

Rotavirus

The Search for the Next Generation Vaccine

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A new rotavirus vaccine is much needed, especially for children in the developing world. Every child in the world could be infected with rotavirus in the first few years of life, and every child could ultimately benefit from a vaccine, with a critical distinction: in developed countries, rotavirus leads to doctor visits, hospitalization, lost parent workdays, economic expense, but very rarely deaths; whereas in developing countries, the morbidity as well as the death toll are much higher.

In a developed country such as the United States, few children die of rotavirus and the disease is generally mild. About 10% of cases lead to dehydration requiring a doctor's visit and eventual hospitalization. Children can begin oral rehydration treatment when the first signs of vomiting and diarrhea appear and escape the severe form of the disease. In this setting, a vaccine will impact mainly on health economic costs.

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In developing countries, where 1 in 250 children will die of the dehydration caused by rotavirus, the risk-benefit analysis is different. There, rotavirus causes approximately half a million child deaths each year, and a vaccine could prevent this most common cause of death in children. Regardless of the difference in disease impact, a vaccine has the potential to prevent severe disease in any setting.

There are 4 to 5 main serotypes (G1, G2, G3, G4 and the new emerging strain G9) of rotavirus found worldwide. To be effective the vaccine must demonstrate protective efficacy against these principal serotypes. The G1 serotype is prevalent in the United States, Europe and worldwide. In Latin America (where G1, G2, G3, G4 and especially G9 circulate), eg, Brazil, unusual serotypes have emerged, perhaps from contact with cows or pigs, which also have rotavirus infections. Some evidence exists that genes of rotavirus of animal origin can reassort and infect humans. These situations appear to be rare but will require some monitoring of strains over time and underline the need for a vaccine that is able to protect against new emerging strains as well.

The only way to determine whether a new vaccine protects against the main serotypes of rotavirus is to conduct large scale field trials in a variety of settings. Trials with new vaccines are being conducted in many countries of Latin America, Asia, the United States and Europe. Meanwhile, a vaccine has already been licensed in China, and several other new vaccines could potentially be licensed in India and Indonesia in the next 5-7 years.

Early studies with the rhesus vaccine that was given to nearly 1 million children in the United States demonstrated that the vaccine was highly effective and relatively safe. It was withdrawn because of the rare adverse event of intussusception. This safety issue is the biggest hurdle to overcome for the next generation of vaccines. It requires that large trials be conducted to ensure vaccine safety. It also requires that investigators conducting trials have in place a mechanism to identify children with symptoms that might represent intussusception, which can be assessed and adequately treated by a quality care facility.

The current trials of new vaccines are raising expectations for a vaccine that is as effective as the first vaccine, but

with a better safety profile and fewer adverse events. Among the rotavirus vaccines in development, 2 live attenuated vaccines that are administered orally at the time of other routine childhood immunizations have advanced to Phase III clinical trial stage: a human monovalent vaccine given in 2 doses at 2 and 4 months of age (GlaxoSmithKline, GSK Biologicals); and a bovine-human reassortant pentavalent vaccine given in 3 doses at 2, 4 and 6 months of age (Merck).

The safety profile of these 2 vaccines will be better known on completion of the ongoing Phase III trials. Furthermore, there is no evidence that natural human rotavirus is implicated as a cause of intussusception, so it is hoped that this applies to the GSK Biologicals vaccine as well. For the Merck vaccine, the bovine strains replicate less than the rhesus strains and cause less fever than the rhesus strains, meaning that they are more attenuated. These milder infections hopefully will also be associated with fewer adverse events.

Many studies during the past 20 years drew necessary attention to the fact that rotavirus is a major problem. Addressing rotavirus is high on the global public health agenda,

and a new vaccine is needed to meet goals of immunizing 80% of the world's children against rotavirus and decreasing rotavirus mortality by 60% within the next 10 years. The successful development and delivery of the rotavirus vaccines currently being assessed will contribute in a profound way to improve infant health and survival around the globe.

One of the main challenges ahead is the introduction of a new vaccine into the routine immunization programs. In the past, it has been several years between the availability of a vaccine and general use to benefit the populations most in need. However, the introduction of a rotavirus vaccine into national immunization programs will pose little logistic problem: they will be given orally, simultaneously with other vaccines already included in these programs. Therefore, it will be incumbent upon Governments to ensure that resources are available and allocated for the early introduction of the rotavirus vaccine once it becomes available. This is particularly important in developing countries such as those in Latin America where thousands of infants die of this disease annually.