

Happily, at the time of this writing, both Rotarix[®] (GSK) and RotaTeq[®] (Merck) have satisfied the primary endpoints of their respective large phase III studies, and neither showed any increase in the incidence of intussusception in the vaccinated population compared to the placebo recipients. Protection against rotavirus AGE has been confirmed; in the case of the Merck vaccine (for which the author has easiest access to data), protection against disease of any severity was similar to that reported in the smaller studies above. In addition, a substantial reduction in health care costs was demonstrated in the vaccinated population. Both vaccines have been filed for licensure with several regulatory agencies around the world.

VACCINE IMPLEMENTATION

It appears that at least two new rotavirus vaccines should become available in the near future. As we move into the vaccine implementation phase, we will face a series of predictable questions (and probably some we have not thought of yet).

- *Is rotavirus disease sufficiently burdensome to justify the expense and effort of vaccination?* Prior to the approval of RotaShield[®] in 1998, several studies addressed this question and concluded that vaccination was cost-effective, especially when the indirect societal costs (lost wages, etc.) were considered. Recent studies show that the true burden of rotavirus disease is in fact greater than previously believed, in part because of a now recognized underdiagnosis of rotavirus infection. Therefore, the cost-benefit equation should shift further in favor of rotavirus vaccination. In the United States, we would save a few lives and a considerable amount of money. In the developing world, if we can get there, we should be able to save hundreds of thousands of lives and some money. The health care utilization reduction seen in the clinical trials confirms this notion. Vaccination is worth the effort.
- *What about the cases of intussusception that will inevitably follow vaccination once these new vaccines reach the general population?* This will require a sophisticated postmarketing surveillance program. The incidence of intussusception following the introduction of RotaShield[®] was quantifiable owing to the relatively low level of penetration into the market and the short period of use. There was an unvaccinated cohort to compare with the vaccinated cohort. The coming introduction of these vaccines will provide the same opportunity but for (we hope) a similarly short time. We will need to make the best use of this time. A second important aspect of this question is that of age at first dose. Both GSK and Merck's larger studies limited the age at first dose of vaccine to ~6–12 weeks. This was done in order to have a low background rate of intussusception (which is very rare at this age) over which we could see a small signal of vaccine-related intussusception, if it existed. In the real world, many children may miss this window for the first

dose. Unless vaccine labeling can be worded to allow some flexibility for the first dose, the utility of these vaccines will be limited. We also recognize that these vaccines, administered later, will be linked in time with the naturally increasing rate of intussusception in older infants. This needs to be dealt with up front.

- *How will we deliver these vaccines to the children who need them in developing countries?* Both of these vaccines have been tested in multiple countries so far as part of their phase III development. GSK has the more substantial experience with Rotarix in a large Latin American population; Merck has some experience with RotaTeq in Latin America as well. The effectiveness of these vaccines now needs to be established by controlled clinical studies in truly developing countries. This effort is getting under way now. However, having vaccines that work does not guarantee that these vaccines will be delivered. Funding for rotavirus vaccination programs needs to be secured, and the delivery infrastructure needs to be established. Fortunately, both vaccines fit within the 6-10-14 weeks-of-age schedule of the World Health Organization's Expanded Program for Immunization. Local epidemiological data and vaccine demonstration trials will be necessary. We are fortunate to have the collaboration of Global Alliance for Vaccines and Immunization, Program for Appropriate Technologies in Health, WHO, the CDC, and other international organizations to help solve this part of the problem.
- *What kind of data will be required to license follow-on vaccines?* Vaccines in general are not generic products. Their safety and efficacy profiles are the product of antigen (or strain) selection, raw materials used in production, the production process itself, and multiple other variables that make them unique. RotaTeq and Rotarix both seem to have passed the "intussusception test," and this may reduce to some extent the concern about a class effect, but some product-specific clinical data will probably be needed for future vaccines.

CONCLUSIONS

At the risk of jinxing an entire field, it would appear that we have met the challenge of developing new rotavirus vaccines. It has been a long process if one considers the early 1980s as the starting point. Twenty-five years, however, is not unusual for vaccine development. These are long-haul programs requiring an exceptional level of dedication of time, intellect, money, political will, and plain hard work on the part of literally thousands of people around the world in the public and private sectors. We are now embarking on implementation—in a way, the more challenging aspect of the program. It is a more diffuse exercise on multiple fronts with perhaps less easily identifiable victories in the short term. I am confident that we will all look back in a few years and agree that the public health result is worth the effort.

DISCLOSURE STATEMENT

As an employee of Merck and Co., the author was involved in the development of Merck's rotavirus vaccine, RotaTeq®.

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