# Introduction: Rotavirus—from Basic Research to a Vaccine

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In 1976, Jon Rohde, highlighting the importance of diarrhea as a prime killer of children in the developing world, beckoned the scientific community to "take science where the diarrhea is!" [1]. While researchers were discovering many new etiologic agents that cause diarrhea, progress in preventing diarrheal deaths—then estimated at about 5 million per year—was slow. Twenty years later, despite massive efforts to prevent diarrheal mortality with programs of oral rehydration therapy, diarrhea still ranks as the first or second most common cause of death and disability-adjusted life years lost among children in developing countries [2, 3]. An estimated 3–3.2 million children still die each year from diarrhea (23 deaths/1000 live births), making diarrheal disease a major contributor to infant mortality in the developing world. The need for simple, effective, and inexpensive interventions, not only to treat diarrhea but to prevent its occurrence, is urgent and abundantly clear.

The discovery of rotavirus by Bishop and colleagues in 1973 initiated a line of research that has progressed rapidly toward the goal of prevention of rotavirus diarrhea by vaccination [4]. First was the development of simple, sensitive, and inexpensive diagnostic tests that allowed epidemiologists to search for rotavirus in fecal specimens of children with diarrhea [5]. Rotavirus proved to be the most common cause of severe diarrhea, responsible for 20%–70% of hospitalizations for diarrhea among children worldwide [6, 7]. Moreover, diarrhea was traditionally considered to be a disease spread by fecally contaminated food and water or by poor hygiene and, thus, concentrated among children in the developing countries; however, rotavirus is a "democratic" virus that infects nearly all children in the world, rich or poor, by the age of 3–5 years. Clearly, improvements in food, water, or hygiene would have little impact on the control of rotavirus infection. Although early studies documented the tremendous disease burden of rotavirus, little could be done to prevent disease.

The prospect that vaccines might prevent rotavirus in children was appreciated early. Natural immunity was suggested by the concentration of disease among children in the first 2 years of life and the decreased incidence of disease with increasing age [8–11]. Follow-up of infants neonatally infected with rotavirus confirmed that subsequent rotavirus infections were associated with less severe diarrhea. The discovery of methods to propagate rotavirus provided a simple technique to prepare vaccine seed lots by using traditional methods of tissue culture and allowed work with the virus to proceed in the laboratory.

The first rotavirus vaccine was tested by Vesikari et al. [12] in 1983, and the success of these trials laid the groundwork for the current strategy for vaccine development. A single oral dose of a live vaccine prepared from a bovine rotavirus was effective (>80%) in preventing clinically significant rotavirus diarrhea in Finnish infants. This led to a flurry of studies to identify immune proxies for protection, animal models of disease, and ways to increase the efficacy of vaccines among other populations by using the technique of gene segment reassortment. These studies, methods, and results are all well described in this supplement. The outcome has been the successful field testing of several candidate reassortant live rotavirus vaccines.

While reassortant rotavirus vaccines are being prepared for licensure in the United States, many research questions remain. None of these live oral vaccines, like natural immunity itself, is fully protective against rotavirus diarrhea. Hence, the door is open for the development of an improved vaccine that might immunize by a principle different from that of natural infection with a live strain of rotavirus. Many approaches, such as the use of baculovirus-expressed virus-like particles or naked DNA vaccines, are discussed in this volume. Even though much has been learned about immunity to rotavirus, current measures of immunity are not reliable in predicting protection by vaccines, and better measures are urgently needed. Animal models have provided many insights into the pathogenicity and immune mechanisms of rotavirus disease, but their relevance to human disease is uncertain. While much is known about the gene-coding assignments and structure-function relations of the virus, key principles, such as genes encoding virulence, attenuation, or host range, are still being explored [13].

Despite these shortcomings in our understanding of many rotavirus vaccine research issues, progress with live oral "Jennerian" reassortant vaccines may soon lead to the first licensed vaccine. Two field trials of the rhesus reassortant vaccine have been completed, and a trial with a bovine reassortant candidate vaccine has demonstrated similar efficacy [14–16]. The considerations for licensure by the US Food and Drug Administration are reviewed in this supplement, as are the many hurdles that remain to take these vaccines from licensure to widespread use in the United States with the goal of disease reduction.

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The major presentations of the Fifth International Rotavirus Vaccine Workshop are being published with the hope that pediatricians, public health practitioners, and scientists in the United States and abroad will be stimulated to consider how this first vaccine can be used to specifically prevent the disease burden of rotavirus diarrhea. Initial efforts to license and introduce these vaccines have been targeted at children in the United States and other industrialized countries where the disease burden is measured in terms of doctor visits, hospitalizations, parent work time lost, and overall cost [17]. Additional, more dramatic, benefits lie in the prevention of rotavirus deaths among children in developing countries, where more than 2000 deaths occur each day [18]. The ultimate goal of a rotavirus vaccine should be its incorporation into the schedule of routine childhood immunizations promoted by the World Health Organization's Expanded Programme for Immunization. The widespread use of a rotavirus vaccine could go a long way toward achieving the goals of world leaders who declared at the World Summit for Children (New York City, 1990) their desire to effect a "halving of child deaths caused by diarrhea and a one-quarter reduction in the incidence of diarrheal disease by the year 2000" [2]. Our next target must be the prevention of rotavirus diarrhea among children in the developing world.

**References**


1. Rohde JE, Northrup RS. Taking science where the diarrhoea is. In: Ciba Foundation Symposium. Acute diarrhoea in children. Amsterdam: Elsevier, **1976**:339-65.
2. World Bank. World Bank development report 1993: investing in health. New York: Oxford University Press, **1993**.
3. Bern C, Martines J, de Zoysa I, Glass RI. The magnitude of the global problem of diarrhoeal disease: a ten year update. Bull World Health Organ **1992**;70:705-14.
4. Bishop RF, Davidson GP, Holmes IH, Ruck BJ. Virus particles in epithelial cells of duodenal mucosa from children with viral gastroenteritis. Lancet **1973**;1:1281-3.
5. Yolken RH, Kim HW, Clem T, et al. Enzyme-linked immunosorbent assay (ELISA) for detection of human reovirus-like agent of infantile gastroenteritis. Lancet **1977**;2:263-7.
6. Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. Bull World Health Organ **1990**;68:171-7.
7. Kapikian AZ, Chanock RM. Rotaviruses. In: Fields BN, Knipe DM, Howley PM, et al., eds. Fields virology. 3rd ed. Vol 2. Philadelphia: Lippincott-Raven Press, **1996**:1657-708.
8. Bishop RF, Barnes GL, Cipriani E, Lund JS. Clinical immunity after neonatal rotavirus infection: a prospective longitudinal study in young children. N Engl J Med **1983**;309:72-6.
9. Bhan MK, Lew JF, Sazawal S, Das BK, Gentsch JR, Glass RI. Protection conferred by neonatal rotavirus infection against subsequent diarrhea. J Infect Dis **1993**;168:282-7.
10. Velazquez FR, Matson DO, Calva JJ, et al. Natural protection conferred by rotavirus infection: implications for vaccine strategies. N Engl J Med **1996** (in press).
11. Bernstein DI, Sander DS, Smith VE, Schiff GM, Ward RL. Protection from rotavirus reinfection: 2-year prospective study. J Infect Dis **1991**; 164:277-83.
12. Vesikari T, Isolauri E, D'Hondt E. Protection of infants against rotavirus diarrhea by RIT 4237 attenuated bovine rotavirus strain vaccine. Lancet **1984**;1:977-81.
13. Estes M. Rotaviruses and their replication. In: Fields BN, Knipe DM, Howley PM, eds. Fields virology. 3rd ed. Vol 2. Philadelphia: Lippincott-Raven Press, **1996**:1625-55.
14. Bernstein DI, Glass RI, Rodgers G, Davidson BL, Sack DA. Evaluation of rhesus rotavirus monovalent and tetravalent reassortant vaccines in US children. JAMA **1995**;273:1191-6.
15. Clark HF, Offit PA, Ellis RW, et al. The development of multivalent bovine rotavirus (strain WC3) reassortant vaccine for infants. J Infect Dis **1996**;174(suppl 1):S73–80.
16. Rennels MB, Glass RI, Bernstein DI, Pichichero ME, Dennehy PH. Safety and efficacy of high dose rhesus human reassortant rotavirus vaccines—report of the national multicenter trial. Pediatrics **1996**;97:7–13.
17. Smith J, Haddix A, Teutsch S, Glass RI. Cost effectiveness analysis of a rotavirus immunization program for the United States. Pediatrics **1995**; 96:609-15.
18. De Zoysa I, Feachem RV. Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization. Bull WHO **1985**;63:569-83.