International Journal of Infectious Diseases (2007) 11 (Supplement 2), S29–S35

http://intl.elsevierhealth.com/journals/ijid

Efficacy of a pentavalent rotavirus vaccine in reducing rotavirus-associated health care utilization across three regions (11 countries)

Timo Vesikari [a,*], Robbin Itzler [b], David O. Matson [c], Mathuram Santosham [d], Celia D.C. Christie [e], Michele Coia [b], John R. Cook [b], Gary Koch [f], Penny Heaton [g]

[a] *University of Tampere Medical School, Tampere, Finland*
[b] *Merck & Co., Inc., West Point, PA, USA*
[c] *Eastern Virginia Medical School, Norfolk, VA, USA*
[d] *Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA*
[e] *University of the West Indies, Jamaica*
[f] *University of North Carolina, Chapel Hill, NC, USA*
[g] *Novavax, Malvern, PA, USA*

KEYWORDS
Rotavirus;
Vaccine;
Human-bovine reassortant pentavalent rotavirus vaccine;
Health care utilization;
Hospitalizations;
Emergency department

Summary
Objective: To evaluate the effect of a human-bovine reassortant pentavalent rotavirus vaccine (PRV) on health care encounters in nearly 70 000 subjects randomized in three regions – Europe, the United States, and Latin America/the Caribbean – in the Rotavirus Efficacy and Safety Trial (REST).
Methods: Healthy 6- to 12-week-old infants received 3 doses of PRV or placebo at 4- to 10-week intervals. The exact binomial method for ratios of Poisson counts was used to evaluate the effect of PRV on the rate of rotavirus-related hospitalizations and emergency department (ED) visits involving rotavirus G-types 1–4 occurring $\geq$14 days after the third dose of vaccine for up to 2 years.
Results: In fully vaccinated infants, reductions in rotavirus-associated hospitalizations and ED visits were 94.7% (95% CI: 90.9, 96.9) in Europe, 94.9% (95% CI: 84.0, 98.9) in the United States, and 90.0% (95% CI: 29.4, 99.8) in the Latin American/Caribbean regions.
Conclusions: PRV reduced hospitalizations and ED visits within each region in REST. Results were consistent across regions and across the overall study cohort.

Introduction

Rotavirus gastroenteritis is an important cause of morbidity and mortality worldwide, resulting in more than 600 000 deaths, 2.3 million hospitalizations, and 24 million outpa-

* Address correspondence and reprint requests to: Timo Vesikari, MD, University of Tampere Medical School, Department of Pediatrics, Virology/Vaccine Research Centre, Finn-Medi 3, 33014 Tampere, Finland. Tel.: +358-3-3551-8444; Fax: +385-3-3551-8450.
E-mail address: timo.vesikari@uta.fi

1201-9712/$32.00

tient visits among infants and young children each year.[1] Rotaviruses infect nearly all infants by 5 years of age regardless of socioeconomic status or country of birth and there is no method to reliably predict which infants will experience a more severe course of illness.[2] Recently, the *New England Journal of Medicine* reported the results of the Rotavirus Efficacy and Safety Trial (REST), a large-scale Phase III clinical trial demonstrating the safety and efficacy of a pentavalent human-bovine reassortant rotavirus vaccine expressing human rotavirus G-types G1, G2, G3, and G4, and P type P1A[8] (PRV [pentavalent rotavirus vaccine], RotaTeq™, Merck & Co., Inc., Whitehouse Station, New Jersey, USA).[3]

The large study population in REST provided the opportunity to evaluate the efficacy of the vaccine in reducing rotavirus-associated health care resource utilization during the trial, i.e., hospitalizations, emergency department (ED) visits, which can be considered a surrogate for severe disease, and office visits for rotavirus gastroenteritis. Overall, among the 28 646 subjects in the vaccine group and 28 488 subjects in the placebo group who comprised the per-protocol analysis in which all infants were fully vaccinated (i.e., received 3 doses), PRV reduced the incidence of hospitalizations and ED visits for rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 occurring 14 or more days after the completion of the 3-dose series for up to 2 years by 94.5% (95% CI: 91.2, 96.6). Individually, the rate of hospitalizations was reduced by 95.8% (95% CI: 90.5, 98.2) and the rate of ED visits was reduced by 93.7% (95% CI: 88.8, 96.5).

Among a subset of 2173 subjects in the vaccine group and 2278 subjects in the placebo group in which efficacy against rotavirus gastroenteritis of any severity was evaluated (efficacy subset), PRV reduced office visits for rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 in fully vaccinated children for up to 2 years after vaccination by 86% (95% CI: 73.9, 92.5).

The REST study was conducted in 11 countries representing 3 regions with different populations and health care delivery systems – Europe, the United States, and Latin America/the Caribbean. Historically, the efficacy of rotavirus vaccines has varied according to geographic region, generally demonstrating reduced efficacy in less developed areas.[1,4] Here we report the efficacy of PRV in reducing health care utilization associated with episodes of rotavirus gastroenteritis in these 3 regions. The participating countries in Europe included Finland, Germany, Belgium, Sweden, and Italy and in the Latin American/Caribbean region, Jamaica, Costa Rica, Mexico, and Guatemala. Although a self-governing island that is part of the commonwealth of the United States, Puerto Rico was included in the Latin American/Caribbean region for these analyses (Figure 1). Taiwan was excluded from the analysis because health care utilization was not reported from this country.

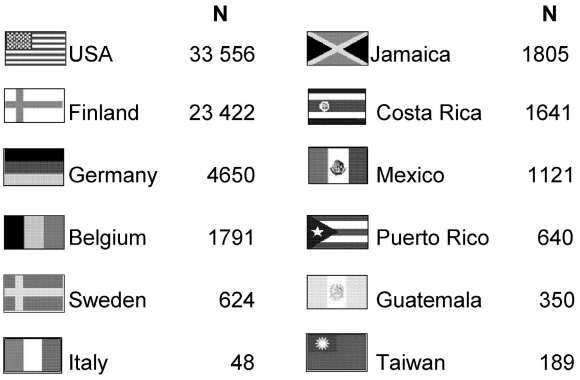

Figure 1 Enrollment in the Rotavirus Efficacy and Safety Trial by country.

Methods

A complete description of the study methodology of REST has been published previously.[3] REST was a blinded, placebo-controlled, randomized trial conducted from 2001 to 2004. Healthy infants 6 to 12 weeks of age were randomized to receive 3 oral doses of PRV or placebo at 4- to 10-week intervals. Active surveillance for hospitalizations and ED visits for gastroenteritis was to be conducted on Days 7, 14, and 42 after each dose and every 6 weeks thereafter via telephone contact. Subjects in the safety subset were to be followed for 365 days after the first dose. In a subset of subjects in Finland, the United States, and Puerto Rico (efficacy subset), efficacy against rotavirus gastroenteritis of any severity (ie, all episodes) was evaluated. Subjects in this subset also were to be contacted on Days 7, 14, and 42 after each dose and then more frequently thereafter via telephone (i.e., every 2 weeks during the rotavirus season). All health care encounters for gastroenteritis, including office visits, were to be documented for these subjects. The subjects in the efficacy subset were followed for a maximum of 2 years. The duration of follow up was dependent on when the infants were enrolled in the study in relation to the rotavirus season defined in the protocol. If the infant was enrolled in the midst of the rotavirus season, the infant was followed until the end of the next rotavirus season.

The case definition for rotavirus gastroenteritis required that subjects meet both clinical and laboratory criteria. The clinical criterion was the occurrence of 3 or more watery or looser-than-normal stools within a 24-hour period and/or at least 1 episode of forceful vomiting. The laboratory criterion was rotavirus antigen detection by enzyme immunoassay in a stool specimen taken within 14 days of onset of symptoms. Rotavirus antigen in stools was identified using an enzyme immunoassay. The presence of wild-type rotavirus was confirmed and the serotype identified using a one-step reverse transcriptase polymerase chain reaction assay and negative results on plaque assay as confirmation.[5]

Each hospital admission and ED visit was counted as a separate event if the ED visit occurred 2 or more days before the hospital admission. If these events occurred within 2 days, the health care contacts were counted as a single hospitalization. The definition of a hospitalization was consistent across regions. However, administration of emergency care and routine care occurred at a wide variety of facilities. Therefore, before the study began in each region, the facilities at which emergency care and routine care were given were identified and visits to

these facilities were prespecified as ED and office visits, respectively. In Finland, for example, children with acute gastroenteritis requiring emergency care are likely to be treated in designated Finnish Health Care Centers or Nonroutine Hospital Outpatient Clinics. Thus, visits to facilities designated as "Finnish Health Care Center Emergency" or "Nonroutine Hospital Outpatient Clinic Visit" in Finland or "Outpatient Clinic for Emergency" and "Visit to Hospital" in Sweden were considered equivalent to an ED visit. "Office visits" in REST included visits to a health care provider in a physician's office, Finnish Health Care Center for nonemergencies, the study clinic, or other private clinics, and urgent care centers.

In this post-hoc analysis, the rates of health care encounters were expressed as the annual number of encounters per 1000 person-years because the duration of follow up differed among subjects. Poisson regression was used to compare the rates of health care encounters in the vaccine and placebo groups utilizing generalized estimating equations to adjust the standard errors in the overall per-protocol population.[6,7] Generalized estimating equations are robust to violations of the underlying assumptions of the Poisson model but may not be optimal in small samples. Thus, the exact binomial method for ratios of Poisson counts was used to estimate the confidence intervals for the subgroup analyses by region, given the number of rotavirus-related health care encounters within each region.[8]

Analyses were based on the per-protocol population with use of the protocol case definition, which was the occurrence of G1–G4 rotavirus gastroenteritis 14 or more days following the third dose. Subjects were excluded from the analyses if protocol violations occurred, no follow-up occurred 14 days after the third dose, or if the subject was regarded as not evaluable. Subjects were classified as not evaluable if a stool specimen was positive for wild-type rotavirus prior to 14 days post dose 3, if they had incomplete clinical and/or laboratory results, or if stool samples were collected outside of the 14-day range after symptom onset.

Results

Subjects

In total, data for 69 274 randomly assigned subjects were available in the clinical database. Among the 68 038 subjects who received at least 1 dose of vaccine, 14% (*n* = 9518) were excluded because of protocol violations (555 subjects encountered temperature excursions among administered vials, 8773 subjects received fewer than 3 vaccinations, 43 subjects were cross-treated or prematurely unblinded, and 147 subjects experienced a combination of these reasons), 2% (*n* = 1335) were excluded because they were not evaluable (i.e., incomplete clinical and/or laboratory results or stool specimens collected out of day range), and 0.07% (*n* = 51) of subjects were excluded because they did not have follow up beyond 14 days following dose 3 (Table 1).*

There were 57 134 subjects who contributed to this overall per-protocol analysis of hospitalizations and ED visits (Table 1). By region, 49% (*n* = 28 002) of the evaluable subjects were from Europe, 43% (*n* = 24 463) were from the United States, and 8% (*n* = 4489) were from the Latin American/Caribbean countries. As indicated earlier, there were an additional 189 subjects from Taiwan who were excluded from this analysis.

In the efficacy subset, 5673 subjects received at least 1 dose of vaccine. Of these subjects, 10% (*n* = 566) were excluded because of protocol violations, 11% (*n* = 639) were considered not evaluable, and 0.2% (*n* = 17) were excluded because of insufficient follow up. By region, 51% of the evaluable subjects (*n* = 2271) were from Finland, 41% (*n* = 1815) were from the United States, and 8% (*n* = 365) were from Puerto Rico.

Urgent health care encounters

In the overall cohort, the reduction in the rate of hospitalizations and ED visits was 94.4% (95% CI: 90.9, 96.6) for those with a maximum of 1 year of follow up. Among the 2502 evaluable subjects with more than 1 year of follow up, the reduction in the rate of hospitalizations and ED visits was 96.7% (95% CI: 82.1, 99.9).

In the overall per-protocol analysis, 314 of the 28 488 evaluable placebo recipients (1.1%) reported at least one hospitalization or ED visit for rotavirus gastroenteritis, and a total of 369 such encounters combined occurred among the placebo recipients (Table 2). The number and percentage of subjects reporting at least 1 hospitalization or ED visit for rotavirus gastroenteritis and the rate of such urgent health care encounters varied greatly by region. In Europe, 257 of the 13 984 placebo recipients (1.8%) reported 301 urgent health care encounters (rate of 32.0 per 1000 person-years.) In the United States, 51 of the 12 179 placebo recipients (0.4%) reported 58 urgent health care encounters (rate of 8.0 per 1000 person-years), whereas, in the Latin American/Caribbean region, 9 of the 2237 placebo recipients (0.4%) reported 10 urgent health care encounters (rate of 8.0 per 1000 person-years).

Despite the high variation in rates of health care resource utilization for rotavirus gastroenteritis, vaccination with PRV reduced the rates of hospitalizations and ED visits combined uniformly across the 3 regions (Table 2). The reduction in rotavirus-associated hospitalizations and ED visits was 94.7% (95% CI: 90.9, 96.9) in Europe, 94.9% (95% CI: 84.0, 98.9) in the United States, and 90% (95% CI: 29.4, 99.8) in the Latin American/Caribbean region.

Nonurgent health care encounters

The reductions in the rate of office visits for rotavirus gastroenteritis in the efficacy subset in Finland and the United States were similar (Table 3). The reduction in the rate of office visits for rotavirus gastroenteritis was 87.2% (95% CI: 67.5, 94.7) in Finland. In the United States, the reduction was 84.2% (95% CI: 66.2, 95.1). There were no office visits reported in Puerto Rico.

*This reflects the data available for analysis of the health care resource utilization endpoints in REST.

Table 1 Patient disposition by region

Region	Number of subjects (%) in			
	Analysis of urgent health care encounters		Analysis of office visits	
	Vaccine	Placebo	Vaccine	Placebo
		Overall [a]		
Number receiving ≥1 dose	34 035	34 003	2 834	2 839
Excluded				
Protocol violations	4 740 (13.9)	4 778 (14.1)	295 (10.4)	271 (9.5)
Not evaluable	623 (1.8)	712 (2.1)	355 (12.5)	284 (10.0)
Lost to follow-up	26 (0.1)	25 (0.1)	11 (0.4)	6 (0.3)
Evaluable	28 646 (84.2)	28 488 (83.7)	2 173 (76.7)	2 278 (80.2)
	Europe		*Finland*	
Number receiving ≥1 dose	15 057	15 018	1 344	1342
Excluded				
Protocol violations	790 (5.2)	756 (5.0)	75 (5.6)	66 (4.9)
Not evaluable	247 (1.6)	274 (1.8)	168 (12.5)	103 (7.7)
Lost to follow-up	2 (0.1)	4 (0.1)	1 (0.1)	2 (0.1)
Evaluable	14 018 (93.1)	13 984 (93.1)	1 100 (81.8)	1 171 (87.3)
		United States		
Number receiving ≥1 dose	16 170	16 178	1 274	1279
Excluded				
Protocol violations	3 530 (21.8)	3 597 (22.2)	207 (16.2)	182 (14.2)
Not evaluable	341 (2.1)	385 (2.4)	175 (13.7)	171 (13.4)
Lost to follow-up	15 (0.1)	17 (0.1)	2 (0.2)	1 (0.1)
Evaluable	12 284 (76.0)	12 179 (75.3)	890 (69.9)	925 (72.3)
		Latin America/Caribbean (including Puerto Rico)		
Number receiving ≥1 dose	2 713	2 713	216	218
Excluded				
Protocol violations	418 (15.4)	423 (15.6)	13 (6.0)	23 (10.5)
Not evaluable	34 (1.3)	49 (1.8)	12 (5.6)	10 (4.6)
Lost to follow-up	9 (0.3)	4 (0.1)	8 (3.7)	3 (1.4)
Evaluable	2 252 (83.0)	2 237 (82.5)	183 (84.7)	182 (83.5)

[a] Includes data from 189 subjects from Taiwan, which were not included in the regional analysis. Nine subjects were excluded from this country (4 protocol violations, 5 not evaluable).

Discussion

In REST, the efficacy of PRV against rotavirus gastroenteritis caused by serotypes G1–G4 during the first full rotavirus season after vaccination was 98% against severe disease and 74% against disease of any grade of severity. These favorable results translated into significant reductions in rotavirus-associated health care encounters, including a 94.5% reduction in hospitalizations and ED visits and an 86.0% reduction in office visits in the first 2 years after vaccination.[3] Our subsequent analyses showed that the rate reductions in the first and second year after vaccination were high and consistent, with a reduction in the rate of hospitalizations and ED visits of 94.4% (95% CI: 90.9, 96.6) for those with a maximum of 1 year of follow up and 96.7% (95% CI: 82.1, 99.9) among the 2502 evaluable subjects with more than 1 year of follow up. Despite the relatively smaller sample size of this subset of subjects with more than 1 year of follow up, the 95% confidence interval for the point estimate was relatively narrow (i.e., 95% CI: 82.1, 99.9), suggesting a robust and reliable result.

Our analysis extends the results of the original study of the overall cohort by evaluating the efficacy against health care encounters by region. Results from each region were consistent with those of the overall population, with reductions in the combined endpoint of hospitalizations and ED visits of 94.7% in Europe, 94.9% in the United States, and 90.0% in Latin America/the Caribbean.

The efficacy of the vaccine was consistent with the protection observed following natural infection. In a cohort study of 200 infants from Mexico, Velázquez and colleagues[2] determined that protection against severe disease was afforded following multiple infections. The adjusted efficacy in protecting against rotavirus-associated diarrhea was 77% after 1 infection, 83% after 2 infections, and 92% after 3 infections. These results provided a basis for vaccine development, suggesting that similar protection would be anticipated following multiple doses of a multivalent vaccine.

Table 2 Efficacy of pentavalent rotavirus vaccine (PRV) against hospitalizations and emergency department visits for rotavirus gastroenteritis by region

Type of health care encounter within each region	Number (rate [a]) of health care encounters		% Rate reduction	95% CI
	Vaccine	Placebo		
Overall [b]	(*N* = 28 646)	(*N* = 28 488)		
Hospitalizations	6 (0.3)	144 (8.0)	95.8	90.5, 98.2
ED Visits	14 (0.8)	225 (12.6)	93.7	88.8, 96.5
Combined	20 (1.1)	369 (20.6)	94.5	91.2, 96.6
Europe	(*n* = 14 018)	(*n* = 13 984)		
Hospitalizations	5 (0.5)	126 (13.4)	96.0	90.3, 98.4
ED Visits	11 (1.2)	175 (18.6)	93.7	87.8, 96.8
Combined	16 (1.7)	301 (32.0)	94.7	90.9, 96.9
United States	(*n* = 12 284)	(*n* = 12 179)		
Hospitalizations	0 (0.0)	16 (2.2)	100.0	73.8, 100.0
ED Visits	3 (0.4)	42 (5.8)	92.9	77.4, 98.6
Combined	3 (0.4)	58 (8.0)	94.9	84.0, 98.9
Latin America/Caribbean (including Puerto Rico)	(*n* = 2252)	(*n* = 2237)		
Hospitalizations	1 (0.8)	2 (1.6)	50.2	<0.0, 99.1
ED Visits	0 (0.0)	8 (6.4)	100.0	41.2, 100.0
Combined	1 (0.8)	10 (8.0)	90.0	29.4, 99.8

Combined = hospitalizations and emergency department (ED) visits.
[a] The rates of events represent the incidence density and are expressed as the annual number of events per 1000 person-years.
[b] Includes data from 189 subjects from Taiwan that were not included in regional analysis.

Table 3 Efficacy of pentavalent rotavirus vaccine (PRV) against office visits for rotavirus gastroenteritis by region in the efficacy subset

	Vaccine	Placebo	% Rate Reduction	95% CI
Overall Cohort				
Number of subjects contributing to the analysis	2173	2278		
Number of health care encounters	13	98		
Rate (encounters per 1000 person-years)	5.5	39.7	86.0	73.9, 92.5
Finland				
Number of subjects contributing to the analysis	1100	1171		
Number of health care encounters	7	58		
Rate (encounters per 1000 person-years)	4.7	37.0	87.2	67.5, 94.7
United States				
Number of subjects contributing to the analysis	890	925		
Number of health care encounters	6	40		
Rate (encounters per 1000 person-years)	0.8	53.5	84.2	66.2, 95.1
Puerto Rico				
Number of subjects contributing to the analysis	183	182		
Number of health care encounters	0	0		
Rate (encounters per 1000 person-years)	0	0	NA	NA

Unlike the consistency of the regional results with PRV presented here, the previous rhesus-based rotavirus vaccine was somewhat less efficacious in Latin America[9,10] than in the United States[11] or Finland.[12]

Our analysis did find that the rates of health care encounters among placebo recipients varied by region. A number of factors may have contributed to these regional differences. First, the rates of health care encounters likely varied in part because of differences in treatment practice patterns in the different regions. Variations in

treatment practice patterns by geographic region have been well documented. Patients in different geographic areas with illness of similar severities may receive markedly different care.[13] For rotavirus gastroenteritis, variations in treatment practice patterns may affect the likelihood of admission to a hospital or visits to other health care providers. These differences in practice patterns are reflected in previous epidemiologic studies. These studies estimated that by 5 years of age, 1 in 54 children in Europe overall, 1 in 33 in Finland, and 1 in 70 in the United States are hospitalized for rotavirus.[14-16] Other potential reasons for the differences in the rates of health care utilization by region include differences in the level of care and patient education provided in a controlled clinical trial, differences in compliance with the protocol such as differences between regions in submission of stool specimens for testing, and the greater frequency of telephone contacts for subjects participating in the efficacy subset compared with other subjects. In evaluating the reasons for the differences in rates of health care utilization, however, it is important to bear in mind that REST was a randomized, placebo-controlled study, the purpose of which was to compare the rate of rotavirus-associated health care encounters in the vaccine versus placebo groups. Therefore, randomization utilizing blocking factors ensured near equal distribution of vaccine and placebo recipients in a given region. Thus, the study was designed to account for differences in health care practices that might be observed. As the regional analyses show, the efficacy and reduction in rotavirus-associated health care encounters is the same despite the observed differences in disease rates across regions.

Our results demonstrated high and consistent reductions in health care encounters regardless of geographic region or different health care practices. The present results suggest that PRV will likely be effective against rotavirus-associated hospitalizations, other urgent visits, and office visits among children throughout the world. The greatest expected challenge will be in developing world populations where children are malnourished, immunocompromised, and have intestinal colonization with a variety of pathogens, where previous candidate rotavirus vaccines have not been efficacious.[17,18] Studies of PRV in Africa and Asia are expected to begin in the near future.

Acknowledgments

Writing assistance for this paper was provided by Lori Lush, PharmD, of JK Associates, Inc., and funding was provided by Merck & Co., Inc., Whitehouse Station, NJ 08889.

Conflict of Interest statement

Timo Vesikari has received honoraria and consultation fees from GlaxoSmithKline, from Merck & Co., Inc., and from MedImmune.

Robbin Itzler, John R. Cook, and Michele Coia are full-time employees of Merck & Co., Inc., and may potentially own stock and/or hold stock options in the company.

Dr. Matson is a grant recipient from NIH, Merck, and GSK, and a consultant to Merck, GSK, and PATH, all of which have rotavirus vaccine initiatives.

Dr. Santosham was an investigator in the Merck-sponsored REST trial. He has also served on the scientific advisory board for Merck and has accepted fees for lectures sponsored by Merck.

Dr. Celia D.C. Christie was an investigator in the Merck-sponsored REST trial. She also accepted fees for lectures sponsored by Merck & Co., Inc.

Gary G. Koch, PhD, has served as the Principal Investigator of a co-operative agreement between Merck & Co., Inc., and the University of North Carolina at Chapel Hill through its Department of Biostatistics. This agreement addressed statistical matters for this manuscript as well as statistical issues for other studies of Merck. Gary G. Koch, PhD, also serves as the Principal Investigator of such agreements for many other sponsors, but these activities have no real relationship to this manuscript. Gary G. Koch, PhD, has no other competing interests to declare.

Dr. Penny Heaton was an employee of Merck & Co., Inc., at the time the study was conducted.

References

1. Glass RI, Bresee JS, Parashar U, et al. Rotavirus vaccines: past, present, and future. Arch Pediatr 2005;12:844–7.
2. Velázquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as a protection against subsequent infections. N Engl J Med 1996;335:1022–8.
3. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354:23–33.
4. Vesikari T. Rotavirus vaccines against diarrhoeal disease. Lancet 1997;350:1538–41.
5. DiStefano DJ, Kraiouchkine N, Mallette L, et al. Novel rotavirus VP7 typing assay using a one-step reverse transcriptase PCR protocol and product sequencing and utility of the assay for epidemiological studies and strain characterization, including serotype subgroup analysis. J Clin Microbiol 2005;43:5876–80.
6. Stokes M, Davis C, Koch G. Categorical data analysis using the SAS system. Cary, NC: SAS Institute, Inc. 2000.
7. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics 1988;44:1049–60.
8. Jovanovic B, Zelenski R. Safety evaluation and confidence intervals when the number of observed events is small or zero. Ann Emerg Med 1997;30:301–6.
9. Linhares AC, Gabbay YB, Mascarenhas JD, et al. Immunogenicity, safety and efficacy of tetravalent rhesus-human, reassortant rotavirus vaccine in Belem, Brazil. Bull World Health Organ 1996;74:491–500.
10. Pérez-Schael I, Guntiñas MJ, Pérez M, et al. Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. N Engl J Med 1997;337:1181–7.
11. Rennels MB, Glass RI, Dennehy PH, et al. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines – report of the National Multicenter Trial. United States Rotavirus Vaccine Efficacy Group. Pediatrics 1996;97:7–13.
12. Joensuu J, Koskenniemi E, Pang XL, Vesikari T. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205–9.
13. Isaacman D, Kaminer K, Veligeti H, et al. Comparative practice patterns of emergency medicine physicians and pediatric emergency medicine physicians managing fever in young chil-

dren. Pediatrics 2001;108:354–8.
14. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-12):1–13.
15. Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J 2006;25(1 Suppl):S7–S11.
16. Vesikari T, Rautanen T, Von Bonsdorff CH. Rotavirus gastroenteritis in Finland: burden of disease and epidemiological features. Acta Paediatr Suppl 1999;88:24–30.
17. Georges-Courbot MC, Monges J, Siopathis MR, et al. Evaluation of the efficacy of a low-passage bovine rotavirus (strain WC3) vaccine in children in Central Africa. Res Virol 1991;142:405–11.
18. Hanlon P, Hanlon L, Marsh V, et al. Trial of an attenuated bovine rotavirus vaccine (RIT 4237) in Gambian infants. Lancet 1987;1:1342–5.