

## CORRESPONDENCE



## Rotavirus Vaccines

**TO THE EDITOR:** The rotavirus vaccines in the clinical trials reported on by Ruiz-Palacios and colleagues and Vesikari and colleagues (Jan. 5 issue)<sup>1,2</sup> may reduce mortality from rotavirus less efficaciously in Third World regions where rotavirus expresses the VP4, VP6, and VP7 serotypes not included in the vaccines. Furthermore, because of the “original antigenic sins” of B cells<sup>3</sup> and T cells,<sup>4</sup> infants who are vaccinated before contracting natural rotavirus infections may become hyporesponsive to indigenous rotavirus because of the development of recall immunity, which is anamnesticly more reactive with vaccine than with local serotypes. Paradoxically, if this recurrent vaccine-specific response at each reinfection is focused more on homotypic epitopes than on heterotypic epitopes, it may be considered harmful to vaccines, since it dampens the protective responses. It remains to be confirmed whether Rotarix (GlaxoSmithKline) and RotaTeq (Merck) are less protective against antigenically different indigenous rotaviruses. If this were to be found, then type-specific rotavirus vaccines might solve efficacy problems due to viral diversity and original antigenic sins.

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1. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11-22.
2. 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.
3. Francis T Jr. Influenza: the new acquaintance. *Ann Intern Med* 1953;39:203-21.
4. Klenerman P, Zinkernagel RM. Original antigenic sin im-

pairs cytotoxic T lymphocyte responses to viruses bearing variant epitopes. *Nature* 1998;394:482-5.

**TO THE EDITOR:** The recent reports of two new rotavirus vaccines conclude that these vaccines are both efficacious and safe. However, neither vaccine has been shown to be safe in immunocompromised patients. Oral poliovirus vaccine is also an orally administered, live attenuated vaccine. Because of its transmissibility and its ability to cause severe illness, oral poliovirus vaccine is contraindicated for immunocompromised patients and their close contacts. The rotavirus vaccine Rotarix is of particular concern, because, as noted by the editorialists Glass and Parashar,<sup>1</sup> the vaccine strain is shed by more than 50 percent of vaccine recipients after the first dose. It remains to be shown whether the new rotavirus vaccines can be safely given to immunocompromised patients.

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1. Glass RI, Parashar UD. The promise of new rotavirus vaccines. *N Engl J Med* 2006;354:75-7.

ule with the potential to eliminate the risk of intussusception. *J Infect Dis* 2005;192:Suppl 1:S22-S29.

**TO THE EDITOR:** Glass and Parashar note that because the risk of intussusception associated with RotaShield (Wyeth) — the first licensed rotavirus vaccine — is age-dependent, second-generation vaccines “might cause intussusception if administered to older infants.” Studies conducted after licensure of the vaccine will be critical, because in the prelicensure trials conducted by GlaxoSmithKline<sup>1</sup> and Merck,<sup>2</sup> the vaccine was administered to infants with a mean age at the first dose of approximately 60 and 70 days, respectively, leaving the effect of first doses on older infants unstudied.

In retrospect, RotaShield might have been used safely in a two-dose schedule completed by 60 days of age.<sup>3,4</sup> Such a schedule would have discouraged “catch-up” immunization of older infants, a practice that led to 81 percent of the vaccine-associated cases of intussusception that caused the withdrawal of RotaShield from the market.<sup>3</sup> In contrast, no cases of intussusception occurred in the approximately 70,000 infants who received a first dose at less than 60 days of age. A neonatal schedule would also avoid the administration of the vaccine to infants four to nine months of age — the period of highest susceptibility to both vaccine-related and “background” intussusception events.<sup>3,4</sup> Because intussusception might also beset new vaccines if given to older infants, the prudent course would be to discourage catch-up immunization. No one wants to see rotavirus vaccines suffer another setback.

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Dr. Kapikian reports being one of the developers of the RotaShield vaccine.

1. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11-22.

2. 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.

3. Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. *J Infect Dis* 2005;192:Suppl 1:S36-S43.

4. Kapikian AZ, Simonsen L, Vesikari T, et al. A hexavalent human rotavirus-bovine rotavirus (UK) reassortant vaccine designed for use in developing countries and delivered in a sched-

**TO THE EDITOR:** Glass and Parashar mention that RotaShield was withdrawn from the market because it was associated with an intussusception rate of 1 case per 10,000 infants vaccinated.<sup>1</sup> The package insert for RotaShield recommended that the first dose be given to infants at two months of age. Simonsen et al.<sup>2</sup> recently reported that many cases of intussusception attributed to RotaShield reflected the later age (three to seven months) at receipt of the first dose among infants who received this vaccine. They reported that there were no cases in 71,058 infants receiving their first dose of RotaShield before 60 days of age, and 9 cases among 268,202 infants receiving their first dose before 90 days of age (0.0034 percent). The effect of age may apply also to other vaccines: in younger infants, Vesikari et al. report that intussusception occurred in none of 34,035 infants after receiving their first dose of RotaTeq at 6 to 12 weeks of age, but there were a total of 12 cases within one year of the first dose in the same 34,035 who later received their second and third doses (0.035 percent). Ruiz-Palacios et al. report similar results with Rotarix. Considering these data, our plan is to bring RotaShield back to the market with a defined dosing schedule.

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Dr. Ruiz reports being the president and chief executive officer of and a shareholder in BIOVIRx, which is moving toward commercialization of the oral rotavirus vaccine RotaShield.

1. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001;344:564-72. [Erratum, *N Engl J Med* 2001;344:1564.]

2. Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. *J Infect Dis* 2005;192:Suppl 1:S36-S43.

**DR. RUIZ-PALACIOS AND COLLEAGUES REPLY:** Heterotypic protection has been suggested previously in animal models<sup>1</sup> and in community-based studies of the natural history of rotavirus infection.<sup>2</sup> Our clinical trial suggests that a monovalent attenuated G1P[8] human rotavirus (HRV) vaccine can induce heterotypic protection against other strains. The HRV vaccine proved to be highly protective against severe rotavirus infections caused by G1, G3, and G9 serotypes that share the same

VP4 antigen (P[8]); a similar efficacy is likely against G4 strains. Protection against G2P[4] strains, which differ from the vaccine strain in containing both VP7 and VP4 antigens, is less,<sup>3</sup> but it is still approximately 67 percent (95 percent confidence interval, 15 to 87 percent) in a meta-analysis of all studies involving HRV.<sup>3</sup> Serotypes G1, G2, G3, and G4 and genotypes P[8] and P[4] have predominated in episodes of rotavirus in the industrialized and developing world during the past couple of decades, perhaps because those serotypes and genotypes are more adapted to the human intestine than other serotypes. Thus, we believe that the HRV vaccine will probably have a substantial effect on rotavirus-associated morbidity and mortality in the developing world. However, continuous serotype surveillance and monitoring of vaccine performance are warranted.

The recommendation is to administer the first dose of the HRV vaccine to infants between 6 and 14 weeks of age, because children often are infected at a very young age. We believe that the data on HRV convincingly show that the vaccine is not associated with intussusception when given at this age. Vaccination of older children, however, might be indicated during an outbreak, as part of overall outbreak management.

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1. Feng N, Vo PT, Chung D, Vo TV, Hoshino Y, Greenberg HB. Heterotypic protection following oral immunization with live heterologous rotavirus in a mouse model. *J Infect Dis* 1997;175:330-41.
2. Velazquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. *N Engl J Med* 1996;335:1022-8.
3. Perez-Schael I, Linhares AC, Vesikari T, et al. Two doses of the human attenuated rotavirus vaccine RIX4414 (Rotarix) show heterotypic protection in Latin America and Europe. Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., December 16-19, 2005.

**DR. VESIKARI AND COLLEAGUES REPLY:** Dr. Ping-Ing Lee raises the issue of giving live vaccines to immunocompromised infants. Only healthy infants were enrolled in the Rotavirus Efficacy and Safety Trial, so that our study cannot address this

question. Live viral vaccines are generally not recommended for infants with severe immunodeficiencies. However, since rotavirus infects nearly all children, the effect of wild-type disease should be considered along with the potential risks and benefit of vaccination with an attenuated rotavirus vaccine.

Drs. Molinaro and Lee ask whether vaccine strains will provide sufficient protection in the developing world. Human serotypes G1, G2, G3, and G4 and P[8] were included in the pentavalent human-bovine (WC3) reassortant vaccine, because they cover more than 85 percent of the strains circulating during the past two decades in both developed and developing countries. With rotavirus, in contrast to influenza, the phenomenon of "original antigenic sin" does not appear to limit robust immune responses to diverse serotypes.<sup>1</sup> Primary immunity to wild-type infection is predominantly serotype-specific and is followed by a broadening of immune responses with subsequent infections. The development of homotypic immunity against each vaccine serotype, unbiased by previously induced immune responses, is possible with multiple doses. Vaccine efficacy in the developing world, where unusual serotypes may be encountered, will soon be evaluated in studies in Africa and Asia.

Dr. Simonsen and colleagues caution against catch-up vaccinations with the new rotavirus vaccines on the basis of the age-related incidence of intussusception associated with the rhesus-human reassortant rotavirus (RRV) vaccine (RRV-TV, Wyeth Laboratories). Our study was designed with the first dose of vaccine given at 6 to 12 weeks of age, when the background incidence of intussusception is low, in order to detect an increased risk of intussusception as early as possible. The absence of association between intussusception and the pentavalent vaccine may be explained by its differences from the RRV vaccine. In contrast to studies of RRV,<sup>2</sup> in our study the frequencies of fever, vomiting, diarrhea, and hematochezia were similar among recipients of the pentavalent vaccine and of placebo. Rhesus rotaviruses have been shown to invade gut-associated lymphoid tissue in experiments in animals to a greater extent than do bovine rotaviruses,<sup>3</sup> suggesting that intussusception may be a particular complication of RRV. Because of the inclusion criteria used for the phase 3 studies, these data can support only a recommendation for giving the first vaccine dose at ap-

proximately two months of age and completing the full series by six to eight months of age. The trade-off is that age restrictions may have untoward public health consequences, such as potentially preventable morbidity from rotavirus gastroenteritis among unvaccinated older children.

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1. Clark HF, Lawley D, Shrager D, et al. Infant immune response to human rotavirus serotype G1 vaccine candidate reassortant WI79-9: different dose response patterns to virus surface proteins VP7 and VP4. *Pediatr Infect Dis J* 2004;23:206-11.
2. Haber P, Chen RT, Zanardi LR, et al. An analysis of rotavirus vaccine reports to the Vaccine Adverse Event Reporting System: more than intussusception alone? *Pediatrics* 2004;113:e353-e359.
3. Moser CA, Dolfi DV, Di Vietro ML, Heaton PA, Offit PA, Clark HF. Hypertrophy, hyperplasia, and infectious virus in gut-associated lymphoid tissue of mice after oral inoculation with simian-human or bovine-human reassortant rotaviruses. *J Infect Dis* 2001;183:1108-11.

**THE EDITORIALISTS REPLY:** The association between the age at which rotavirus vaccine is administered and the risk of intussusception has become a central issue in reassessing the future of RotaShield and in testing and recommending the next generation of rotavirus vaccines. When the ages of patients with intussusception from the Centers for Disease Control and Prevention (CDC) case-control study to assess the association of RotaShield with intussusception<sup>1</sup> were compared with the ages at vaccination with RotaShield of infants in the National Immunization Survey<sup>2</sup> for a similar set of states in which the case-control study was conducted, no cases of intussusception were identified among approximately 70,000 infants vaccinated at less than 60 days of age, 9 were reported in the approximately 200,000 infants immunized between 60 and 89 days of age, but 36 occurred in the approximately 165,000 infants vaccinated at 90 days of age or older. This finding has emboldened Dr. Ruiz to bring RotaShield back into commercial production and Dr. Simonsen and colleagues to suggest that administering two doses to infants less than 60 days of age might be safe. Although the data are most suggestive, the confidence limits around this age-associated risk are

wide.<sup>3</sup> The World Health Organization's Global Advisory Committee on Vaccine Safety concluded that the evidence for this lower risk in younger infants still remains inconclusive.<sup>4</sup>

With regard to the two newer vaccines (Rotarix and RotaTeq), clinical trials involving approximately 130,000 infants who received their first doses at 6 to 12 weeks of age have demonstrated no association with intussusception. The CDC's Advisory Committee on Immunization Practices (ACIP) has just recommended routine use of the Rotarix vaccine for American children<sup>5</sup> but limited the initial dose to infants less than 90 days of age. This decision seems reasonable for two reasons. First, although the vaccine is not associated with intussusception, administering the first dose to young infants will reduce the number of background cases of intussusception that would occur by chance alone. Second, if the vaccine were associated with a small increase in the relative risk of intussusception that was not detected in the trials, the number of cases attributable to the vaccine might be amplified only in older infants who are also more susceptible to natural intussusception. The age restriction recommended by the ACIP should avoid the problem of catch-up immunization (i.e., starting immunizations in older infants who missed their first scheduled dose).

Neonatal immunization with RotaShield, as proposed by Simonsen et al., might reduce the risk of intussusception. However, a preliminary study<sup>6</sup> demonstrated that even though neonatal immunization with RotaShield reduced the side effect of fever, it also dampened the immune response to vaccine.

Finally, we agree with Dr. Ping-Ing Lee that rotavirus vaccines will need to be studied in immunocompromised patients, particularly in children infected with the human immunodeficiency virus, before the vaccines are recommended for widespread use. These studies are just being initiated.

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1. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001;344:564-72. [Erratum, *N Engl J Med* 2001;344:1564.]
2. Smith PJ, Schwartz B, Mokdad A, et al. The first oral rotavirus vaccine, 1998-1999: estimates of uptake from the National Immunization Survey. *Public Health Rep* 2003;118:134-43.
3. Rothman KJ, Young-Xu Y, Arellano F. Age dependence of the

relation between reassortant rotavirus vaccine (RotaShield) and intussusception. *J Infect Dis* 2006;193:898.

4. Global Advisory Committee on Vaccine Safety, 1–2 December 2005. *Wkly Epidemiol Rec* 2006;2:15–7. (Also available at <http://www.who.int/wer/2006/wer8102.pdf>.)

5. CDC's advisory committee recommends new vaccine to pre-

vent rotavirus. Press release of the Centers for Disease Control and Prevention, Atlanta, February 21, 2006. (Accessed March 30, 2006, at <http://www.cdc.gov/od/oc/media/pressrel/r060221.htm>.)

6. Vesikari T, Karvonen A, Forrest BD, et al. Neonatal administration of rhesus rotavirus tetravalent vaccine. *Pediatr Infect Dis J* 2006;25:118–22.

## Intensive Diabetes Treatment and Cardiovascular Disease

**TO THE EDITOR:** The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study research group (Dec. 22 issue)<sup>1</sup> reports that intensive therapy for diabetes reduced the risk of cardiovascular events by 42 percent without any mention of the adverse events associated with such therapy. The article from the DCCT research group<sup>2</sup> published in the *Journal* in 1993 reported the incidence of severe hypoglycemia to be 62 episodes per 100 patient-years in the intensive-therapy group, as compared with 19 such episodes per 100 patient-years in the conventional-therapy group. The cardiovascular-event rates were 0.80 per 100 patient-years and 0.38 per 100 patient-years, respectively. The reported hypoglycemic episodes were not trivial, since approximately 25 percent resulted in coma or seizure, and it was speculated that one resulted in two fatalities from a motor vehicle accident. Although the DCCT/EDIC study showed a significant beneficial effect on the cardiovascular complications of diabetes, the magnitude of this benefit needs to be considered in light of the risk of hypoglycemia.

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1. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353:2643–53.

2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–86.

**TO THE EDITOR:** In the editorial accompanying the DCCT/EDIC study,<sup>1</sup> Dr. Cefalu details the continuing accumulation of evidence in favor of tight glycemic control. However, no evidence will be of any benefit if the resultant recommendations can-

not be implemented. Sadly, that is exactly the case. Now, more than 12 years after the publication of the initial results of the DCCT study, reimbursement for the care of children with type 1 diabetes has only deteriorated. Until payers accept some other way to compensate for care provided outside the face-to-face office visit, the only providers capable of giving adequate care will be those subsidized by their grants or institutions, such as the providers at the study sites in the DCCT trial.

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**THE AUTHORS REPLY:** Dr. Weissman suggests that the 42 percent reduction in cardiovascular disease we observed in the original DCCT intensive-therapy group, as compared with the conventional-treatment group, should be reconsidered in light of the heightened risk of severe hypoglycemia accompanying intensive therapy. The risk of hypoglycemia was three times as high in the intensive-therapy group as in the conventional-therapy group (16 vs. 5 episodes of seizure or transient coma per 100 patient-years); nevertheless, intensive therapy has been adopted internationally as the standard of care for type 1 diabetes since 1993.<sup>1</sup> The rationale for intensive therapy was not predicated on a reduction in cardiovascular disease but on the major reduction in retinopathy, nephropathy, and neuropathy as demonstrated during the mean DCCT follow-up of 6.5 years. The salutary effects of intensive therapy have been projected to add, on average, 5.6 to 7.7 years in which patients are free from blindness, renal failure, and amputations and to increase life span by 5 years,<sup>2</sup> even before its very welcome additional beneficial effects on cardiovascular disease are taken