differed, with the duration of follow-up in REST+FES greatest for those who were enrolled early in REST. The mean duration of follow-up in FES was 573 days (range, 29–1,126 days). The FES added 18,655 person-years of follow-up and identified 31% more cases than REST alone. The number of evaluable subjects refers to that for the entire analysis.

Table 1 Demographic characteristics of the infants enrolled in the Finnish Extension Study

Variable	RV5	Placebo
Children assigned to group, *n*	10,367	10,365
Gender, *n* (%)		
Boys	5245 (50.6)	5229 (50.5)
Girls	5122 (49.4)	5136 (49.6)
Age at entry, weeks		
Mean±SD	10.4±1.3	10.4±1.4
Median	11.0	11.0
Range	6–13	6–13
Race or ethnic group, *n* (%)		
White	10,263 (99.0)	10,271 (99.1)
Hispanic	0	0
Black	5 (0.1)	0
Multiracial	94 (0.9)	89 (0.9)
Asian	5 (0.1)	5 (0.1)
Native American	NA	NA
Other	0	0

RV5 pentavalent rotavirus vaccine, *NA* not applicable

Viral findings

During the FES, 270 samples fulfilling the criteria of gastroenteritis were collected, and 177 (66%) were rotavirus-positive. Of the remaining samples, 254 were available for studies of human caliciviruses, and 30 were positive. These included 27 noroviruses and three sapoviruses; other gastroenteritis viruses were not studied. The results of this investigation will be published separately.

Vaccine efficacy in the per-protocol population

Among the Finnish infants in REST, there were a total of 17 RVGE-related hospitalisations and ED visits among vaccine recipients and 310 among placebo recipients providing an overall rate reduction of 94.5% (95% CI: 91.2–96.9). During the 3.1 years of follow-up time post vaccination, RV5 significantly reduced the rate of hospitalisations and ED visits for RVGE in Finland (Table 2). Overall, in REST+FES, 21,941 subjects with 34,407 person-years of follow-up time were followed for rotavirus-related health care encounters. There were 28 health care encounters among vaccine recipients and 449 among placebo recipients. Among the vaccine recipients, 22 of the health care encounters occurred in year 1, six occurred in year 2, and there were none in year 3 of follow-up. None of the health care encounters that occurred beyond the first year among the vaccine recipients were the result of a recurrent episode. Among the placebo recipients, 351 of the 449 health care encounters occurred in year 1, 97 occurred in year 2, and there was one in year 3. Overall, 39% of all RVGE hospitalisations and ED visits in the vaccine group and 31% in the placebo group in REST+FES in Finland occurred during the follow-up period of FES.

Overall, in REST+FES, vaccine efficacy at reducing hospitalisations and ED visits combined in Finland was 93.8% (95% CI: 90.8–95.9%) for up to 3.1 years following the last dose of vaccine. In the first year post vaccination, vaccination with RV5 reduced the rate of hospitalisations and ED combined by 93.7% (95% CI: 90.4–96.1%). In the second year post vaccination, among the 16,189 evaluable infants in REST+FES, the vaccine reduced the rate of

Table 2 Rate reductions in all RVGE health care encounters, by year and for up to 3.1 years post vaccination, in the per-protocol and intention-to-treat population of REST+FES

Any serotype	Number of evaluable subjects	Total follow-up time in person-years	Mean follow-up time in person-days (min, max)	ED visits			Hospitalisations			ED visits+hospitalisations		
				Number		% Rate reduction (95% CI)	Number		% Rate reduction (95% CI)	Number		% Rate reduction (95% CI)
				RV5	Placebo		RV5	Placebo		RV5	Placebo	
Year 1[a]												
Per-protocol[b]	21,941	20,667	344 (29, 365)	14	198	92.9 (87.9, 96.2)	8	153	94.8 (89.4, 97.8)	22	351	93.7 (90.4, 96.1)
Intention-to-treat[c]	22,917	22,606	360 (29, 365)	15	182	91.8 (85.9, 95.5)	12	153	92.2 (85.8, 96.0)	27	335	92.0 (88.0, 94.7)
Year 2[a]												
Per-protocol	16,189	10,904	246 (3, 365)	1	43	97.7 (86.3, 99.9)	5	54	90.8 (76.9, 97.1)	6	97	93.9 (86.0, 97.8)
Intention-to-treat	20,115	13,883	252 (1, 365)	4	81	95.1 (86.7, 98.7)	7	69	90.0 (77.7, 96.0)	11	150	92.7 (86.4, 96.4)
Year 3[a]												
Per-protocol	6032	2829	171 (2, 365)	0	1	100 (<0.0, 100)	0	0	NA	0	1	100 (<0.0, 100)
Intention-to-treat	8503	4528	195 (1, 365)	0	1	100 (<0.0, 100)	0	6	100 (14.0, 100)	0	7	100 (29.7, 100)
Overall												
Per-protocol	21,941	34,407	573 (29, 1126)	15	242	93.8 (89.6, 96.6)	13	207	93.7 (89.0, 96.7)	28	449	93.8 (90.8, 95.9)
Intention-to-treat	22,917	41,244	657 (29, 1212)	19	264	92.9 (88.4, 95.7)	19	228	91.7 (86.6, 95.0)	38	492	92.3 (89.2, 94.6)

CI confidence interval, *ED* emergency department, *FES* Finnish Extension Study, *ITT* intention-to-treat, *NA* not applicable, *PP* per-protocol, *REST* Rotavirus Efficacy and Safety Trial, *RV5* pentavalent rotavirus vaccine, *RVGE* rotavirus gastroenteritis

[a] Eight additional cases involving RVGE-associated hospitalisations and ED visits were collected during FES (year 1: two cases [zero RV5, two placebo]; year 2: four cases [zero RV5, four placebo]; year 3: two cases [zero RV5, two placebo]). These stool samples were positive by enzyme immunoassay, but failed to yield a valid result on the plaque assay; therefore, they failed to meet the full preset definition and, thus, were not included in the analysis. However, it was confirmed that these rotavirus-positive samples contained wild-type human rotaviruses, as determined by a newly developed VP6 reverse transcriptase–polymerase chain reaction assay

[b] Infants who received three doses of RV5 or placebo; follow-up started 14 days after dose 3

[c] Infants who received at least one dose of RV5 or placebo; follow-up analysis started after the receipt of the last dose

hospitalisations and ED visits combined by 93.9% (95% CI: 86.0–97.8%), with a 90.8% (95% CI: 76.9–97.1%) reduction in hospitalisations, and a 97.7% (95% CI: 86.3–99.9%) reduction in ED visits. In the third year post vaccination, FES followed 6,032 evaluable subjects. During this time, there was only one RVGE-related health care encounter, an ED visit by a placebo recipient.

Vaccine efficacy in the intention-to-treat population

The intention-to-treat population included all infants who received at least one dose of vaccine, and for whom health care encounters were counted beginning immediately after the administration of the first dose rather than 14 days after the third dose (Table 2). Overall, during REST+FES, RV5 reduced the rate of hospitalisations and ED visits combined by 92.3% (95% CI: 89.2–94.6%), with a 91.7% (95% CI: 86.6–95.0%) reduction in hospitalisations, and a 92.9% (95% CI: 88.4–95.7%) reduction in ED visits in the intention-to-treat population. In the first and second years post vaccination, RV5 reduced the rate of combined hospitalisations and ED visits by 92.0% (95% CI: 88.0–94.7%) and 92.7% (95% CI: 86.4–96.4%), respectively. In the third year post vaccination, vaccine efficacy against RVGE health care encounters was 100% (95% CI: 29.7–100%), but there were only seven encounters among 8,503 subjects in REST+FES, all of which occurred in placebo recipients (Table 2).

Vaccine efficacy at reducing health care encounters by individual rotavirus serotype

In the per-protocol analysis, the efficacy of RV5 in reducing the need for hospitalisations and ED visits caused by episodes of RVGE associated with rotavirus G-types G1, G2, G3, G4, and G9 was also determined (Table 3). During the 3.1 years of follow-up in REST+FES in Finland, 90.3% of the hospitalisations and ED visits in Finland were associated with G1 rotaviruses (18 episodes among vaccine recipients and 383 among placebo recipients). RV5 reduced the rate of combined hospitalisations and ED visits caused by G1 rotaviruses by 95.3% (95% CI: 92.5–97.2%). RV5 also reduced the rate of combined hospitalisations and ED visits resulting from G3 and G9 rotaviruses by 91.7% (95% CI: 43.5–99.8) and 92.3% (95% CI: 48.5–99.8). Vaccine efficacy against G4 rotaviruses was 66.8% (95% CI: <0–94.2%), but the result was not significant. There were too few G2 RVGE health care encounters (1 in the vaccine group and 3 in the placebo group) to demonstrate efficacy against G2 RVGE. In the corresponding intention-to-treat analysis, the efficacy of RV5 in reducing the need for hospitalisations and ED visits caused by episodes of RVGE associated with rotavirus G-types G1, G2, G3, G4, and G9 was similar to that of the per-protocol analysis (data not shown).

Table 3 Serotype-specific rate reductions in RVGE health care encounters in REST+FES (for up to 3.1 years post vaccination) in the per-protocol population[a]

Serotype	Number of evaluable subjects	Total follow-up time in person-years	Mean follow-up time in person-days (Min, Max)	ED visits			Hospitalisations			ED visits+hospitalisations		
				Number		% Rate reduction (95% CI)	Number		% Rate reduction (95% CI)	Number		% Rate reduction (95% CI)
				RV5	Placebo		RV5	Placebo		RV5	Placebo	
G1	21,942	34,409	573 (28, 1126)	10	204	95.1 (90.8, 97.7)	8	179	95.5 (91.0, 98.1)	18	383	95.3 (92.5, 97.2)
G2	21,924	34,380	573 (28, 1126)	0	1	100 (<0, 97.4)	1	2	50.1 (<0, 89.6)	1	3	66.8 (<0, 75.8)
G3	21,924	34,380	573 (28, 1126)	1	6	83.4 (<0, 99.6)	0	6	100 (14.8, 100)	1	12	91.7 (43.5, 99.8)
G4	21,925	34,382	573 (28, 1126)	1	4	75.1 (<0, 99.5)	2	5	60.1 (<0, 96.2)	3	9	66.8 (<0, 94.2)
G9	21,946	34,401	573 (28, 1126)	0	8	100 (41.1, 100)	1	5	80.1 (<0, 99.6)	1	13	92.3 (48.5, 99.8)

[a] Infants who received three doses of RV5 or placebo; follow-up started 14 days after dose 3

CI confidence interval, *ED* emergency department, *FES* Finnish Extension Study, *NA* not applicable, *REST* Rotavirus Efficacy and Safety Trial, *RV5* pentavalent rotavirus vaccine, *RVGE* rotavirus gastroenteritis

Table 4 Efficacy of RV5 against all RVGE health care encounters, by age of the child at time of RVGE, in the per-protocol population of REST+FES

Age (months)[a]	ED visits			Hospitalisations			ED visits+hospitalisations		
	Number		% Rate reduction (95% CI)	Number		% Rate reduction (95% CI)	Number		% Rate reduction (95% CI)
	RV5	Placebo		RV5	Placebo		RV5	Placebo	
4–11	9	113	92.0 (84.3, 96.5)	3	84	96.4 (89.2, 99.3)	12	197	93.9 (89.1, 96.9)
12–23	6	123	95.1 (89.1, 98.2)	7	108	93.5 (86.2, 97.5)	13	231	94.4 (90.2, 97.0)
24–35	0	6	100.0 (14.1, 100.0)	3	15	80.2 (28.5, 96.2)	3	21	85.9 (51.6, 97.2)
36–43[b]	0	0	NA	0	0	NA	0	0	NA
Total	15	242	93.8 (89.6, 96.6)	13	207	93.7 (89.0, 96.7)	28	449	93.8 (90.8, 95.9)

Infants who received three doses of RV5 or placebo; follow-up started 14 days after dose 3

CI confidence interval, *ED* emergency department, *FES* Finnish Extension Study, *NA* not applicable, *REST* Rotavirus Efficacy and Safety Trial, *RV5* pentavalent rotavirus vaccine, *RVGE* rotavirus gastroenteritis

[a] Stratification of age of the child was based on the actual birthday of each child and age was rounded down to the last full month (i.e., 11.9 months would be presented as 11 months)

[b] There were 2,454 subjects aged 36–43 months followed for 618.7 person-years

Vaccine efficacy at reducing health care encounters by age of the child

In the per-protocol analysis, vaccine efficacy at reducing health care encounters for RVGE was also calculated based on the age of the child at the time of the contact rather than time after the third dose (Table 4). The reductions in the rate of hospitalisations and ED visits combined during the first, second, and third years of life were 93.9% (95% CI: 89.1–96.9%), 94.4% (95% CI: 90.2–97.0%), and 85.9% (95% CI: 51.6–97.2%), respectively. Of the cases in the placebo group, 197 (43.9%) occurred in children 4–11 months of age, 231 (51.4%) occurred in children 12–23 months of age, and 21 (4.7%) occurred in children 24–35 months of age (Table 4). Of the cases in the vaccine group, 12 (42.8%) hospitalisations and ED visits occurred in children 4–11 months of age, 13 (46.4%) in children 12–23 months of age, and 3 (10.7%) in children 24–35 months of age. Figure 1 shows the accumulation of all RVGE cases requiring hospitalisations and ED visits, respectively, by age, in all Finnish participants of REST, and those followed in FES. As shown in Fig. 1, in Finland, the majority of RVGE healthcare encounters occurred in the first two years of life, and vaccination with RV5 dramatically reduced the number of rotavirus-attributable healthcare encounters.

RV5 efficacy at reducing health care encounters for AGE of any aetiology

In an intention-to-treat analysis, during the combined period of REST+FES, vaccine efficacy against combined hospitalisations and ED visits for AGE was 62.4% (95% CI: 57.6–66.6%), with a 64.8% (95% CI: 57.6–70.9%) reduction in hospitalisations and a 60.6% (95% CI: 54.1–66.2%) reduction in ED visits.

Intussusception

There were no cases of intussusception during the FES period.

Discussion

FES was designed to evaluate whether the protection observed in REST 365 days after the last dose of RV5

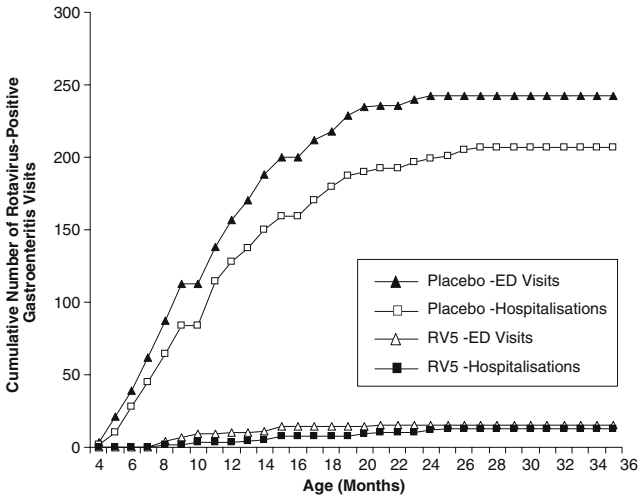

Fig. 1 Cumulative number of all reported ED visits and hospitalisations due to RVGE, regardless of serotype, in Finnish infants followed in REST and FES by age. ED visits, *triangles*; hospitalizations, *squares*

was sustained in the second and third years of life for children in Finland. The results from FES confirm previous findings demonstrating that hospitalisations and ED visits for RVGE continue to be common in the second year of life for children from Finland [17]. Here, we show that the protection of RV5 is sustained into the second year post-vaccination, and possibly into the third year post-vaccination. Overall, in Finland, RV5 reduced the rate of combined hospitalisations and ED visits due to RVGE, regardless of the rotavirus serotype, by 93.8% (95% CI: 90.8–95.9%) for up to 3.1 years after the last vaccine dose. The results were consistent from year to year and between studies, regardless of whether the analysis was based on the per-protocol population or the intention-to-treat population. The results in year 2 are consistent with year 1, and clearly show that protection does not wane during this period, when the disease burden is greatest. The results of FES are very encouraging and confirm the high level of protection observed in the Finnish cohort of REST, shown here, and the large-scale safety study of REST, the results of which have been published previously [15]. In other regions of the world, the monovalent G1P1A[8] vaccine, RV1, has also shown high efficacy against hospital admissions in children followed for up to 2 years of age in Latin America [5] and Asia [9]. In a cohort of 15,183 infants from ten Latin American countries, RV1 reduced hospital admissions by 83.0% (95% CI: 73.1–89.7%) in children up to 2 years of age [5]. In a cohort of 10,708 infants from three Asian countries, RV1 reduced hospital admissions by 93.8% (95% CI: 80.6–98.8%) in children followed up to 2 years of age [9].

In REST+FES in Finland, vaccine efficacy at reducing the rate of combined hospitalisations and ED visits was 93.9% in children <12 months of age and 94.4% in children 12–23 months of age. Therefore, no reduction in vaccine efficacy against hospitalisations and ED visits combined, indicators of severe RVGE, was seen up to the age of 24 months. In the third year of life, the point estimate for the combined end point was 85.9%, but the CI was wide. Definitive conclusions regarding vaccine efficacy beyond 24 months of age cannot be drawn from these results, but one could speculate that the relatively few RVGE-related hospitalisations and ED visits, or decreased relative attack rate in the third year of life was probably due to naturally acquired immunity [18].

RV5 also significantly reduced all AGE-related health care encounters. In the Finnish cohort of REST, RV5 reduced hospitalisations for episodes of AGE of any aetiology by 58.6% (95% CI: 48.2–66.9%) (data not shown), which is comparable to the original REST study (58.9%; 95% CI: 51.7–65.0%) [15]. This is not surprising, considering that the majority of cases of AGE in REST were collected in Finland. During the 3.1 years of follow-up time in REST+FES, RV5 reduced AGE hospitalisations and ED visits combined by 62.4% (95% CI: 57.6–66.6%). Taken together, the results show that, over 3.1 years of follow-up time, RV5 markedly decreased the use of health care resources for RVGE and any AGE among Finnish infants. In the United States, RV5 has been highly effective postlicensure [20]. RV5 reduced hospitalizations and ED visits for RVGE by 100% and AGE by 59% over the course of two rotavirus seasons. Furthermore, RV5 was associated with a 66% reduction in the number of AGE-related hospitalisations and ED visit days, and a 74% reduction in related costs.

Analysis by individual rotavirus G-type indicated that vaccination with RV5 provided a high level of sustained protection against RVGE due to genotypes G1, G3, and G9. G2 was rare in Finland at the time of REST and FES, and there were too few health care encounters to show significant protection against G2 RVGE. After the completion of FES, G2 rotaviruses have become more common in Finland [14]. Recent reports have shown that infants vaccinated with the monovalent G1P1A [8] vaccine, RV1, are susceptible to outbreaks with other genotypes [2, 7]. As for RV5, it is not known whether the efficacy against G2 RVGE will be greater than that provided by RV1. Regarding G4, there were only 12 G4-related hospitalisations and ED visits, too few to demonstrate significant efficacy, but it would be reasonable to assume that Finnish infants would be afforded a high level of protection against G4 rotavirus-related hospitalisations and ED visits similar to that demonstrated in the original REST study [12, 15].

In conclusion, the results from FES show that, in Finland, RV5 vaccination provides a high level of protection from RVGE through the second year and probably in the third year of life. These results support the decision by the Finnish government to introduce routine rotavirus vaccination with RV5 into the national immunisation schedule [6], and provide an estimate of the benefits expected to be seen as a result of the universal mass vaccination with RV5. Continued postlicensure surveillance will determine whether the benefits of universal rotavirus vaccination in Finland will correspond to the findings of REST+FES shown here.

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