Rotavirus Serotype G9 Is Associated with More-Severe Disease in Latin America

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(See the editorial commentary by Kang on pages 315–6)

The association between rotavirus serotypes and severity is not well established. Analysis of a clinical trial conducted in Latin America points at more-severe disease associated with serotype G9. Thus, demonstration of efficacy against G9 will be an important asset of any rotavirus vaccine to be introduced into a Latin American country or any country where G9 has been shown to be prevalent.

Rotavirus (RV) strains are usually grouped according to the neutralization specificity of both VP7 (or G-type) and VP4 (or P-type) viral proteins. The most commonly used classification is based on G types, of which 10 have been recovered from humans (G1–6, G8–10, and G12) [1]. Globally, 4 RV types—G1, G2, G3, and G4—have been responsible for most cases of RV disease in children <5 years of age [1, 2]. Their importance may differ, however, by region. In Europe, North America, and Australia, G1, G2, G3, and G4 have historically been linked to 90%–95% of RV cases [1, 2], compared with 68% in South America and Asia and 50% in Africa [1].

Relatively recently, G9 RV types have emerged in different parts of the world. G9 is now considered to be among the 5 most important RV G types [3]. The most common P genotypes associated with G9 are P[8] and, to a lesser extent, P[6] [1]. In Latin America, G9 was first detected in Belém, Brazil, during 1990–1992, at a frequency of 1.2% [4]. In Argentina, low frequencies (0.4%–0.8% annually) were recorded during 1996–1998, but the proportion increased to 18% during 1998–1999 [5]. A study in conducted in 2 Brazilian cities revealed G9 as the third most frequent RV type (12.1%), after G1 and G2, during 1997–1999. The frequency increased markedly from 1997 to 1999 [6]. Although the originally detected strains were associated with P[6], G9P[8] was the most common G- and P-genotype combination during this period [6, 7]. More recently, RV samples with G9 specificity were found in 78.8% of hospitalized children in Salvador, Bahia, Brazil [8]. In Paraguay, G9 was found in 5.7% of the cases during 1999–2000 [9].

Given the epidemiological variability in RV G-type distribution and the spectrum of clinical manifestations of RV disease, we decided to investigate whether G9 is associated with more-severe or less-severe RV disease, compared with the most common G1 type, using data from a clinical trial conducted with a live attenuated human RV vaccine [10]. This is of importance in light of RV vaccines that are currently being developed.

Data and methods. Data are presented from a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 2 doses of a live attenuated human RV vaccine (RIX4414) in healthy infants that was conducted from 2001 through 2003 in Brazil, Mexico, and Venezuela [10]. The infants were ~2 months of age at the first dose and were followed up until they were ~1 year of age.

The severity of G1 and G9 infections was compared among RV-positive children from the placebo arm of the trial using Fisher's exact test and the Wilcoxon rank-sum test (cases with other serotypes were not included). All comparisons were 2-sided, and a P value of .05 was considered to be statistically significant. The severity of RV disease was assessed using the Vesikari scaling system, which provides an aggregate score for the severity of gastrointestinal infections [11]. Only RV episodes occurring in the placebo group were analyzed to avoid a potential bias introduced by vaccine-induced protection. RV positivity was determined by ELISA, and serotype was determined by RT-PCR.

Results. Among the 454 infants who received placebo in the vaccine trial, 51 infants experienced an acute gastroenteritis episode with test results positive for RV. The predominant RV serotypes in the 51 placebo recipients were G1 (30 patients; 59%) and G9 (15 patients; 29%); the remaining serotypes were G2 (3 patients; 6%), G3 (2 patients; 4%), and 1 canine serotype (1 patient; 2%). All RV episodes were of the P[8] type.

Table 1 compares the demographic data for the infants who experienced a G1 or G9 type of RV gastroenteritis, as well as

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Table 1. Rotavirus serotype and disease severity data from the placebo arm of a rotavirus vaccine efficacy trial from Latin America.

Variable	Serotype G1 (n = 30)	Serotype G9 (n = 15)	P
Sex			
Female	70.0	40.0	.105
Male	30.0	60.0	
Age at hospitalization, median weeks (range)	33 (21–58)	37 (24–54)	.470
Loose stools for ⩾6 days	13.3	46.7	.026[a]
Six or more loose stools within 24 h	60.0	80.0	.315
Duration of vomiting ⩾3 days	33.3	53.3	.218
Three or more episodes of vomiting within 24 h	36.7	40.0	1
Temperature ⩾39°C	36.7	26.7	.738
Hospitalization	6.7	66.7	<.001[a]
Dehydration ⩾6% of body weight	0	46.7	<.001[a]
Vesikari severity score, median (range)	11 (2–18)	16 (6–20)	.003[a]

NOTE. Data are % of patients, unless otherwise indicated.

[a] Statistically significant.

the severity of the episodes. There was no significant difference in the median age of the infants. The median Vesikari score, however, was significantly more elevated among the G9 RV episodes, compared with the G1 episodes (median Vesikari score, 16 vs. 11). In particular, G9 was associated with a significantly longer duration and higher frequency of diarrhea, longer duration of vomiting, increased hospitalization rate, and more-severe dehydration. The most marked difference was observed for the severe dehydration rates (0% for the G1 group vs. 47% for the G9 group) and, as a likely consequence, the hospitalization rate (7% vs. 67%).

Discussion. These data from the placebo arm of a vaccine efficacy trial in 3 Latin American countries indicate that serotype G9 infection is associated with more-severe disease than serotype G1 infection. This is consistent with studies from the United Kingdom that have shown that the proportion of G9 strains (P[6] and P[8]) was significantly higher among patients admitted to the hospital than among patients being treated at the community level [12]. Another hospital-based study conducted in London found a higher proportion of cases requiring intravenous rehydration among RV G9 cases, compared with other common G types [13]. However, 2 studies conducted in Italy and the United States did not find differences in disease severity between patients with serotype G9 infection and patients with infection due to other G types [14, 15].

Differences in disease severity may be caused not only by variation in virulence between different RV strains but also by the introduction of new strains into a community. When an RV strain is newly introduced into a community, one could expect more frequent and more-severe cases than are associated with the common RV strains because of a lack of maternal antibodies and lack of prior exposure to this specific RV type. G9, for example, has been associated with serious neonatal outbreaks when introduced into a community [16]. The same is true for introduction of other new RV types. In a Brazilian study, the increased severity of G3P[4] infection was felt to be attributable to the emergence of a new RV type into the community [17]. However, this explanation is not supported by the observation that vaccination with the monovalent G1P1AP[8] strain has been shown to provide protection against infection with serotype G9 [10].

In conclusion, G9 serotype RV infections were highly prevalent in the placebo arm of a vaccine efficacy trial conducted in 3 Latin American countries, confirming the epidemiological importance of this emerging serotype. Our findings suggest that infection with RV G9 is associated with more-severe disease than infection with RV G1, which is still the most common serotype. Newly developed RV vaccines should, therefore, demonstrate efficacy against G9 serotype before their introduction into the vaccination schedule of a Latin American country or any country where serotype G9 infection has been shown to be prevalent.

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