

EDITORIAL



Rotavirus Vaccine — A Powerful Tool to Combat Deaths from Diarrhea

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Rotavirus infection, the leading cause of severe childhood diarrhea in both developed and developing countries, results in over half a million deaths each year.¹ Currently, two rotavirus vaccines (Rotarix [GlaxoSmithKline Biologicals] and RotaTeq [Merck]) are licensed in many countries and used routinely in several. Until recently, available efficacy data were from developed and developing countries with relatively low mortality rates among children younger than 5 years of age.

In this issue of the *Journal*, efficacy trials conducted in Africa by Madhi and colleagues² and a postmarketing study conducted in Mexico by Richardson and colleagues³ are described. The data support the use of rotavirus vaccines in the poorest countries in the world, a finding that is consistent with previous reports.⁴ Recently, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization recommended the use of rotavirus vaccines worldwide.⁵ The widespread use of these vaccines has the potential to prevent about 2 million deaths over the next decade.⁴ Madhi and colleagues report a pooled efficacy of 61.2% in South Africa and Malawi; the country-specific efficacy was 76.9% and 49.4%, respectively. Despite the lower efficacy in Malawi, the vaccine prevented many more episodes of severe gastroenteritis due to rotavirus in that country than in South Africa or other regions where the vaccine has been evaluated, because of the higher rates of severe gastroenteritis in Malawi. Another important finding of the study was a 30% decrease in the incidence of severe gastroenteritis from any cause; similar findings have been reported in other studies.^{6,7} This decrease in severe gastroenteritis from any

cause suggests that the available tests for detecting rotavirus are failing to detect some cases of rotavirus disease.

The Mexico study provides data suggesting that the introduction of the rotavirus vaccine resulted in a substantial reduction in deaths from rotavirus. Documentation of the reduction in mortality for most interventions is extremely difficult. It is commendable that the excellent surveillance system in Mexico enabled the investigators to make this observation.

Can the data from Malawi and South Africa be extrapolated to other countries in the region? The available data suggest that vaccine efficacy is inversely correlated with mortality among children younger than 5 years of age, populations in which the burden of disease from rotavirus infection is often highest.⁵ Thus, as suggested by the WHO Strategic Advisory Group of Experts, it is reasonable to assume that the efficacy would be similar in regions with socioeconomic characteristics, social structure, nutritional conditions, and risks contributing to mortality like those in Malawi and South Africa.⁵ Although not evaluated in the studies in this issue of the *Journal*, herd immunity has been shown to be induced by rotavirus vaccines (as an indirect effect) by reducing the exposure of unvaccinated persons to the organism.⁵ Thus, introduction of the vaccine into countries is likely to have a greater effect than that predicted on the basis of the efficacy trials.

Despite this potential for rotavirus vaccines to substantially reduce the risk of death from diarrhea, there are considerable challenges to implementing their use in the poorest countries of the world. First, the storage and shipment require-

ments to avert cold-chain breaks of rotavirus vaccines are far greater than those of typical childhood vaccines, which will make the logistics of vaccination programs in developing countries more difficult.

Second, the rotavirus vaccines are currently recommended for administration during a narrow window: the first dose between 6 and 15 weeks of age, and the third dose no later than 32 weeks of age.⁵ This recommendation is a serious impediment to the widespread use of rotavirus vaccines, especially in countries with the highest child mortality, which tend to have the lowest vaccine coverage and the lowest rate of on-time immunization.⁸ This recommendation for age-restricted vaccine administration is based on the age-dependent occurrence of intussusception with the use of the RotaShield vaccine (manufactured by Wyeth Lederle Vaccines), which was withdrawn from the market a year after it was licensed in 1998. There is no evidence of increased frequency of intussusception with either of the two current rotavirus vaccines; thus, additional data regarding the safety and efficacy of the current vaccines as administered within wider age windows are urgently needed to ensure optimal coverage.

A report by Patel and colleagues⁹ in this issue of the *Journal* describes prolonged rotavirus disease and viral shedding in three infants with severe combined immunodeficiency after receipt of a rotavirus vaccine. Diarrhea caused by rotavirus acquired through transmission of a vaccine-type virus is likely to be much less severe than disease caused by the wild-type virus. To date, there is no evidence that rotavirus vaccine causes disease in children infected with the human immunodeficiency virus or that the vaccine is tolerated less well by such children than by other children, although this possibility will need to be carefully monitored in the future.

Third, the current cost of the rotavirus vaccines per dose in the United States is far beyond the means of most middle-income countries and the poorest countries. Fortunately, cofinancing is available, at least for the short term, from GAVI (formerly known as the Global Alliance for Vaccines and Immunization) — resulting in a cost of 15 to 30 cents per dose, depending on the economic status of the country. The remainder of the cost is absorbed by GAVI; therefore, it is

imperative that the global donor community continues to support programs such as GAVI to ensure that the poorest children have access to these new lifesaving vaccines.

The WHO currently has regional surveillance systems in place to document rates of disease from rotavirus.¹⁰ It is critical to maintain such surveillance systems to track the safety and effectiveness of the vaccine and shifts in serotype distribution.

In the 10-year period since RotaShield was withdrawn from the market, more than 5 million children have died from rotavirus disease. Thus, current vaccines should be widely used now, while trials of other vaccine candidates are continued in various populations and mechanisms to improve vaccine efficacy are investigated. Since rotavirus is only one of many pathogens that cause diarrhea, the use of rotavirus vaccine will need to be supplemented by other preventive and treatment strategies to reduce the high mortality from diarrheal diseases. Unfortunately, the coverage for known effective interventions, such as oral rehydration therapy, in parts of Africa and South Asia is less than 35%.¹¹

We now have another powerful weapon to add to our armamentarium to combat deaths from diarrhea — rotavirus vaccines. The vaccines should be introduced immediately in areas with high mortality from rotavirus infection, and their introduction should be used to energize diarrhea-control programs and improve coverage for all the proven interventions for diarrhea. It is time to act to combat the 1.8 million unnecessary deaths from diarrhea that continue to occur each year.¹

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