

# Rotavirus Vaccines

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**Abstract.** Rotavirus is the leading cause of severe childhood gastroenteritis in both developed and developing countries and results in over half a million deaths each year, with over 120,000 deaths occurring annually in India.

Rotaviruses are classified based on the proteins that make up the three layers of the virus and Group A rotaviruses are most important for human health. Human rotaviruses of VP7 genotypes G1-4, G9 and G12 and VP4 P genotypes P[4], P[6] and P[8] are predominant worldwide.

Currently two Rotaviruses vaccines (Rotarix<sup>®</sup>, GSK Biologicals and Rotateq<sup>™</sup>, Merck Research Laboratories), are licensed in many countries in the world, and in routine use in several national immunization programs. Other candidate vaccines are under development in India and other countries. Vaccines were licensed based on large trials conducted in several countries in Europe and America, which showed high efficacy against the common circulating rotavirus types. Recent data from developing countries indicates that vaccine efficacy is lower than seen in Europe and America, but still has a substantial public health impact. Based on these data, the World Health Organization has recommended that all national immunization program should adopt these vaccines, but considerations of cost and supply are important factors in determining more widespread use.

Safe and effective vaccines are available and in development against this major cause of childhood morbidity and mortality, but their deployment in national immunization programs requires an evaluation of disease burden, cost-effectiveness and programmatic issues of delivery.

**Key words :** Rotavirus; Vaccine; Immunization; Viral gastroenteritis; India

## Introduction

The discovery of human rotavirus in 1973 was key to understanding the viral etiology of winter diarrhea among young children in industrialized countries. Rotaviruses are now known to be the primary etiological agents of severe gastroenteritis in children less than 5 yrs of age, estimated to be the cause of nearly 40% of hospitalizations for acute gastroenteritis.<sup>1</sup> The incidence of rotavirus disease has been observed to be similar in both industrialized and developing countries, suggesting that although improvements in hygiene do delay the age of infection, viral gastroenteritis continues to occur in settings with good water supply, hygiene, and sanitation - therefore suggesting that controlling the disease burden would require other interventions.<sup>2</sup> Treatment of rotavirus illness is limited to supportive measures, such as oral or intravenous rehydration, and the only specific method to combat rotavirus disease is vaccination.

## Rotavirus Disease and Burden

Rotavirus infection is transmitted mainly by the fecal-oral route and contact and has a short incubation period of

between 1-3 days. Rotavirus disease is characterized by sudden onset of acute watery diarrhea, often accompanied by fever and vomiting.<sup>3</sup> The virus infects and replicates almost exclusively in the mature enterocytes at the tips of the intestinal villi. It is believed that destruction of the villi, with resultant loss of absorptive capacity of sodium, glucose and water is associated with gastro-intestinal symptoms of the infection. Rotavirus infection is often accompanied by serious fluid and electrolyte loss with dehydration, especially in infants.<sup>4</sup>

Rotavirus is the most common cause of severe diarrhea disease in infants and young children worldwide. Over 500,000 children die every year from rotavirus, mainly in developing countries, and this figure represents about 5% of all deaths in children younger than 5 yrs.<sup>5</sup> Mortality is greatest in South Asia and sub-Saharan Africa - approximately 120,000 or more children die of rotavirus disease in India alone.<sup>6,7</sup> Virtually all children worldwide have been infected by the time they reach 2-3 yrs of age. Most symptomatic episodes occur between 3 months and 2 yrs of age with a peak incidence between 7 and 15 months.

## Rotavirus Strain Diversity

Rotaviruses are triple layered particles, with the middle coat protein VP6 determining the group, and the outer coat proteins VP7 (G-) and VP4 (P-) responsible for the

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further classification into geno-/serotypes. Human rotaviruses are mainly group A and VP7 genotypes G1-4, G9 and G12 and VP4 P genotypes P[4], P[6] and P[8] are the common strains seen worldwide. G9 strains emerged during the 1990s, and in the past decade, G12 strains have been identified in many parts of the world.<sup>8</sup> Other strains, such as G8 and G5 are seen in Africa and South America with occasional reports from other parts of the world. Similarly, the distribution of the VP4 or P-type strains is different according to regions: P[6] strains are seen in some parts of Asia and Africa, whereas P[8] and P[4] are associated with most rotavirus strains from the rest of the world.<sup>9</sup>

### Rotavirus Strains in India

Until 2001, data from published epidemiological studies from 18 Indian cities showed that about 20% of hospitalizations for acute gastroenteritis were associated with rotavirus and G1 was the single most common G type identified in all parts of India, except for western India.<sup>6</sup> Data from a surveillance network run by the Indian Council for Medical Research from 2005 to 2008, showed that more recently, the proportion of gastroenteritis hospitalizations associated with rotavirus is 39% and that the most common strains are G2P [4] (25.7%), G1P [8] (22.1%), and G9P [8] (8.5%). G12 strains were seen in combination with P[4], P[6] and P[8] and together made up 6.5% of strains.<sup>10</sup> In addition to these common strains, human infections with strains G3P[3], G6, G8, G10P[11], G11P[25] and G9P[19], which may occur as a result of zoonotic transmission of bovine and porcine rotaviruses, were reported from western, southern, and eastern India.

### Rotavirus Vaccines

All currently licensed rotavirus vaccines are live, orally administered vaccines that aim to mimic the protection given by naturally occurring rotavirus infection. Attenuation of rotaviruses for use as oral vaccines may be achieved in several ways. The most extensively evaluated approach is based on the "Jennerian" concept, involving immunization of infants with animal or modified animal-human rotaviruses that are considered attenuated for humans. More recently, rotaviruses obtained from children, attenuated by passage in cell culture, have been developed and tested. Finally, rotaviruses recovered from asymptomatic neonates that are animal-human reassortants and considered naturally less virulent are being developed as oral vaccine candidates.

### Monovalent Animal Rotavirus Vaccines

Research to develop a safe, effective rotavirus vaccine began in the mid-1970s when investigators demonstrated

that previous infection with animal rotavirus strains protected laboratory animals from experimental infection with human rotaviruses. Three non-human rotavirus vaccines, two bovine rotavirus strains, RIT 4237 (P[1]G6) and WC3 (P[5]G6) and simian (rhesus) RRV strain (P[3]G3), were studied.<sup>11</sup> These vaccines demonstrated variable efficacy in field trials and gave disappointing results in developing countries. Currently, a lamb-derived monovalent (P[12]G10) live-attenuated oral vaccine developed by the Lanzhou Institute of Biomedical Products, is licensed and used in China, although it is not in the national immunization program. The efficacy of this vaccine is not known as it was not tested against a placebo in a controlled phase III trial.<sup>12</sup>

The early studies with monovalent animal rotavirus based vaccines gave inconsistent results, so further vaccine development efforts began to use either naturally attenuated human rotavirus strains or reassortant rotavirus strains bearing a human rotavirus gene for the VP7 protein together with the other genes from an animal rotavirus strain.

### Early Licensed Rotavirus Vaccines

The next generation of vaccines was formulated to include more than one rotavirus G serotype to provide homotypic and heterotypic immunity. The ability of rotaviruses to reassort or mix to produce progeny viruses that differ from the parent strains during mixed infections *in vivo* allowed the production of reassortant vaccines, termed the "modified Jennerian" approach. Both VP4 and VP7 which are neutralization antigens were thought to be important in protection; therefore, human-animal reassortant rotaviruses for use as vaccines include either human VP7 or VP4 genes to provide protective immune responses.<sup>11</sup> The first multivalent live oral reassortant vaccine developed, RRV-TV, contained a mixture of five virus strains representing G types G1 to G4. This vaccine was evaluated in field trials and proved highly effective (80-100%) in preventing severe diarrhea due to rotavirus. After this vaccine was included in the immunization schedule in USA and over 600,000 infants immunized, cases of vaccine-associated intussusception were reported. The period of greatest risk of intussusception was shown to be 3-10 days after the first of three oral doses.<sup>13</sup> The manufacturer withdrew the vaccine from the US market and although still licensed, the vaccine has not been tested since then.

### Currently Licensed Rotavirus Vaccines

A pentavalent human-bovine (WC3) reassortant (G1, G3, G4 and P[8]) live-attenuated, oral vaccine, RotaTeq

has been developed by Merck Research Laboratories.<sup>14</sup> RotaTeq™ is administered in three doses at 1-2 month intervals beginning at 6-12 wks of age. This pentavalent vaccine (PRV) was tested in trials involving 70,000 children in 11 countries, with the United States and Finland accounting for more than 80% of all enrolled subjects. There was no evidence of an increased risk of intussusception and the efficacy against rotavirus gastroenteritis of any severity was 74% and against severe rotavirus gastroenteritis, efficacy was 98%.<sup>15</sup> RotaTeq™ was licensed in February 2006 by the US Food and Drug Administration (FDA) for use among US infants and is routinely recommended as a three dose schedule at 2, 4 and 6 months of age.<sup>16</sup> It is now licensed in over 80 countries.

A live, attenuated human rotavirus G1P[8] vaccine (strain 89-12) was originally developed by tissue culture passage of a rotavirus isolate from an infant.<sup>17</sup> This vaccine, given as two doses at 1-2 month intervals, was taken up for further development by GlaxoSmithKline Biologicals and tested in 60,000 children in Europe and South America. It was safe, with no association with intussusception and gave 96% protection against severe rotaviral gastroenteritis.<sup>18</sup> Rotarix® is licensed in over 100 countries. There is one published report of immunogenicity from India, where 182 infants received vaccine and 181 received placebo at 8 and 12 wks of age and seroconversion was seen in 58% of vaccines and 6% of placebo recipients. Interestingly, 27% of infants had IgA antibodies at 8 wks of age, indicating high levels of early exposure.<sup>19</sup>

#### **Testing of Licensed Vaccines in Developing Countries**

In recently published data, a trial with Rotarix® reported a pooled efficacy of 61.2% from South Africa (76.9%) and Malawi (49.4%).<sup>20</sup> Despite the lower efficacy in Malawi, which was similar to that seen in early vaccine trials with monovalent animal strains, the vaccine prevented many more severe rotavirus gastroenteritis episodes compared to South Africa or other settings where the vaccine has been evaluated because the background rates of severe gastroenteritis were much higher. Data presented and recently published for Rotateq™ from trials conducted in Africa and Asia<sup>21</sup> show that results for this multivalent vaccine are similar to those with Rotarix®, with both vaccines demonstrating reduced vaccine efficacy (50-60%) against severe gastroenteritis in developing countries, but with a high public health impact because of the high burden of disease in these regions. Another important finding of the Rotarix® study was that there was a 30% decrease in severe all-cause gastroenteritis.<sup>20</sup> Similar

findings have been reported in other studies, suggesting that the available tests for detecting rotavirus are missing some cases, and efficacy may therefore be higher than reported in these trials.

#### **Vaccines under Development in India**

Indian vaccine manufacturers are in the process of developing two categories of vaccines: a human neonatal strain, and human-bovine reassortant strains.

Bharat Biotech International Ltd is developing an oral rotavirus vaccine using 116E, a human neonatal, naturally reassorted and 'asymptomatic' strain of Indian origin. This strain has been evaluated in phase I and II studies, and immunogenicity with this strain in Indian infants is much higher than has been reported with Rotarix®, when also tested in Indian infants.<sup>22,23</sup> The 116E vaccine candidate is now entering phase III trials. Serum Institute of India Ltd, Shantha Biotechnics Ltd and Biological E Ltd are developing vaccines based on the UK bovine strain, which has been licensed from the National Institutes of Health,<sup>24</sup> and is a bovine-human Reassortant, which will resemble Rotashield™. These candidates are currently in early phase trials.

#### **Effect of Vaccination on Diarrhea**

Rotavirus vaccines were licensed and introduced into national programs in some parts of the world in 2006, and data are just emerging on the impact of vaccination on morbidity and mortality. A study from Mexico published in 2010 suggests that the introduction of rotavirus vaccine resulted in substantial reduction in rotavirus deaths.<sup>25</sup> Mexico has a very seasonal pattern of rotavirus and a well-established surveillance system and this may have aided in the investigators in the difficult task of clearly documenting the decrease in mortality over several seasons.

Nationally representative data on morbidity are available from the US, where hospitalization rates for acute gastroenteritis for children under 5 yrs of age, showed a reduction of 28-50% for different age strata in 2007 and 2008 when compared to 2000-2006.<sup>26,27</sup> Similar reductions have been reported from Israel, Australia and other high income countries.<sup>28,29</sup> Because the changes in rotavirus activity appear more pronounced than might be attributed to direct protective effects of vaccination alone, these results suggest that vaccination of a proportion of the population might offer indirect benefits to unvaccinated children (*i.e.*, herd protection) by reducing transmission of rotavirus in the community.<sup>30</sup>

### Global Recommendations for Rotavirus Vaccines

Rotavirus vaccines were introduced into national immunization programs rapidly following licensure. In 2005, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization recommended the introduction of these vaccines in Europe, the United States, and Latin America, on the basis of results of phase III clinical trials. However, SAGE withheld a global recommendation until clinical trials could show satisfactory efficacy in Africa and Asia. Based on the clinical trials of Rotarix® completed in 2008, in June 2009, SAGE recommended that all countries include infant rotavirus vaccination in their national immunization programs.<sup>31</sup> It has recently been estimated that with 70% coverage in the 72 countries eligible for funding by the GAVI Alliance, vaccinating one single birth cohort would prevent about 55% of rotavirus associated deaths. Using the WHO's cost-effectiveness threshold of per-capita GDP, the vaccines would be cost-effective in 94% of GAVI eligible countries at a cost of 25 international dollars for each immunized child.<sup>32</sup> However, in countries with large birth cohorts as in India, there are many factors which determine the ability of a national health care system to deploy a new vaccine.

### Conclusions

Data from countries that have introduced the rotavirus vaccine into national immunization programs are exciting and encouraging. However, in developing countries, differences in age of first infection, strain distribution, occurrence of mixed infections, seasonality and risk of mortality can affect decisions about vaccine composition and delivery. Higher doses of vaccine or additional doses may be required to overcome the inhibitory effects of competing intestinal flora, and high levels of humorally transferred maternal and breast-milk antibodies against rotavirus.<sup>33</sup> In summary, vaccines are effective in developed countries and appear to have delayed and decreased disease, but they are somewhat less effective in developing countries. Nonetheless, given the high public health impact, their use for individual children and communities should be considered immediately, in parallel with research to enhance immunogenicity and efficacy of existing vaccines and develop new, low-cost effective vaccines.

**Conflict of Interest :** None.

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