Vaccines Against Rotavirus Gastroenteritis

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WORLDWIDE IMPORTANCE OF AN EFFECTIVE ROTAVIRUS VACCINE

Diarrheal diseases are among the most common illnesses of mankind and the first or second most common cause of death, hospitalization, and doctor visits among children worldwide (1,2). They almost always result from infection, and over the past three decades, more than 25 distinct infectious agents have been identified as etiologic agents of diarrheal diseases. For most children, episodes of diarrhea are self-limiting, the disease is mild, and recovery occurs within several days. However, in some children, the disease can be severe, progressively leading to dehydration, hospitalization, and death. Of the many diarrheal illnesses, rotavirus has been identified as the most common cause of severe diarrhea in children.

Several key features define the epidemiology of rotavirus disease and suggest that prevention and control will likely best be achieved with vaccines (3). First, infections are universal and all children worldwide are infected within their first three years of life. This suggests that improvements in food and water sanitation are unlikely to alter the incidence of disease; therefore, other approaches are necessary. Second, initial infections with rotavirus that occur several months after birth are often associated with severe diarrhea. Immunity to disease develops after each rotavirus infection, so second and subsequent infections are usually not associated with illness, and the incidence of rotavirus disease diminishes with increasing age (4). Finally, despite global efforts to diminish the severity of diarrhea through the use of oral rehydration, diarrhea related to rotavirus remains a major cause of hospitalization and death.

Global interest in the development of rotavirus vaccines has been driven by the burden of fatal disease in developing countries (Fig. 1) and by medical and societal costs in industrialized countries (5,6). In developing countries, rotavirus is estimated to cause approximately 530,000 (475,000–570,000) childhood deaths each year (Fig. 2). This represents about 5% of the 10,000,000 deaths worldwide annually among children less than five years of age, or about one death per 270 children born worldwide (ca 135,000,000 births/year) (7). In both developed and industrialized countries, rotavirus accounts for between 20% and 60% of hospitalizations for diarrhea, and recent surveys suggest that one child in every 30 to 120 will be hospitalized for rotavirus diarrhea before his/her fifth birthday. In the United States, efforts to include a rotavirus vaccine in the national immunization schedule were prompted by estimates that rotavirus diarrhea results in 600,000 doctor or emergency room visits, 55,000 to 70,000 hospitalizations, and 20 to 40 deaths each year (6). The cost of this illness has been estimated to exceed US$400 million in medical expenses and more than US$1 billion when societal costs (e.g., parents' lost work time) are included.

ROTAVIRUS STRUCTURE AND REPLICATION

The rotavirus particle (Fig. 3) is ca 100 nm in diameter and has a capsid composed of three concentric protein layers (8,9). The outer layer contains 780 molecules of VP7 and 60 trimers of VP4 (10–12). Both are neutralization proteins and define the G and P serotypes (genotypes) of the virus, respectively. VP4 forms spike-like projections that extend through and 11 to 12 nm beyond the VP7 layer (8,9,13,14). VP4 is anchored to an intermediate layer composed of 780 molecules of VP6 protein (10,11). The innermost layer contains 120 molecules of VP2 protein that interact with 12 molecules each of the viral transcriptase (VP1) and guanylyltransferase (VP3) along with 11 segments of the double-stranded RNA genome. These segments encode the six structural proteins of the virus designated VP1-VP6 and six nonstructural proteins designated NSP1-NSP6 (Table 1).

The replication cycle of rotavirus is activated by cleavage of VP4 by trypsin-like proteases but the VP5* and VP8*