

other diarrheal diseases in Africa.<sup>3</sup> Beyond the immediate threat of death lies the menace of the silent, long-term effect of repeated or persistent diarrheal illnesses that impair the physical and cognitive development of impoverished children, who may be robbed of intellectual potential — up to 10 IQ points, according to some estimates — by the lack of safe water and sanitation.<sup>4</sup>

Although it is clear that resources and political will must be mobilized to bring the sanitary and treatment revolutions to sub-Saharan Africa, critical questions remain about cholera prediction, prevention, and response in Africa. We are only beginning to understand the interactive microbial and societal virulence factors that influence the spread of *V. cholerae*. Recently shed vibrios, for example, appear to be substantially more infectious than those that have adapted to their aquatic environment — a finding that highlights the importance of disruptions in water and sanitation. Rising water temperatures, which lead to plankton blooms, may increase the prevalence of vibrios in the natural environment and the risk of epidemic cholera in areas where drinking water is obtained

from untreated surface sources. Vibriophage, on the other hand, may dampen an epidemic and might provide a biologic tool for epidemic control. Inexpensive techniques for household water treatment (including point-of-use chlorination, filtration, and solar disinfection) can prevent cholera and other waterborne diseases but have not been scaled up to reach the hundreds of millions of people who could benefit from them while awaiting access to piped treated water. An oral cholera vaccine is widely marketed, but despite a successful field trial in Mozambique,<sup>5</sup> the number of doses, time required to engender protective immunity, short duration of protection, and cost have limited its usefulness in epidemic response and in the control of endemic disease. A less expensive and simpler single-dose formulation of this vaccine is currently in field trials.

In 2005, the reported incidence of cholera in Africa was 95 times that in Asia and 16,600 times that in Latin America. In 2007, the reported rate of death from cholera in Africa was seven times that in Asia; no cholera-related deaths have been reported in Latin America since 2001.<sup>1</sup> These preventable cases and deaths result from a

lack of essential infrastructure, inadequate health care delivery, and the failure of the global community to muster the political will necessary to extend the benefits of the sanitary and treatment revolutions to all people. The lion is in our human village, and we must do more than sound the alarm.

No potential conflict of interest relevant to this article was reported.

The views presented here are those of the authors and are not necessarily those of the Centers for Disease Control and Prevention.

Dr. Mintz is leader of the Diarrheal Diseases Epidemiology Team, Enteric Diseases Epidemiology Branch, Centers for Disease Control and Prevention, Atlanta. Dr. Guerrant is the director of the Center for Global Health at the University of Virginia School of Medicine, Charlottesville.

1. Gaffga NH, Tauxe RV, Mintz ED. Cholera: a new homeland in Africa? *Am J Trop Med Hyg* 2007;77:705-13.
2. Ram PK, Choi M, Blum LS, Wamae AW, Mintz ED, Bartlett AV. Declines in case management of diarrhoea among children less than five years old. *Bull World Health Organ* 2008;86(3):E-F.
3. Roy SK, Hossain MJ, Khatun W, et al. Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial. *BMJ* 2008;336:266-8.
4. Guerrant RL, Oriá RB, Moore SR, Oriá MOB, Lima AAM. Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutr Rev* 2008;66:487-505.
5. Lucas MES, Deen JL, von Seidlein L, et al. Effectiveness of mass oral cholera vaccination in Beira, Mozambique. *N Engl J Med* 2005;352:757-67.

Copyright © 2009 Massachusetts Medical Society.

## GLOBAL HEALTH

# Rotavirus Vaccines — Early Success, Remaining Questions

Umesh D. Parashar, M.B., B.S., M.P.H., and Roger I. Glass, M.D., Ph.D.

In 2006, the results of pivotal clinical trials of two new rotavirus vaccines — RotaTeq (Merck) and Rotarix (GlaxoSmithKline) — were published, and high efficacy (85 to 98%) against severe rotavirus diarrhea was reported for both products.<sup>1,2</sup> Perhaps even

more important, neither vaccine was associated with intussusception, an adverse effect that had led to the withdrawal of another rotavirus vaccine — RotaShield, made by Wyeth–Lederle — from the U.S. market in 1999. The rapid resurgence of rotavirus vaccines

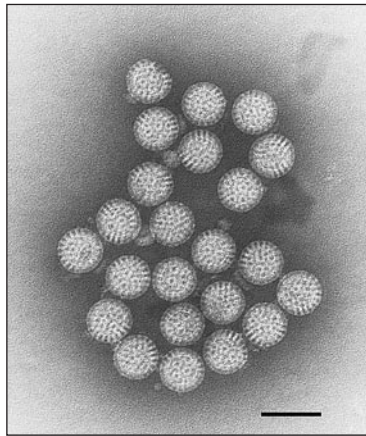
after the abrupt and devastating setback associated with the withdrawal of RotaShield was remarkable, reflecting the commitment of the public health community and the vaccine industry to preventing this most common cause of severe diarrhea in children. In

the United States, rotavirus causes an estimated 3 million cases of diarrhea each year; medical attention is sought for more than 500,000 children, and 60,000 to 70,000 are hospitalized. In the developing world, the disease kills more than half a million children annually. Both vaccines have been recommended for routine immunization of U.S. infants (RotaTeq in February 2006 and Rotarix in June 2008) and have also been introduced in the routine immunization programs of several countries in Latin America and Europe, and in Australia.

In the United States, more than 20 million doses of RotaTeq had been distributed as of June 2008. Although nationally representative data on rotavirus vaccine coverage are not yet available, information from six sentinel sites indicates that median coverage with one dose of rotavirus vaccine among infants 3 months of age has increased steadily since the launch of RotaTeq vaccination and had reached 58% (range, 51 to 68) by December 2007.<sup>3</sup> If these data reflect vaccine uptake nationwide for the rotavirus season from early winter 2007 through spring 2008, an estimated 31% of U.S. children under 2 years of age would have received at least one dose of rotavirus vaccine. The rate of uptake of rotavirus vaccines among U.S. children appears to be similar to that of other recently introduced childhood vaccines (e.g., pneumococcal conjugate vaccine and varicella vaccine), allaying concerns about the potentially negative effect the adverse experience with RotaShield could have had on the use of new rotavirus vaccines.

Despite the fairly modest estimated rotavirus vaccine coverage among U.S. children, several surveillance reports presented at the

annual joint meeting of the Infectious Diseases Society of America and the Interscience Conference on Antimicrobial Agents and Chemotherapy in October 2008 ([www.icaacidsa2008.org](http://www.icaacidsa2008.org)) show remarkable changes in U.S. rotavirus activity in 2008. For example, data from a national network of sentinel laboratories showed that



**Negative-Stain Electron Micrograph of Rotavirus A.**

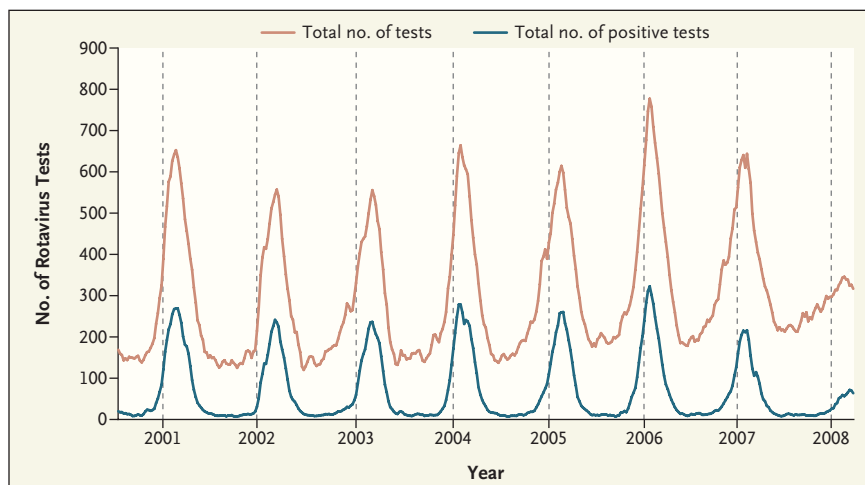
The virus is 70 to 75 nm in diameter and has three protein layers, two of which are visible, which is typical of rotavirus. This specimen was stained with 2% methylamine tungstate. The bar represents 100 nm.

the onset and peak of the 2008 rotavirus season were delayed by 15 weeks and 8 weeks, respectively, as compared with the six consecutive seasons preceding the introduction of the first new vaccine (see graph).<sup>4</sup> Furthermore, in 2008, the number of positive rotavirus tests decreased by 67% as compared with 2000 through 2006, and the proportion of all rotavirus tests performed in 2008 that were positive was 69% lower than the median proportion during the rotavirus seasons from 2000 through 2006. The observed change in rotavirus activity appears to be greater than what would have been expected on the basis of estimated vaccine coverage; this change has also been noted among children

over the age of 3 years, who would have been too old to be eligible for vaccination in 2007 and 2008. These findings suggest that vaccination of a proportion of the population could be conferring indirect benefits on unvaccinated persons, thanks to reduced viral transmission in the community (i.e., herd immunity), a hypothesis that needs to be further evaluated as additional data are gathered.

Although the clinical trial data on safety with respect to intussusception were reassuring, post-licensure monitoring for this potential adverse event is ongoing in the United States and other countries that are routinely vaccinating against rotavirus. Available data from 2 years of monitoring in the United States do not indicate that RotaTeq is associated with intussusception.<sup>5</sup> An intussusception risk similar in magnitude to that of RotaShield can be ruled out on the basis of the safety data available to date; however, continued monitoring is necessary for complete assessment of the safety profile of RotaTeq and to assess the safety of Rotarix in clinical use.

Because the risk of intussusception with RotaShield might have been greater among infants vaccinated after 3 months of age and because there is a lack of safety data on new rotavirus vaccines in older infants, current guidelines recommend against initiating rotavirus vaccination after 14 weeks of age. A high level of compliance with this recommendation has been observed in the United States, with 86 to 93% of first doses being administered between 6 and 12 weeks of age.<sup>3</sup> These stringent age restrictions, however, have the potential to result in major reductions in vaccine coverage in developing countries, where delays in the timing of vaccination are com-



**Total Number of Rotavirus Tests and Number of Positive Test Results from 32 Continuously Reporting U.S. Laboratories, July 2, 2000–May 3, 2008.**

Data are from the U.S. National Respiratory and Enteric Viruses Surveillance System, Centers for Disease Control and Prevention.

mon and exact age is not accurately recorded — an issue that will need to be considered in formulating policy for vaccine use in these settings.

Despite the promising early data from the United States, a key unanswered question is whether rotavirus vaccines will work equally well in the developing world, where they offer the greatest potential lifesaving benefits. Experience with previous candidate rotavirus vaccines, as well as vaccines against polio, cholera, and typhoid fever, has shown that the efficacy of live, oral vaccines can be impaired in developing countries. Several host and environmental factors — such as interference by maternal antibodies, concurrent administration of oral polio vaccine, prevalent viral and bacterial infections of the gut, and malnutrition — could affect the processing of vaccine in the infant gut and impair an infant's ability to generate an effective immune response. For these reasons, the World Health Organization (WHO) has recommended evaluation of the efficacy of rotavirus

vaccines in developing countries of Asia and Africa before issuing a recommendation for global vaccine use. Both RotaTeq and Rotarix are being tested in these regions, and the results of these trials are eagerly anticipated.

If rotavirus vaccines demonstrate acceptable efficacy in developing countries and the WHO issues a global recommendation for their use, mechanisms for financing the introduction of the vaccines and securing a sustainable and affordable supply will be key to ensuring that they reach children in the poorest countries, where the vast majority of deaths from rotavirus occur. The Global Alliance for Vaccines and Immunization (GAVI) has already approved financial support for the purchase of rotavirus vaccines for eligible countries (those with a gross national income of less than \$1,000 per capita) in Latin America and Europe, where vaccine efficacy has been proven, with a copayment for countries of 15 to 30 cents for a full vaccine series for each child. GAVI will decide whether to provide financial sup-

port for the purchase of rotavirus vaccine for countries in Asia and Africa after data from trials in these areas become available.

With financial support and recommendations from the WHO and other international health organizations, the long wait for safe and effective vaccines to prevent deaths and severe disease from rotavirus diarrhea among children in the developing world may soon be over. In countries where these vaccines are currently being used as part of childhood immunization programs, their benefits are becoming readily apparent. In the United States, with increasing uptake of vaccine, we anticipate significant respite for children, parents, physicians, and health care facilities from the large burden of rotavirus disease in the current rotavirus season.

No potential conflict of interest relevant to this article was reported.

The views expressed in this article are those of the authors and do not necessarily represent those of Centers for Disease Control and Prevention.

Dr. Parashar leads the Viral Gastroenteritis Epidemiology Team in the Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta. Dr. Glass is the director of the Fogarty International Center, National Institutes of Health, Bethesda, MD.

1. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11-22.
2. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23-33.
3. Rotavirus vaccination coverage and adherence to the Advisory Committee on Immunization Practices (ACIP)-recommended vaccination schedule — United States, February 2006–May 2007. *MMWR Morb Mortal Wkly Rep* 2008;57:398-401.
4. Delayed onset and diminished magnitude of rotavirus activity — United States, November 2007–May 2008. *MMWR Morb Mortal Wkly Rep* 2008;57:697-700.
5. Haber P, Patel MM, Izurieta HS, et al. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. *Pediatrics* 2008;121:1206-12.

Copyright © 2009 Massachusetts Medical Society.