Update on Rotavirus Trends and the Importance of Surveillance

Sachin N. Desai, MD, and Marietta Vázquez, MD

Key Words: rotavirus, rotavirus vaccines, surveillance for rotavirus

Pediatr Infect Dis J 2010;29: 1130 –1132

Rotavirus remains the number one cause of severe diarrhea in children aged <5 years in the United States and worldwide. Each year in the United States, rotavirus is responsible for approximately 600,000 outpatient medical visits, 55 to 70,000 hospitalizations, and 20 to 60 deaths. Disease caused by rotavirus is extremely common as almost every child is infected in the first 5 years of life. Rotavirus infections in the United States come at a high price: the estimated annual health and societal costs related to rotavirus amount to total 1 billion dollars each year. Rotavirus infections are common in developing countries where the morbidity and the mortality are far greater.

THE VIRUS

Rotavirus is a double-stranded RNA virus, in the family of Reoviridae, which is classified into various groups, subgroups, and serotypes. There are at least 15 different serotypes of rotavirus; presently, 5 serotypes of rotavirus (G1, G2, G3, G4, and G9) account for the majority of the strains circulating worldwide. Surface antigens VP7 (G protein) and VP4 (P protein) are 2 important structural viral proteins that are involved in eliciting the immune response through neutralizing antibodies. Rotavirus has substantial diversity, with a possible 132 separate G-P combinations. The ability of the virus to mutate and reassort allows for the potential of new and emerging serotypes of rotaviruses. Serotype predominance fluctuates yearly, seasonally, and by geographic location. Furthermore, multiple rotavirus serotypes can circulate within the same region at the same time. Therefore, continued surveillance of rotavirus strains remains an important component in defining the virus’s epidemiology.

ROTAVIRUS VACCINES

In 1998, RotaShield, a rhesus rotavirus tetravalent vaccine became the first rotavirus vaccine to be licensed in the United States. Unfortunately, Rotashield was withdrawn from the market by the manufacturer 1 year after its licensure because of a rare association with intussusception among vaccine recipients. This association was an unexpected and sudden setback, because the potential benefits of preventing mortality due to rotavirus in the developing world could have outweighed the rare risk of intussusception. Recently, 2 different oral rotavirus vaccines have been licensed by the US Food and Drug Administration and recommended by the Advisory Committee on Immunization Practices for routine use in infants for the prevention of rotavirus gastroenteritis. Rotarix (RV5) is a pentavalent human-bovine reassortant live-attenuated oral vaccine licensed in 2006; and Rotarix (RV1) is a monovalent live-attenuated human strain vaccine, licensed in 2008, which shares neutralizing epitopes against the most common rotavirus serotypes. Separate Phase III randomized controlled trials that enrolled more than 60,000 infants from different countries, demonstrated efficacy of these rotavirus vaccines.

Since the introduction of these 2 rotavirus vaccine products in the United States, RV5 (Rotateq) and RV1 (Rotarix), there has been a dramatic reduction in the number of cases of rotavirus gastroenteritis and hospitalizations. By 2008, rotavirus vaccine had been licensed in >100 countries and initiated as part of 17 national rotavirus immunization programs worldwide. Although both vaccines were proven to be safe and highly efficacious in the United States and Europe soon after introduction, several clinical questions remained. Unanswered questions such as the vaccines’ efficacy in the setting of host differences (such as immunocompromised state and malnutrition); the interference of maternal antibody in the host’s immune response; the vaccines’ efficacy in the presence of infection with multiple enteropathogens; and the efficacy in the setting of limited access to primary healthcare, in part, led to the conduct of separate clinical trials of rotavirus vaccine in developing nations. In 2009, the World Health Organization (WHO) recommended universal use of both vaccines following phase III trials throughout Africa and Asia. The effect that the introduction of rotavirus vaccination will have, if any, on the evolution of rotavirus strains worldwide has yet to be fully elucidated.

GLOBAL SURVEILLANCE FOR ROTAVIRUS

As rotavirus vaccination continues to increase worldwide, global surveillance of rotavirus has become an important focus of the...
vaccination programs. Global surveillance is important to describe serotype distributions in different countries and their regions; identify the potential development of newly emerging strains; monitor impact of vaccines by identifying successes and gaps; and identify causes of diarrhea other than rotavirus. However, successful surveillance is complex, as well as expensive, and involves many steps including data collection, sharing, and standardized reporting. Funded by the Global Alliance for Vaccines and Immunizations, the Rotavirus Vaccine Program—a partnership with the WHO and the US Centers for Disease Control and Prevention—conducts surveillance of disease burden both locally and regionally in resource limited countries.9 Coordinated monitoring efforts by the WHO involve 196 sites in 59 countries; WHO advocates for global vaccination by supporting the introduction and maintenance of national rotavirus immunization programs (Fig. 1).

A review in 2005 evaluated the worldwide distribution of rotavirus serotypes from 1989 to 2004 and found that although substantial geographic differences were noted, 95% of infections were predominantly due to 5 serotypes (G1–G4, G9),11 >70% of infections in the United States, Europe, and Australia were caused by G1P[8] and <30% of infections in South America, Asia, and Africa were due to G1P[8] (Table 1). Unusual and nontypeable serotypes have been noted in epidemiologic surveys, likely because of ability of the virus to undergo constant genetic variation through mutation and reassortment.

While data from the United States collected from 1996 to 2005 revealed that >85% of rotavirus strains included G or P types that are already covered by the currently licensed rotavirus vaccines,3 newer data are starting to emerge demonstrating the presence of nonvaccine serotypes. Data from Indonesia show that only 56% of strains collected and typed contained G or P antigens that are common to both vaccines, and that 23% of strains were made up of types not represented in either vaccine.12 Both G9 and G12 types have emerged and spread globally over the past decade.13

Seasonal variances and changing trends in the epidemiology of rotavirus emphasize the need for continued monitoring and surveillance. Surveillance is integral to global vaccination initiatives. Furthermore, the efficacy of rotavirus vaccines could be compromised if important factors, such as the emergence of new strains by genetic reassortment, predominate, yet fail to be detected.

**IMMUNITY TO ROTAVIRUS**

Immunity to rotavirus has been shown to have both homotypic and heterotypic components. Homotypic immunity occurs when primary infection elicits serotype specific protection. Heterotypic immunity develops with repeat rotavirus infections, which can be acquired either naturally or via vaccination, and leads to the development of cross neutralizing antibodies and subsequent broader protective immunity that includes multiple serotypes. RV5, containing G1–G4 and P1A types,7 aims to protect by introducing these 5 antigenic

---

**TABLE 1. Geographic Distribution of Rotavirus Serotypes**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>73%</td>
<td>6%</td>
<td>1%</td>
<td>3%</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Australia</td>
<td>82%</td>
<td>14%</td>
<td>2%</td>
<td>11%</td>
<td>4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Europe</td>
<td>72%</td>
<td>9%</td>
<td>2%</td>
<td>11%</td>
<td>4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>South America</td>
<td>34%</td>
<td>23%</td>
<td>2%</td>
<td>9%</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>Asia</td>
<td>34%</td>
<td>13%</td>
<td>1%</td>
<td>20%</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Africa</td>
<td>23%</td>
<td>2%</td>
<td>21%</td>
<td>4%</td>
<td>7%</td>
<td>27%</td>
</tr>
</tbody>
</table>

types that commonly cause disease in children, whereas RV1 induces a heterotypic immune response similar to that obtained by repeated natural infections.

**ROTAVIRUS TRENDS IN INDUSTRIALIZED NATIONS**

Studies in the United States have shown a decline of approximately 85% to 95% in rotavirus cases during the 2008 season compared with previous seasons.\(^2\) Data from the Natural Respiratory and Enteric Virus Surveillance System (NREVSS) detected a decrease of >50% of rotavirus positive samples and a delay of time to disease onset by 3 months in the 2007–2008 season of rotavirus when compared with the period of 1991–2006.\(^1\) Since 2006, the New Vaccine Surveillance Network has undertaken active surveillance for acute rotavirus gastroenteritis in 3 US counties, and found an 80% reduction in hospitalization and emergency room visits in 2008, at a time when RV5 was the only vaccine licensed for use. Laboratory surveillance in this cohort also revealed an increase in the G3P[8] strain.\(^14\) Investigations are currently underway to evaluate the effectiveness of RV1 on rotavirus disease in the United States since its licensure in 2008.

Australia introduced its rotavirus immunization program in 2007; individual states within Australia used either RV1 or RV5 exclusively. Higher prevalence of G2 and G9 types were noted in states using RV1, while G3 was increased in states using RV5.\(^15\) Continued surveillance will be necessary to distinguish between immune selection and natural fluctuations, which have been previously observed every 2 to 3 years in Australia. As with the data from the United States, it may be too early to arrive at definitive conclusions, linking trends in serotype epidemiology to the rotavirus vaccination program.

**ROTAVIRUS TRENDS IN THE DEVELOPING WORLD**

A recent randomized clinical trial of pentavalent rotavirus vaccine (RV5) conducted in Bangladesh and Vietnam showed the vaccine to be 48% efficacious against severe disease in young infants.\(^16\) Despite lower estimated vaccine efficacy,\(^16\) and given the high rates of rotavirus infection in resource-limited areas, use of these vaccines has dramatically decreased severe disease and mortality from infection in resource-limited settings. Studies are needed to distinguish changes in seroepidemiology due to natural genotypic fluctuations over time in different geographic regions, from potential community serotype shifting mediated by regional vaccination programs. In the pre-vaccine era, natural variation has led to the introduction of G9 as a globally significant strain in the 1990s, the emergence of G12 this decade, as well as cyclic variability of more common serotypes such as G2.\(^13\) Similarly, following the introduction of RV1 into the Brazilian National Immunization Program (2006), a 77% reduction of severe rotavirus diarrhea in children 6 to 11 months of age was observed.\(^17\) Of interest, prevalence of G2P[4] serotype increased from 7% prior to 2006 to 95% in 2008, which led to speculation that selective advantage may have played a part due to presumed lack of coverage by RV1 against a heterotypic G2P[4] serotype. However, similar increases in G2P[4] were noted in 2006 in other Latin American countries in which vaccine had not yet been introduced. Therefore, it is presumed that this trend is more likely secondary to natural fluctuation than to vaccination.

RV5 was introduced into the Nicaragua Immunization Program, where vaccine effectiveness was measured at only approximately 50%.\(^18\) Unlike the United States and Australian RV5 experiences, a G2P[4] shift was noted in 88% of postvaccinated cases. Trials of RV1 in Malawi yielded vaccine effectiveness of 49%, but no significant difference in effectiveness against common strains as compared with the trials in developed nations.\(^19\)

**CONCLUSION**

Rotavirus vaccines have affected the burden of rotavirus disease in the United States and other developed countries. Emerging data show that even in resource-limited areas, and despite lower estimated efficacy, rotavirus vaccine can still substantially reduce childhood deaths as a much higher prevalence of severe disease and mortality exists. The challenges of the rotavirus vaccination program in the developing world are many and ongoing, such as, availability of vaccine; delivery to the population (refrigeration); and additional needs for a comprehensive diarrheal control (improving water quality, hygiene, and sanitation), just to name a few.

The evolving story of rotavirus vaccines is unique in that these new lifesaving vaccines have been initiated in both developed and developing countries at the same time. Continued surveillance is necessary for vaccines to contribute to reducing childhood mortality by one-third from 1990 to 2015 in accordance with the United Nations Millennium Development Goals. Ongoing epidemiologic surveillance will assist in answering whether observed regional differences in serotype data can affect the future of rotavirus vaccine effectiveness and possible selection of rotavirus with the ability to evade vaccine immunity. It remains to be confirmed whether currently available rotavirus vaccines are less protective against antigenically different indigenous rotaviruses. Surveillance data will feed into cost-effectiveness studies, the results of which will be important to support advocacy of sustainable financing. The need for long-term monitoring and epidemiologic strain surveillance should continue to effectively assess the affect of rotavirus immunization programs.

**REFERENCES**