

ID CONSULT

Rotavirus Vaccine Offers Many Benefits



BY CHRISTOPHER J. HARRISON, M.D.

We now have one—and will probably soon have a second—new and improved rotavirus vaccine, with which we will be able to prevent much of the winter-spring infant gastroenteritis misery. Further, a lower economic

burden will result from fewer lost parental workdays. And there's another bonus: Reactogenicity is lower with the new vaccines, compared with the old RotaShield, which was withdrawn from the market in 1999.

The design of the trials that were submitted for Food and Drug Administration approval of the new vaccines included a very large sample size—with over 60,000 children each for both Merck & Co.'s bovine-derived RotaTeq and GlaxoSmithKline's human-derived Rotarix—and close follow-up. Both vaccines have been highly effective against rotavirus disease in the first year of life, including the most severe forms of illness and hospitalizations, with lower rates of vaccine-associated fever, irritability, and loose stools.

Importantly, neither vaccine appears to increase the risk for intussusception, the adverse event that caused the removal of the previous rhesus-derived RotaShield vaccine from the market. Of course, we can't be absolutely certain until the new vaccines are in widespread use—that's when the problem with RotaShield was detected. However, it's likely that the problem would have revealed itself sooner if the recalled vaccine had been tested in 60,000 subjects prior to approval.

Moreover, it makes clinical sense that if a vaccine causes less systemic response (fever, irritability, and loose stools), it also might lead to lesser reactions in the gut-associated lymphoid tissue, a proposed mechanism for the vaccine-provoked intussusceptions.

About 400,000 rotavirus-associated deaths occur each year in the developing world, but rotavirus disease usually isn't lethal for children in the United States (20-60 deaths per year). In this country, cost effectiveness is the

prime issue, particularly with regard to reducing the 50,000 annual rotavirus-associated hospitalizations.

According to one estimate, rotavirus costs the United States more than \$1 billion a year, including direct medical costs and parental lost workdays. Compare that with the \$770 million a year to immunize the estimated 4.1 million infants in an annual birth cohort with Rotateq, which Merck has just announced will cost \$62.50/dose when purchased in 10 single-dose packs. Overall, this looks like we can still come out ahead.

The benefits of a protective rotavirus vaccine also may extend beyond simply preventing gastroenteritis. This winter, an 11-month-old ill-appearing child was transferred to our facility with a sepsis picture. He had a high fever, lethargy, vomiting, and a tense fontanelle. However, he had no diarrhea and had CSF pleocytosis (WBC count of 28, half neutrophils). The next day, he developed green, mucus-laden diarrhea, which tested positive for rotavirus antigen. This was a case of aseptic meningitis due to rotavirus infection.

Such nondiarrheal initial presentations of rotavirus infection during the winter and early spring are not all that rare. Indeed, in active surveillance of 763 children aged 15 days through 4 years and admitted to the hospital between November 1997 and June 1998 with eventual rotavirus diagnosis, 9% presented initially without diarrhea (Pediatr. Infect. Dis. J. 2002;21:221-7). Rotavirus as a cause of aseptic meningitis also has been confirmed using polymerase chain reaction detection of rotavirus RNA in the cerebrospinal fluid of children who present with seizures (J. Clin. Microbiol. 2002;40:4797-9).

Although most children with a nondiarrheal initial presentation develop the classic rotavirus stools within 48 hours, the initial sepsislike picture occurs most often in infants under 1 year of age. If the rotavirus antigen assay comes back positive in such patients, you can sometimes avoid adding to the diarrhea with unnecessary antibiotics. The caveat, however, is that young infants may have

positive stool rotavirus antigen tests in the absence of rotavirus-producing disease (false positive). This is thought to represent a "colonization" that occurs in most younger infants, becomes less common after 6 months, and is present in fewer than 10% of children as they reach 1 year of age. For this reason, some laboratories are reluctant to perform rotavirus antigen assays on children less than

6 months of age. So, even with a positive rotavirus assay in a young infant, antibiotics may need to be continued until bacterial cultures are confirmed negative.

Other studies have shown disseminated rotavirus outside the gastrointestinal tract.

One study found rotavirus antigen in 22 of 33 serum samples of children with rotavirus diarrhea, suggesting that the virus can "escape" the GI tract in children, resulting in viremia (Lancet 2003;362:1445-9). The virus itself has also been found in the liver and kidney in immunodeficient children (J. Pediatr. 1992;120:912-7).

Another presentation that can throw you off the rotavirus track is when the presenting symptoms are heavily respiratory in the first 36 hours. Rotavirus has been found in nasopharyngeal secretions of such patients (Diagn. Microbiol. Infect. Dis. 1986;4:87-8), and it makes sense that the upper respiratory tract could be part of the initial portal of infection.

So, beyond a notable reduction in winter diarrhea in infants, the new rotavirus vaccines may also have the added benefit of preventing some febrile seizures and even an occasional case of aseptic meningitis.

I currently have no financial connections with either the Merck or the GSK rotavirus vaccines, although I participated in early studies involving the Merck product more than 5 years ago.

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S. aureus Tops List of Pediatric Pathogens in North America

BY KERRY WACHTER
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WASHINGTON — *Staphylococcus aureus* was the most common pathogen isolated from pediatric patients in North America in 2004, according to data from the SENTRY Antimicrobial Surveillance Program presented as a poster at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The SENTRY program has monitored susceptibility rates and trends of pathogens worldwide since 1997. In 2004, 3,537 clinical isolates were collected from 47 medical centers as part of the program.

S. aureus also topped the list as the most common pathogen worldwide and in Europe but *Escherichia coli* snagged the top spot in Latin America (see table for regional rankings of the most common pathogens).

The 10 most frequently observed pathogens accounted for 84% of the organisms isolated in this study, wrote Kelley A. Fedler and her colleagues at JMI Laboratories in North Liberty, Iowa.

The researchers also noted a direct correlation between increasing patient population age and the frequency of occur-

rence among many pathogens, most notably *S. aureus* and *E. coli*.

S. aureus accounted for 19% of organisms in patients less than 1 year and 35% of organisms in patients aged 12-18 years. *E. coli* predominated in patients less than 1 year of age, at 20.6%. *Klebsiella* species, *Enterobacter* species, enterococci, and coagulase-negative staphylococci decrease in prevalence after age 1, according to the poster presented at the meeting sponsored by the American Society for Microbiology.

The researchers also looked at antimicrobial activity and resistance patterns among pediatric patients. Susceptibility tests were performed by reference broth microdilution methods of the Clinical Laboratory Standards Institute against more than 25 antimicrobial agents. Methicillin-resistant *S. aureus* accounted for 28% of *S. aureus* strains.

Both gatifloxacin and ciprofloxacin exhibited high levels of activity against the pathogens tested, "indicating the fluoroquinolone-naive nature of pediatric pathogens," the researchers wrote.

All of the *S. pneumoniae* strains from North America were susceptible to gatifloxacin and levofloxacin. Two fluoro-

quinolone-resistant strains were identified in Europe, however. No strains of staphylococci tested had developed resistance to linezolid, quinupristin/dalfopristin, ticoplanin, or vancomycin.

Pneumococcal susceptibility was the greatest in North America. *Pseudomonas*

aeruginosa was very susceptible to fluoroquinolones (5% resistance) in North American isolates.

However, β -lactamase-mediated resistance was highest in North America (41%) and Latin America (46%) in contrast with Europe (18%).

Most Common Pediatric Pathogens

Organism	Rank			
	All Regions	North America	Latin America	Europe
<i>Staphylococcus aureus</i>	1	1	2	1
<i>Escherichia coli</i>	2	2	1	2
<i>Pseudomonas aeruginosa</i>	3	3	4	4
<i>Klebsiella</i> species	4	4	3	7
Coagulase-negative staphylococci	5	6	6	9
β -Hemolytic streptococci	6	8	12	3
<i>Enterobacter</i> species	7	5	5	10
<i>Streptococcus pneumoniae</i>	8	10	8/9	5
<i>Enterococcus</i> species	9	7	11	8
<i>Haemophilus influenzae</i>	10	11	15	6

Note: Based on 3,537 clinical isolates collected from 47 medical centers worldwide in 2004. Source: Ms. Fedler