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Rotavirus vaccines: Successes and challenges

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Summary Since 2006, the availability of two new rotavirus vaccines has raised enthusiasm to consider the eventual control and elimination of severe rotavirus diarrhea through the global use of vaccines. Rotavirus remains the most severe cause of acute diarrhea in children worldwide responsible for several hundred thousands of deaths in low income countries and up to half of hospital admissions for diarrhea around the world. The new vaccines have been recommended by WHO for all infants and in more than 47 countries, their introduction into routine childhood immunization programs has led to a remarkable decline in hospital admissions and even deaths within 3 years of introduction. Challenges remain with issues of vaccine finance globally and the problem that these live oral vaccines perform less well in low income settings where they are needed most. Ongoing research that will accompany vaccine introduction might help address these issues of efficacy and new vaccines and novel financing schemes may both help make these vaccines universally available and affordable in the decade.
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Introduction

Since 2006, the availability of new vaccines to prevent rotavirus has improved prospects for the control of this the most common cause of severe diarrhea in children worldwide.[1] Rotavirus infections are ubiquitous, affecting all children in the first few years of life and causing gastroenteritis that is most often mild but can be severe, leading to dehydration, hospitalization, shock, and in low income countries, death. The virus was discovered in 1973 by Ruth Bishop who first visualized the virus in a duodenal biopsy of an infant with acute gastroenteritis.[2] The virus was named rotavirus because of its wheel-like structure (rota = wheel) (Fig. 1). The early development of a simple, sensitive and inexpensive immune assay for rotavirus and the large quantity of viruses in fecal specimens ($>10^{11}$ virus particle per gram of stool) during acute disease facilitated assessment of the burden of disease in many settings.[3] Furthermore, the fact that all children are infected with

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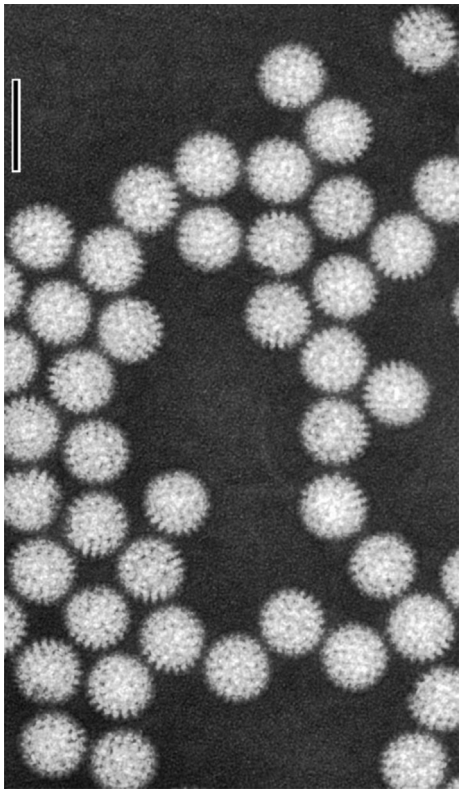

Figure 1 Electron micrograph of rotavirus particles in stool of a child with rotavirus diarrhea (Marker represents 100 microns).

rotavirus early in life, regardless of whether they live in industrialized countries or low resource settings, indicated that improvements in water, food, hygiene or behavior would be unlikely to interrupt the spread of this virus. The demonstration by Bishop that there was protective immunity to the virus laid the groundwork for early efforts to develop vaccines.[4] These vaccines have now been licensed in more than 100 countries, are in the routine immunization programs of more than 47 countries and been recommended by the World Health Organization as part of the routine program of childhood immunization (Fig. 2).[5,6] The early success of these programs to decrease both hospitalizations and deaths from rotavirus diarrhea has encouraged global support and prioritization of rotavirus immunization for all children.

Clinical presentation, diagnosis and management

Rotavirus gastroenteritis has a presentation that is no different from dozens of other infectious agents that cause acute gastroenteritis in children. Infection often presents first with vomiting followed by acute watery diarrhea with symptoms lasting for 3—7 days duration. Most disease is mild and a specific diagnosis is rarely made although simple diagnostic tests are commercially available and are most often based upon the detection of rotaviral antigen in stool by an immunoassay. In about 10% of first episodes, a child will have symptoms severe enough to lead to a doctor or clinic visit and the need for aggressive treatment with oral rehydration fluids (ORT).[7,8] In 1—3%, the infection is so severe that the child may require intravenous rehydration to correct fluid and electrolyte imbalance. In fact, children with rotavirus diarrhea are more likely to vomit and experience dehydration than children with diarrhea due to other causes.[9] In low income countries, other factors such as malnutrition and concurrent infections can make the illness more severe and dehydration and shock can be precursors of a fatal outcome. It had long been believed that infection was confined to the gut but studies have identified viremia with rotavirus antigen and virus circulating in the blood.[10,11] The only other documented extraintestinal infections are rare cases of severe disease when rotavirus antigen has been found in the cerebrospinal fluid.[12] In immunocompromised children, virus shedding can be prolonged, for a year or more, and these cases may represent a potent reservoir of infection.[13,14]

Epidemiology and burden of disease

The epidemiology of rotavirus was first examined among children hospitalized for diarrhea in industrialized countries located in temperate climates.[15] Rotavirus was identified in fecal specimens of 35%—50% of children under 5 years admitted with diarrhea and had a distinct winter seasonality and few cases in the summer and fall. The age distribution was noteworthy because few infants less than 3 months were hospitalized, the peak age of hospitalization was from 6 months to 2 years of age with 40% of cases occurring among those aged less than 1 year. When etiologic studies were conducted among children hospitalized with diarrhea in low income settings in more tropical climates, the epidemiology found was markedly different.[16] First, the disease occurred year round, although sometimes a small winter peak could be identified, and up to 80% of the severe cases occurred in the first year of life (Table 1).[17] Subsequent examination of fecal specimens added an additional dimension to these differences: children in high income settings were usually infected with a few common serotypes of rotavirus and rarely had mixed infections with 2 or more strains, whereas in low income settings, the diversity of serotypes detected was much greater and up to a third of fecal specimens had 2 or more strains.[18—20] These observations suggested an increased force of infection and perhaps, a different mode of transmission. The winter seasonality and rapid spread of infection with a single strain in high income settings seemed consistent with airborne or droplet spread, whereas in low income populations, year round disease with multiple serotypes infecting infants early in life might indicate a greater force of infection and transmission from fecally contaminated water or environmental sources as well as airborne or droplet spread.[21] To date, a thorough understanding of the exact mode of transmission remains elusive although further studies as immunization programs are launched may provide some intriguing clues.[22]

Longitudinal studies of infants from birth to several years of age have demonstrated that in general, first