Sustained High Effectiveness of RotaTeq on Hospitalizations Attributable to Rotavirus-Associated Gastroenteritis During 4 Years in Finland

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INTRODUCTION

Rotaviruses are a major cause of acute gastroenteritis (AGE) in infants and young children [1, 2]. In industrialized countries, rotavirus-related deaths are rare, and thus the main argument for rotavirus vaccination is to prevent related hospital admissions and associated costs [3].

Two live attenuated oral rotavirus vaccines, a pentavalent human-bovine reassortant rotavirus vaccine (RV5 [RotaTeq, Merck]) and a single-strain human rotavirus vaccine (RV1 [Rotarix, GlaxoSmithKline]) were licensed for use in 2006. Both vaccines were shown to be efficacious in prelicensure studies [4–6]. Specifically, RV5 showed 95% efficacy in the Rotavirus Efficacy and Safety Trial, a major part of which was conducted in Finland [5]. This efficacy was sustained in children up to 3 years after vaccination [7].

Rotavirus vaccination (using exclusively RV5) was added to the National Immunization Programme (NIP) of Finland on September 1, 2009, after which coverage quickly reached >95%. The vaccine is given in three doses, one each at the ages of 2, 3, and 5 months. A prospective study carried out in 2009–2011 found that hospital admissions for rotavirus-associated AGE (RV-AGE) in Finland were reduced by 80% in the first season after the introduction of RV5, and no change was seen in the second season [8]. This type of pattern was also reported in the United States, in which a high impact of rotavirus vaccination was seen in the first season after vaccine introduction followed by a rise in rotavirus activity in the second season, low activity in the third season, and so on [9, 10]. Indirect effects of rotavirus vaccination were also reported among unvaccinated...

RESULTS.

The crude estimate of the effectiveness of RotaTeq to prevent RV-AGE hospitalization in NIP age-eligible children was 94.4% (95% confidence interval, 79.8%–98.4%). No change in prevalent wild-type rotavirus genotypes was observed. Vaccine-derived rotaviruses were detected in 8% of the children with RV-AGE, with a probable causal association in 2 children. Hospital discharge records revealed that RV-AGE and AC-AGE hospitalizations in children aged <16 years decreased in the two post-NIP seasons (2009–2013).

CONCLUSIONS.

Over 4 years of follow-up, high rotavirus vaccine coverage in the NIP (>95%) has led to a major reduction in RV-AGE and AC-AGE hospitalizations without a resurgence of rotavirus activity. However, rotavirus continues to circulate in older unvaccinated children.

Keywords: effectiveness; gastroenteritis; impact; RotaTeq; rotavirus; vaccine.
children and adults in the United States, Austria, and Belgium [9, 11, 12]. In contrast, the introduction of RV5 has given rise to some vaccine-derived rotavirus (vdRV) strains. One clinically significant strain is a double-reassortant vdG1P[8], which originates from vaccine strains G1P[5] and G6P[8] [13, 14]. The vdG1P[8] strain can cause disease and infect unvaccinated children and can spread in the environment [15]. Results from the first 3 years of our prospective study show that the effectiveness of RV5 in preventing RV-AGE hospitalizations was 92% for fully vaccinated children [16]. The objective of this study was to estimate the effectiveness and impact of RotaTeq during 4 years of follow-up.

MATERIALS AND METHODS

Surveillance for RV-AGE

Our prospective study was carried out from December 1, 2009, to August 31, 2011, and from October 12, 2011, to August 31, 2013. All children and adolescents aged <16 years admitted to the pediatric ward of Tampere University Hospital or Oulu University Hospital with symptoms of AGE were eligible for enrollment. Parents were interviewed about their child’s rotavirus vaccination (vaccine brand, number of doses, and vaccination date), and this information was confirmed via vaccination cards or medical records. A stool sample was collected either during the hospitalization or at home within 2 weeks of discharge [8, 16]. The study was conducted in accordance with the Declaration of Helsinki, good pharmacoepidemiology practice guidelines, and local laws, rules, and regulations. The ethics committee of the Pirkanmaa Hospital District (Tampere) reviewed and approved the study protocol and amendments. The study also was approved by the head of each hospital. Before enrollment, a parent or legal guardian and children 6 years of age or older signed a written informed-consent form.

Reverse-transcript polymerase chain reaction (RT-PCR) was used to detect rotavirus in stool samples, as described previously [17]. All rotavirus-positive samples underwent nucleotide sequencing to determine the G and P genotypes of the gene segments encoding for the VP7 and VP4 antigens. The gene segment encoding for the inner capsid protein VP6 was also sequenced to determine the presence of vdRV (bovine origin) [18]. When vdRV was detected, the samples were tested by RT-PCR or enzyme-linked immunosorbent assay (ELISA) for other gastroenteritis viruses such as caliciviruses (norovirus and sapovirus), adenovirus, coronavirus, and bocavirus [19, 20]. Nucleotide sequences read from chromatograms were aligned to published sequences from GenBank (http://www.ncbi.nlm.nih.gov/genbank). Each stool specimen was tested for the presence of rotavirus antigen by an ELISA using the ProSpecT rotavirus kit (Oxoid Limited, Basingstoke, United Kingdom).

Analyses of Vaccine Effectiveness

Analyses of vaccine effectiveness were carried out using a test-negative case-control design [16, 21]. The population from the above-described prospective study was restricted to children who were age eligible for the NIP (ie, children born after July 1, 2009, who thus were eligible to receive the first dose [given at 2 months of age] at the date of NIP introduction on September 1). Those who had contraindications for vaccination, who were <6 months old, or whose stool sample was not collected within 14 days of the onset of symptoms were excluded from the analysis. Children whose stool sample tested positive for wild-type rotavirus (wtRV) by both RT-PCR and ELISA were categorized as “cases” and were compared to children whose stool sample tested negative for rotavirus by both RT-PCR and ELISA, who were categorized as “controls.” Controls who were admitted outside the rotavirus season were excluded.

Analyses of Vaccine Impact

Vaccine impact was estimated using hospital discharge records (HDRs) from the 2 study hospitals. Children <16 years of age with an International Classification of Diseases (ICD) discharge code of A00, A01, A02, A03, A04, A05, A06, A07, A08, and/or A09 were included as cases with all-cause AGE (AC-AGE), and those with an ICD discharge code of A08.0 were included as cases with RV-AGE. Records were retrieved for 2001–2006 (prevaccination seasons) and 2009–2013 (ie, after RV5 was added to the NIP [post-NIP seasons]) [17]. Rotavirus seasons were defined as periods during which >25% of samples tested positive for rotavirus, based on weeks in which a minimum of 10 tests were performed.

Statistical Analyses

Statistical analyses were performed using the Mann–Whitney test. Any P value of <.05 was considered significant. For incidence calculations, population data for the years 2010–2013, provided by Statistics Finland for the Tampere University Hospital and Oulu University Hospital catchment areas, were used. Vaccine effectiveness was calculated as 1-odds ratio (OR), and 95% confidence intervals (CIs) were estimated using the exact interval method. All analyses were conducted using SPSS 2.0 (SPSS, Inc., Chicago).

RESULTS

A total of 687 cases were enrolled during the 4-year study period. A stool sample was obtained from 592 (86%) cases, 291 (49%) from Tampere University Hospital and 301 (51%) from Oulu University Hospital. Of these cases, 48% (282 of 592) were <2 years of age, and 75% (442 of 592) were <5 years of age. Of the 592 cases with AGE from whom a stool sample was available, 185 (31%) tested positive for rotavirus by RT-PCR
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(170 had wtRV [ie, “true infection”] [Figure 1], and 15 had vdBV [8.1%]), and of these cases, 143 (77%) also tested positive for rotavirus in an ELISA. Of 156 cases enrolled in the first post-NIP season (2009–2010), 72 (46%) tested positive for wtRV (Table 1), but the proportion of those with wtRV decreased in the remaining seasons (2010–2013) to 22% (P < .01) (24% in 2010–2011, 19% in 2011–2012, and 24% in 2012–2013). The number of RV-AGE cases decreased for the first 3 post-NIP years but increased slightly in the last year of follow-up (2012–2013) (Table 1).

**Surveillance of wtRV-AGE Seasonal Distribution**

During the follow-up period, peak wtRV activity shifted from winter to spring. In the first post-NIP season (2009–2010), the majority of wtRV-AGE was still seen between January and March, and a later peak occurred in May (Figure 2). In the second and third post-NIP seasons, the most active months were March and May. In the last post-NIP season in this follow-up study (2012–2013), a small peak in wtRV-AGE was seen in January, and a second peak occurred in April and May (Figure 2).

**Age Distribution**

The age range of cases with wtRV-AGE was 17 days to 11 years 5 months; 33% of the cases were <2 years old, and 71% were <5 years old. However, as the occurrence of wtRV-AGE decreased in vaccinated children, the age distribution of those with wtRV-AGE shifted toward children who were not age eligible for the NIP (P < .001) (Figure 3). The mean age of wtRV-AGE cases increased from 2 years 7 months in the first post-NIP season (2009–2010) to 4 years 5 months in the second post-NIP season (2010–2011). In the fourth post-NIP season (2012–2013), the mean age of wtRV-AGE cases was 4 years 8 months. Similarly, the most affected age group shifted from 12 to 24 months in the first post-NIP season to 2 to 3 and 5 to 7 years in the second post-NIP season. In the third post-NIP season (2011–2012), the most affected age group was 4 to 5 years. In the last post-NIP season in this follow-up study, the cases of RV-AGE increased in all age groups, but the peak was in the 5- to 7-year age group (Figure 3).

**Genotype Distribution**

In the first post-NIP season, the predominant wtRV genotype was G4P[8] (71%), followed by G1P[8], G9P[8], and G2P[4]. In the second post-NIP season, G1P[8] was predominant (57%), but G4P[8] continued to circulate (31%). In the third post-NIP season, the role of G4P[8] diminished further to 12%, and G1P[8] accounted for 67% of RV-AGE cases. In the fourth post-NIP season, no clear dominance of any rotavirus genotype was seen; G3P[8] was the most common genotype (38%), followed by G1P[8] (33%), G2P[4] (23%), G4P[8] (5%), and an emerging genotype, G12P[8] (5%). Apart from 1 case with a rotavirus strain of canine origin (G3P[3]) in Tampere in the second post-NIP season, no uncommon genotypes were detected during this surveillance (Figure 4). Among the 170 children with wtRV, 16 had been vaccinated (13 with RV5, and 3 with RV1) and were infected with the genotype G1P[8] (n = 6), G4P[8] (n = 4), G3P[8] (n = 2), G2P[4] (n = 2), G9P[8] (n = 1), or G12P[8] (n = 1).

**vdRV Gastroenteritis**

Among the 15 children who tested positive for vdBV by RT-PCR, only 2 tested positive for rotavirus by an ELISA; both of these children had the double-reassortant vdBV in their stool.

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Table 1. Reverse-Transcription Polymerase Chain Reaction Rotavirus Detection in Children With All-Cause Acute Gastroenteritis According to Study Season, Finland, 2009–2013

| Study Season | Wild-Type Rotavirus Positive (n [%]) | Vaccine-Derived Rotavirus Positive (n [%]) | Rotavirus Negative (n [%]) | Total (n) |
|--------------|-------------------------------------|------------------------------------------|---------------------------|-----------|
| 2009–2010    | 72 (46.2)                           | 4 (2.6)                                  | 80 (51.3)                 | 156       |
| 2010–2011    | 35 (24.1)                           | 5 (3.4)                                  | 105 (72.4)                | 145       |
| 2011–2012    | 24 (18.6)                           | 1 (0.8)                                  | 104 (80.6)                | 129       |
| 2012–2013    | 39 (24.1)                           | 5 (3.1)                                  | 118 (72.8)                | 162       |
| All          | 170                                 | 15                                       | 407                       | 592       |

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Figure 1. Wild-type rotavirus-associated acute gastroenteritis (wtRV-AGE) cases in this hospital-based prospective surveillance study, Finland, December 2009–August 2013.
Among the 15 children with vdRV, 14 (93%) were <6 months of age. With the exception of 2 unvaccinated children (a 2-month-old and a 7-year-old), all of the children had received at least 1 dose of RV5. The most commonly detected vdRV genotype was G1, which was detected as a single genotype or concomitantly with other vaccine genotypes in 80% (12 of 15) of the cases. The other detected vdRV G-types were G3 (n = 1), G4 (n = 1), and G6 (n = 2). In five cases, the vaccine G-type G1 was associated with P[8] and formed a potential double-reassortant G1P[8] between vaccine strains G1P[5] and G6P[8]. Two others had bovine G-type G6. In the other 6 cases, the P-type was of bovine origin P[5], the P-type was detected alone or concomitantly with P[8], or no VP4 could be detected (Table 2). Apart from 1 case who tested positive for vaccine type G1 but negative for VP4, all rotavirus cases with a vaccine strain tested positive for bovine VP6 by RT-PCR.

Of the 15 children with vdRV, we had enough material available from 10 cases to perform all tests for the presence of other gastroenteritis viruses and found coinfection with norovirus, sapovirus, or coronavirus in 7, 2, and 1 case, respectively. The vaccine-associated cases have already been reported [16, 18].

**Vaccine Effectiveness**

A total of 134 cases with AGE who were age eligible for rotavirus vaccination in the NIP were included in the vaccine-effectiveness analysis. Of these children, 17 tested positive for wtRV by RT-PCR and ELISA. The remaining 117 children were used as test-negative controls. All test-negative controls tested negative for rotavirus by RT-PCR and ELISA and were seen in the hospital for AGE during an active rotavirus month. Of 17 wtRV-positive cases, 8 had been fully vaccinated with RV5, 1 had received only 1 dose, and 8 were unvaccinated even though they were eligible. Among 117 controls, 107 were fully vaccinated with RV5, 4 had received 1 or 2 doses (2 and 2 children, respectively), and 6 were unvaccinated.

Thus, the crude vaccine effectiveness rate for children who were fully vaccinated with RV5 was 94.4% (95% CI, 79.8%–98.4%). The crude effectiveness rate for children who were vaccinated only partially was 81.2% (95% CI, 78.6%–98.3%) (1 or 2 doses). The results were similar when adjusted according to hospital, season, and age group.

**Vaccine Impact**

The mean incidence of RV-AGE hospitalizations decreased by 79.1% (95% CI, 74.1%–83.2%), from 0.7 case per 1000 children
Table 2. Vaccination Status and Genotype Detection From the 15 Children With Vaccine-Derived Rotavirus, Finland, 2009–2013

| Age   | Vaccination Status (n Doses) | Delay Between Vaccination and Sample Collection (Days) | Rotavirus ELISA Result | G Type(s) | P Type(s) | Presence of Coinfection |
|-------|-----------------------------|------------------------------------------------------|------------------------|-----------|-----------|------------------------|
| 2 mo  | 0                           | —                                                   | Negative               | RotaTeq G1/G4 | P[8]     | Negative               |
| 7 y   | 0                           | —                                                   | Positive               | RotaTeq G1   | RotaTeq P[8] | Coronavirus           |
| 2 mo  | 1                           | 4                                                   | Positive               | RotaTeq G1   | RotaTeq P[8] | Negative               |
| 2 mo  | 1                           | 5                                                   | Negative               | RotaTeq G6   | RotaTeq P[8] | Negative               |
| 2 mo  | 1                           | 6                                                   | Negative               | RotaTeq G1   | RotaTeq P[8] | Negative               |
| 3 mo  | 1                           | 9                                                   | Negative               | RotaTeq G6   | RotaTeq P[8] | Negative               |
| 4 mo  | 1                           | 12                                                  | Negative               | RotaTeq G1   | RotaTeq P[8] | Norovirus GII.4       |
| 3 mo  | 1                           | 14                                                  | Negative               | RotaTeq G1   | RotaTeq P[8] | Norovirus GII.4       |
| 3 mo  | 1                           | 20                                                  | Negative               | RotaTeq G1   | RotaTeq P[8] | Norovirus GII.4       |
| 3 mo  | 1                           | 20                                                  | Negative               | RotaTeq G1   | RotaTeq P[8] | Norovirus GII.4       |
| 3 mo  | 2                           | 1                                                   | Negative               | RotaTeq G1   | RotaTeq P[8] | Norovirus GII.7       |
| 4 mo  | 1                           | 44                                                  | Unsatisfactory         | RotaTeq G4   | RotaTeq P[8] | Negative               |
| 5 mo  | 3                           | 3                                                   | Negative               | RotaTeq G1/G3 | RotaTeq P[8]/P[8] | Norovirus GII.21 |
| 6 mo  | 3                           | 9                                                   | Negative               | RotaTeq G1   | Unknown    | Norovirus GII.7       |
| 7 mo  | 3                           | 47                                                  | Negative               | RotaTeq G1   | RotaTeq P[8] | Norovirus GII.4       |

*No enzyme-linked immunosorbent assays (ELISAs) were performed for the study purpose; rotavirus results were collected from hospital records.

A statistically significant reduction was found in the incidence of AC-AGE cases; the incidence decreased from 1.2 to 0.85 case per 1000 children between the prevaccination and post-NIP years (from 3.8 to 0.4 case per 1000 children) (Figure 5).

The annual mean incidence of RV-AGE in children aged 4 to 15 years was 0.0712 case per 1000 children in the prevaccination years and 0.0685 case per 1000 children in the post-NIP years, but the 4% reduction was not statistically significant. A statistically significant reduction was found in the incidence of AC-AGE cases; the incidence decreased from 1.2 to 0.85 case per 1000 children between the prevaccination and post-NIP seasons, for a total reduction of 30% (Figure 5).

The rotavirus seasons in the prevaccination period were characterized by long durations (18–27 weeks). However, in the post-NIP seasons, it was not possible to identify a rotavirus season because of the small number of samples or the low proportion of rotavirus-positive samples.

**DISCUSSION**

RV-AGE hospitalizations decreased steadily in the first 3 seasons after the introduction of rotavirus vaccination in the NIP in Finland, but they did not continue to decrease in the fourth post-NIP season, which indicates that rotavirus continues to circulate even when vaccine coverage is very high (>95%). In contrast, RV-AGE was kept under better control than has been reported in the United States, where a biennial pattern of rotavirus activity has been found [9].

The absence of rotavirus seasons in the postvaccination period is a good indication that routine vaccination against rotavirus has disrupted its epidemiological pattern.

Among children aged 4 to 15 years, who were not targeted for rotavirus vaccination in the NIP, there was a significant 30% decrease in AC-AGE in the post-NIP seasons. This decrease was not found for RV-AGE in this age group; however, the numbers were extremely small, ranging from only 2 to 13 RV-AGE cases per season. Such a herd effect against RV-AGE and AC-AGE was also observed shortly after the introduction of rotavirus vaccination in countries such as the United States, Australia, Belgium, and Finland [9, 11, 22, 23]. Four years after the introduction of rotavirus vaccination in the NIP, it seems that wtRV is still circulating and infecting older children who have not been vaccinated and may remain naive.

Although our data are based on small numbers, we found changes in the predominant wtRV genotypes in the follow-up period. The genotypes varied from season to season, and it is unlikely that this variation was caused by rotavirus vaccination. In the first post-NIP season, the majority of RV-AGE cases were caused by the G4P[8] genotype, followed by G1P[8] in the second and third post-NIP seasons. In the fourth season,
the dominant genotype was G3P[8], followed by G1P[8]. In Finland, wtRV genotype G3P[8] was less common in the pre-vaccination years; however, this finding has to be considered with caution, because the numbers in the post-NIP years are much smaller than those in the prevaccination years. In addition, an emergent worldwide wtRV genotype (G12P[8]) was observed in the fourth post-NIP season. The emergence of novel genotypes such as G8 and G12 was also noticed elsewhere [24]. Changes in the dominant wtRV genotypes after the introduction of rotavirus vaccination have been seen worldwide, but because similar changes occurred before licensure of the rotavirus vaccines, any causal link to universal rotavirus vaccination is uncertain [25–28].

In prelicensure studies, RV5 was found to be efficacious against all common wtRV genotypes (G1–G4 and G9), but the point estimate for efficacy was highest against the G1 strains, although these results were not statistically significant [5, 7, 29]. It is interesting to note that although the G1 genotype remained predominant in unvaccinated children, we found that no child fully vaccinated with RV5 was hospitalized with this genotype.

We detected vdRV in 8% of the children hospitalized for RV-AGE. Among these strains, genotype G1 was detected in 81%, which is in accordance with the results from a study by Markkula et al [30], who looked for rotavirus shedding in children who were <2 years of age and hospitalized with respiratory diseases in Finland. All children with vdRV were also studied for the presence of AGE possibly caused by other viruses. Only 2 children with double-reassortant vdg1P[8] did not have any sign of coinfection with other pathogens; therefore, these cases of AGE were probably causally related to vdBV. Of those 2 cases, 1 was a recently vaccinated 3-month-old, and the other was an unvaccinated 7-year-old. The number of symptomatic cases associated with vdg1P[8] might be underestimated in the context of this hospital-based surveillance, in which cases of mild gastroenteritis were not captured.

As more sensitive methods are being used, the literature is showing that shedding, whether symptomatic or asymptomatic, is more common than previously thought; 21% to 94% of vaccine recipients have been found to shed RV5 vaccine types at some point after their first immunization [31, 32]. Shedding of rotavirus has also been found after natural infection and has been documented after the administration of all live rotavirus vaccines.

In conclusion, RV5 was found to be highly effective against RV-AGE in a real-life setting, and RV5 vaccination in the post-NIP years was found to have a major impact on RV-AGE and AC-AGE hospitalizations in Finland. The impact of the rotavirus vaccination in Finland might be the highest observed anywhere.

**Notes**

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of rotavirus vaccines produced by Merck and GlaxoSmithKline and is a member of an advisory board of Sanofi Pasteur-MSD; M. U. has received grants and fees for review activities from Sanofi Pasteur-MSD; and M. R. has received grants and travel compensation from Sanofi Pasteur-MSD and is an advisory board member for Abbott. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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