Universal Rotavirus Immunizations

Should rotavirus vaccine be recommended for universal use?

AN AFFIRMATIVE VIEW

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Rotavirus is the most common cause of severe gastroenteritis in preschool-aged children in the United States. Published estimates of annual hospitalizations in the United States range from 23,000 to 110,000, with recent data suggesting approximately 50,000.[1] Based on the estimate of 3.9 million children in the birth cohort, this means that 1 in 78 children will be hospitalized with severe gastroenteritis every year.[2] Rotavirus results in approximately 160,000 emergency department visits and 410,000 physician visits. Ten and a half percent of all children will be seen by a physician in the first 5 years of life for this illness.[2] In comparison with other causes of childhood gastroenteritis, rotavirus results in prominent fever, vomiting, and dehydration. One study found that of all children with rotavirus gastroenteritis 98% have diarrhea, 87% experience vomiting, 84% have a fever, and 18% have abdominal pain.[3] This study also found that 37% of children vomited more than 5 times daily, and 21% had more than 10 bouts of diarrhea daily.[3] Although recovery is usually complete, lactose intolerance has occurred[4] and a link to neonatal necrotizing enterocolitis has been suggested.[5]

Rotavirus is highly contagious since rotaviruses are shed in very high concentrations in human feces (10^{11} particles per gram) but a person can be infected by as low a dose as approximately 10 viral particles. It is transmitted primarily by the fecal-oral route; thus, transmission within families of infants (due, in part, to diaper changing) and within daycare institutions is common.[6,7] Rotaviruses are relatively resistant to many disinfectants, can remain infectious on inanimate articles, and can remain ineffective for months at ambient temperatures.

A live, tetravalent (serotypes G1, G2, G3, and G4) rhesus rotavirus vaccine (RRV), RotaShield, was licensed in 1998. The vaccine is based on a modified Jennerian approach to vaccination. In the Jennerian approach, a virus (eg, cowpox) from one animal is attenuated and given to another animal to prevent infection by a related virus (eg, smallpox). Since a particular rotavirus serotype replicates in primarily one species of animal host — a property called host restriction — nonhuman strains are usually naturally attenuated when given to humans. RRV is further attenuated by passage 16 times in cell culture. RRV is administered orally.

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The efficacy of the rotavirus vaccine is moderately good against diarrhea but very good against dehydration and severe diarrhea. In a multicenter double-blind placebo-controlled trial conducted in the United States that included infants of multiple races, the efficacy of $4*10^5$ pfu RRV over 1 season of observation was 49% (95% confidence interval [CI], 31% - 63%) for gastroenteritis, 73% (95% CI, 54% - 84%) for gastroenteritis resulting in physician intervention, 80% (95% CI, 56% - 91%) for very severe rotavirus gastroenteritis, and 100% for dehydration.[8] The number needed to treat to prevent one physician intervention is 9. Finnish data show that protection lasts several years.[9] In a US multicenter double-blind placebo-controlled trial using a weaker 4*104 pfu RRV-TV, the efficacy over 2 years of observation was 57% (98.3% CI, 29% - 74%) for gastroenteritis and 82% for very severe rotavirus gastroenteritis.[10] The importance of this finding is that protection (ie, effectiveness) should be maintained, even if a portion of the vaccine is regurgitated.

Although most children do not have adverse reactions to RRV, low-grade fever, diarrhea, and irritability sometimes occur. The incidence of a temperature > 38°C in the 5 days following administration of the first dose of the vaccine was 21% in vaccinated subjects compared with 6% in controls; for a temperature > 39°C, the rates were 2% compared with 1%. On rare occasions, the fever after the first dose at 2 months of age might lead to precautionary hospitalization. There is less fever after doses 2 and 3. RRV has been studied in nearly 7000 infants in doses of $4*10^5$ pfu or higher and has generally been well tolerated.

Since approximately 410,000 visits to physicians occur each year for rotavirus diarrhea in children younger than 5 years of age,[2] and since RRV results in a 73% reduction in physician visits for rotavirus gastroenteritis,[8] RRV should prevent 299,300 office visits per year. Thus, physicians with patients in capitated plans will benefit by decreased utilization when the capitation is raised to cover vaccine cost. Authorities recognize that it will take some time to have insurance plans cover RRV cost and have allowed for that in their recommendations. RRV will be covered by the Vaccines for Children Program, so it should be available in 1999 for economically disadvantaged children, including Medicaid-eligible and uninsured children. The spending in the United States associated with rotavirus in 1996 dollars was estimated at $264 million for medical costs, primarily because of hospitalizations for diarrhea and dehydration (66%), and there was a $1.001 billion cost to society, primarily for lost work time for parents. On the basis of cost-effectiveness analyses, RRV should be cost-saving to society.[2]

RRV is unlikely to become a mandatory vaccine since children should not begin the series if they are 7 months of

age or older and since no doses should be given after the first year of life, according to the Advisory Committee on Immunization Practices.

Rotavirus disease, though often mild, results in approximately 50,000 hospitalizations annually due to dehydration in the United States. The rotavirus vaccine is highly efficacious (almost 100%) against dehydration. It will reduce visits to physicians and emergency rooms and will result in cost-savings to society. Since it is given orally, reduces children's suffering due to gastroenteritis, and reduces the parental inconvenience of caring for sick children, it should be well accepted by parents. I would give this vaccine to my own children and will give it to patients in my office.

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AN OPPOSING VIEW

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On June 24, 1998, the Advisory Committee on Immunization Practices (ACIP) voted to recommend the universal rotavirus immunization of newborns. Dr Zimmerman presents a convincing case in favor of the vaccine. I agree with many of the points he makes. There is no question that rotavirus causes significant morbidity and some mortality and that the vaccine offers some reduction in disease severity. There is no doubt that the vaccine is appropriate for a large segment of the population and can be marketed at a price that will make it cost-effective. There is no doubt that the financing of childhood immunizations is a key concern of parents, clinicians, and policy makers and that ACIP approval of a vaccine paves the way for important funding opportunities through the Vaccine for Children (VFC) program.

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Most important, however, I have no doubt that the ACIP should not have recommended the vaccine for universal use. Instead, a permissive approach is justified at this time — one in which parents, educated about the benefits and the availability of the vaccine, choose what they feel is best for their children.

There are several reasons why a permissive approach should be preferred at this time. First, there are concerns regarding patient (or in this case, parental) preferences that extend beyond the academic or philosophic. The American Academy of Family Physicians (AAFP) is committed to patient-centered evidence-based medicine and, in particular, believes that patient preferences are important. This is not to say that patient preferences are paramount. For some previous vaccines, for example, issues of societal benefit overrode the importance of individual patient preferences. These societal benefits result from either herd immunity or from social cost-savings to the health care system. This societal benefit has justified the mandatory aura of ACIP recommendations. (An ACIP recommendation, while not truly a mandate, is not only tied to VFC program funding but is perceived as mandatory by states and by quality measures such

as the Health Plan Employer Data and Information Set. ACIP members, during their June discussion, explicitly denied this power of their collective voice.) Of course, since the rotavirus vaccine confers no herd immunity, there is no societal health benefit from this vaccine.

Second, there is a real potential of decreased acceptance of vaccines in general. Those parents who question their child's need of the 26 immunizations previously recommended in the first 18 months of life may decide that the rotavirus vaccine (bringing the total to 29 immunizations) is the last straw. These parents may keep their child from an immunization visit, thus resulting in not only a lost rotavirus immunization, but a failure to obtain the other immunizations as well. For rotavirus, this is a particularly challenging issue: Those patients at the highest risk of the disease may be at the highest risk for lower compliance. We must ask about the opportunity cost of any new vaccine, especially since there is a large number of vaccines in the pipeline. If it is not an issue now, it will be in the future. If parents accept 29 immunizations, will they accept 50? 100? When will parents revolt? The ACIP did not address this important issue.

Third, there is the question of the cost of the vaccine. When the ACIP voted for universal use, the vaccine manufacturer had not yet set a price for the vaccine. A recommendation (which will be interpreted by many as a mandate) that is not linked to a price provides the manufacturer with unreasonable economic leverage. The ACIP made no comment about this important issue. In addition, since managed care capitation rates are negotiated in advance, clinicians will meet the addition of a new vaccine — especially one that could be quite costly — with hesitation, perhaps decreasing immunization compliance.

Fourth, there is inadequate data for a universal recommendation. The Centers for Disease Control (CDC) staff presented the ACIP pilot data on the vaccine's poor acceptance rate by clinicians. CDC staff argued that more data is needed. Several ACIP members, realizing the vaccine has seen only limited use in a few clinical trials, suggested a 1- to 2-year observation period during which the vaccine would become licensed and a few million immunizations would be given. (That's right, the vaccine was not licensed until August 31, 1998 — almost 10 weeks *after* the ACIP vote! Even at the time of this writing the vaccine cost has not been set.) This observation period would allow us to better assess the effectiveness, acceptability, and potential adverse effects of the vaccine. In the end, the ACIP ignored this important issue.

I suspect that most parents, once informed of the risks and benefits, will choose the rotavirus immunization for their child. But this does not justify the ACIP action. Before offering the mandate that a universal recommendation provides, we need the necessary economic and patient preference information. The vaccine should be optional for now. In a year or two, with a set price and increased experience with the vaccine, we should reconsider whether a universal recommendation is warranted. Until then, not only is there little reason to issue a universal recommendation for this new vaccine, such a recommendation is contraindicated, except perhaps in the highest risk groups, such as inner-city, low socioeconomic groups. This permissive approach is especially attractive since the VFC program could fund the vaccine without the universal recommendation.

So the big question is, "What's the rush?" Why would the ACIP make a decision that unfairly undercuts parental preference and offers financial benefit to a vaccine manufacturer? When confronted, a prominent ACIP member told me, "It's been on our agenda too long. We are tired of dealing with it. It is time to make a decision." So the ACIP voted to recommend universal immunization with a vaccine that was not yet licensed because it was "tired of dealing with" the issue, although CDC staff suggested more information was necessary and people at the meeting noted the lack of experience with the immunization.

Fortunately, the ACIP is only part of the triad (along with the AAFP and the American Academy of Pediatrics) that endorses the harmonized newborn vaccine schedule we all use in our offices. Hopefully, common sense will rule, and the harmonized schedule will not include rotavirus vaccine until more data are available.

Do you have an opinion on the use of rotavirus vaccine?
Go to the *Journal*'s Web site at www.jfp.denver.co.us
and let us know what you think.