

Rotavirus vaccine — a new hope

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Abstract

Diarrhoea due to Rotavirus is the leading cause of mortality among children less than 5 years of age in developing countries. Though Rotavirus vaccine has been approved by FDA since 2006 it has not been incorporated in the EPI schedule of Pakistan. Objective of our study was to explore the clinical efficacy, cost effectiveness and safety of Rotavirus vaccine in infants and children against diarrhoea caused by Rotavirus. Online search yielded a total of 103 articles out of which 31 articles were included for perusal. Newly-developed vaccines have been found to have combined efficacy of 61.2-64.6% in African Countries and 82.1-84.7% in Europe and Latin America against Rotavirus-induced diarrhoea. Rotavirus vaccine is a very effective option in terms of efficacy, cost and safety against viral diarrhoea caused by Rotavirus. Consideration should be given to include this vaccine in EPI programme of developing countries.

Keywords: Diarrhoea, Infant mortality, Rotavirus vaccine, Safety.

Introduction

Rotavirus is the leading cause of gastroenteritis all over the world.¹ According to the World Health Organisation (WHO), diarrhoea has the third highest mortality amongst infectious diseases. Most of these deaths occur in children under 5 years of age.¹⁻³ There have been increased number of hospitalisations associated with gastroenteritis and there are proportionate escalation in cases of nosocomial infection and ultimately morbidity and mortality.^{4,5} Generally, gastroenteritis is not as debilitating and severe in developed countries but limited access to health facilities and malnutrition makes it a fatal disease in many infants of the developing world, including Pakistan.⁶

Not only does diarrhoea affect general health, but it also has social repercussions. Hospital admissions lead to

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increased number of days of work lost by parents and caregivers. Healthcare costs toll and divert available resources in the management and prevention of infectious diseases. Morbidity and mortality is emotionally draining, especially if preventive measures could have halted the progression to severe, full-blown disease. The multifaceted impact of gastroenteritis, particularly in developing countries, undeniably has a health, economic and social burden and draws attention to measures which reduce the severity and incidence of disease.⁷ Rotavirus vaccine is a great tool to combat against this kind of life-threatening infectious disease (Figure-1).

Material and Methods

A narrative clinical review was carried out to assess the efficacy and safety of Rotavirus vaccine. Online articles with free access on Rotavirus were searched on Medline, Cochrane and Google Scholar. Key words used to search articles on the topic were "Rotavirus", "Epidemiology of viral diarrhoea", "Mortality associated with Rotavirus-Induced Diarrhoea", "Prevalence of diarrhoea caused by Rotavirus", "Incidence of diarrhoea caused by Rotavirus vaccine", "Symptomatology of Viral Diarrhoea", "Rotavirus Vaccine", "RotaTeq", "Rotatrix" and "Efficacy of Rotavirus vaccine". Articles from 1995 to 2014 were included. Articles were filtered further and only those addressing safety and efficacy of Rotavirus vaccine were reviewed in detail. We included all diverse studies even if they routed to a single pivotal study. Search results had yielded a total of 97 articles, out of which 31(32%) were selected. Articles were reviewed from October 2013 to April 2014.

What is Rotavirus?

Rotavirus is a part of the Reoviridae family of viruses. Almost every child has at least one Rotavirus infection before the age of 5, making it the most common cause of gastroenteritis in children. The infection can be asymptomatic or symptomatic. The two main symptoms of viral gastroenteritis are diarrhoea and vomiting. Diarrhoea is watery in consistency, copious in amount and foul-smelling. It may contain mucous though it is non-inflammatory and non-bloody; routine examination of stool does not reveal leukocytes. Vomiting occurs early in the course of infection. Other symptoms include low

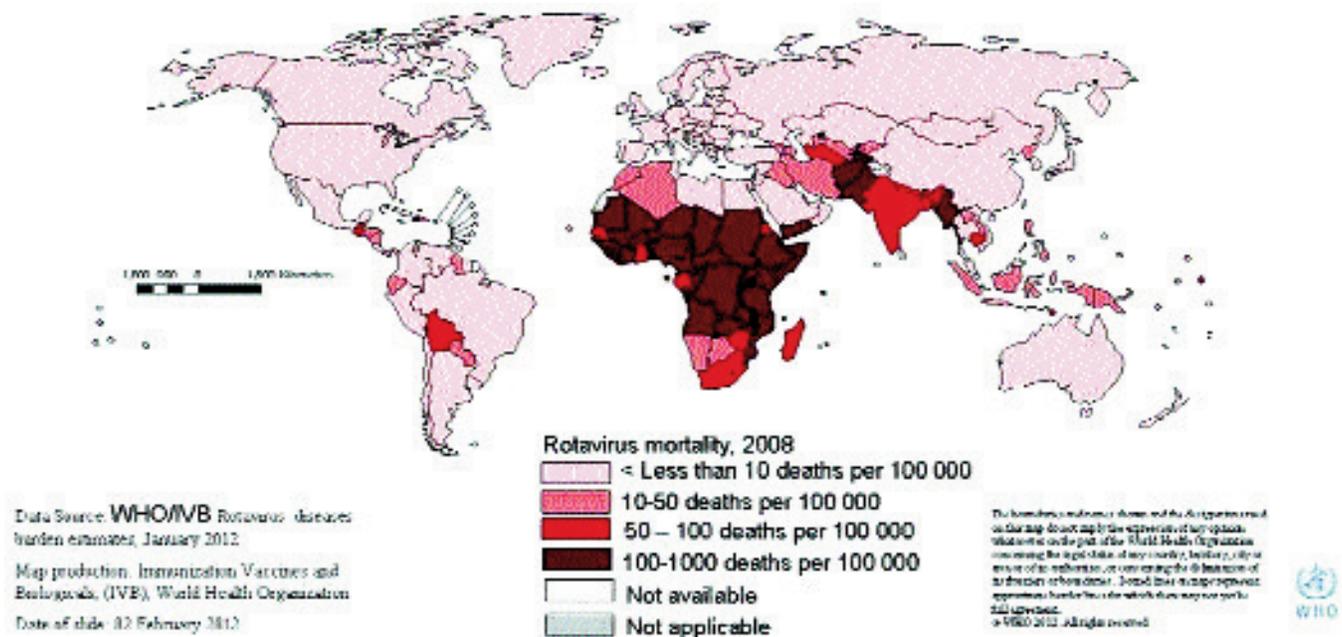


Figure-1: Rotavirus mortality in children younger than 5 years, 2008.

grade fever, occasional headache, chills, poor feeding, abdominal cramps and pain. There is associated malabsorption.

Is There Any Role Of Cleaning Water In Preventing Viral Diarrhoea?

In developing countries, purification of water is imperative in controlling and limiting the spread of several infectious diseases. Improvement in sanitation and hygiene has been found to significantly decrease the incidence of diarrhoea of bacterial origin but viral diarrhoea, by and large, is unaffected by it.^{4,7} Though the role of sanitation and improvement in hygiene cannot be underplayed, there has not been a marked decrease in the number of hospital admissions due to viral gastroenteritis despite good hygiene.

After analysing the epidemiological trends of Rotavirus disease, the use of a vaccine presents as an effective measure to reduce the burden of gastroenteritis. Vaccination is the prime element of primary level healthcare and introduction of routine Rotavirus vaccine can markedly decrease the number of hospital admissions, which are otherwise unaffected by sanitation and hygiene.

What is RotaShield?

RotaShield was introduced in 1998. It was the first vaccine against Rotavirus marketed publicly. Because of Intestinal

intussusception, the Centre for Disease Control (CDC) withdrew the vaccine from the market in October 1999.^{8,9}

What Are The New Vaccines Against Rotavirus?

Currently there are two live, orally-administered Rotavirus vaccines: Rotarix and RotaTeq.¹⁰ Both the vaccines showed excellent safety and efficacy profile in studies conducted so far.¹¹⁻¹³ After the introduction of the vaccines, there has been a marked reduction in the incidence of viral diarrhoea especially in Europe, Australia and the USA. The Rotavirus vaccine has been approved and licensed in more than 100 countries all over the world. A global recommendation for the vaccine and emphasis on the economic and social impact of the disease can lead to a swift introduction of the vaccine. Therefore, the WHO is now recommending the inclusion of Rotavirus vaccine in the EPI schedule globally.

RotaTeq

RotaTeq was approved by FDA in 2006. It contains five live human-bovine re-assortment strains of Rotavirus, which are G1, G2, G3, G4 and P1A,⁸ serotype.¹⁴ Three oral doses are required for effective vaccination, starting with first dose at 6-12 weeks of age, second dose with an interval of 4-10 weeks, and the third dose within 32 weeks.

The vaccine causes an increase in the serum anti-Rotavirus immunoglobulin A (anti-RV-IgA) titer. It is also

shed in the faeces after the first dose of vaccine in 13% of the infants. No faecal shedding was observed after dose 2 and 3. The vaccine is contraindicated for individuals who have a history of hypersensitivity to the vaccine, intussusception or Severe Combined Immunodeficiency Disease (SCID).^{14,15} Immunosuppressive therapies may reduce the immune response to vaccines.¹⁴ Transmission of vaccine virus strains from vaccinees to non-vaccinated contacts has been observed.¹⁶

Data from Phase III clinical trials came from three major placebo-controlled studies spread across 11 countries and including nearly 70,000 infants. One of these studies was the Rotavirus Efficacy and Safety Trial (REST). The study evaluated the protective effect of the vaccine on the basis of rotavirus-related hospitalisations and emergency department (ED) visits in the first year after vaccination as well as the risk of intussusception. REST concluded that RotaTeq vaccine was able to reduce the severity of Rotavirus-associated disease by 74% after successful completion of the three-dose regimen; its efficacy against severe disease was 98%. There was a marked drop in the rates of hospitalisations, emergency visits and office visits.

Adverse effects, particularly intussusception, were evaluated 42 days after the administration of each dose of the vaccine. The study reported six cases of intussusception in the Rotateq group compared to five in the placebo group. Also, none of the cases of intussusception occurred in the 42 days after administration of the vaccine, which was considered to be a high-risk period for the development of intussusception based on the studies of the previously licensed Rotavirus vaccine. The results showed that RotaTeq was not associated with intussusception and it was concluded that the risk of intussusception was similar in vaccine and placebo recipients.¹²

A continuation of REST was carried out in Finland where Finnish participants were observed in the second year of their life and beyond. This study, named Finnish Extension Study (FES), included over 23,000 infants. It reported 150 (31%) more cases of Rotavirus gastroenteritis in Finnish participants beyond REST. There was a decrease in the hospitalisations and hospital visits due to Rotavirus gastroenteritis by 93.8%. This effect lasted till 3.1 years after the last dose of the vaccine. The efficacy of the vaccine against both hospitalisations and ED visits between ages 4 months and 11 months, 12 months and 23 months, and 24 months and 35 months was 93.9%, 94.4% and 85.9% respectively. There was a decrease to 62.4% in the number of hospitalisations and ED visits due

to any cause of acute gastroenteritis.¹⁷

According to phase III clinical trials, serious adverse effects were noted in 2.4% infants who had received RotaTeq compared to 2.6% of placebo recipients during the 42 days after administration of placebo/vaccine. These clinical studies also concluded that there was no increased risk of developing intussusception. Most common adverse effects reported were diarrhoea, vomiting, irritability, otitis media, nasopharyngitis and bronchospasm. The vaccine was also observed to cause Kawasaki disease.¹⁴

After the licensure and introduction of RotaTeq, Post-licensure Rapid Immunization Safety Monitoring (PRISM) programme was responsible for evaluating the incidence of adverse effects of vaccination, since it is an effective vaccine safety system in the US which works to evaluate health outcomes after delivery of vaccines to the target population. The programme had followed up 1.2 million vaccine recipients in temporal association 21 days after vaccine administration. The final report of the Mini-Sentinel PRISM study, released in June 2013, documented an increased risk of intussusception after administration of the first dose, with clustering of cases in the first 7 days after the dose. There was no increased risk after the administration of the second and third doses. The results of the Mini-Sentinel Study translated into 1-1.5 more cases of intussusception per 100,000 after the first dose of RotaTeq.¹⁸

Rotarix

Rotarix was approved in 2008 and has been licensed in 123 countries as of September 2011. It has been incorporated in the National or Regional Vaccination programme of 27 countries. It is a live-attenuated monovalent G1 [P8] human Rotavirus vaccine derived from a human strain.^{19,20} It is approved for use in infants aged 6 to 24 weeks. Two doses of this vaccine are given orally. First dose can be given to infants after 6 weeks of age and the subsequent dose is given after an interval of at least 4 weeks.

It is contraindicated in individuals who have a history of hypersensitivity to the vaccine, uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception and SCID.¹⁹ Common adverse effects of this vaccine are cough, runny nose, vomiting, loss of appetite, irritability and fever. Kawasaki disease and intussusception rarely result from it.^{19,20} A case-control study carried out in 7 hospitals in El Salvador reported that the vaccine did not cause side effects in excess of the control group. However, there were reports of faecal shedding of the virus. This was diagnosed on

enzyme-linked immunosorbent assay (ELISA) and 60-80% of the infants were documented to shed the virus after the first, and some after the second dose of the vaccine. This poses an increased risk of vertical transmission to contacts who are not vaccinated.

Post-licensure studies conducted in Mexico evaluated the adverse effects of the vaccine with intussusception being the prime focus. One study was done by the company which manufactured the vaccine. The results of the study showed a 1.7 fold increase in the risk of intussusception 0-30 days after the administration of the vaccine with majority of the cases clustering in the first week. No intussusception cases were reported within 31 days post-vaccination in a randomised double-blinded study done in Asia.²¹

A randomised, double-blinded, placebo-controlled phase III study conducted in 10 Latin American countries included more than 15,183 healthy infants aged 6-13 weeks. Two oral doses of the vaccine were delivered and the participants were followed up for two years. There were fewer cases of severe gastroenteritis in infants who were vaccinated, and the efficacy of the vaccine against severe Rotavirus hospital admissions was reported to be 83%. The same trial had evaluated rates of intussusception in recipients and non-vaccinees and reported that there was no case of intussusception reported till two years after vaccination.²²

Are New Vaccines Effective?

A randomised, placebo-controlled, multi-centre trial in South Africa reported that vaccination with the Rotavirus vaccine prevented 5 episodes of severe Rotavirus gastroenteritis per 100 infant-years. The overall efficacy of the Rotavirus vaccine in preventing episodes of severe Rotavirus gastroenteritis was shown to be 61.2%.²³ This is comparatively lower than 84.7% observed in one of the largest randomised trials conducted on Rotavirus vaccines.¹¹ This difference between developed and developing countries can be due to malnutrition, faulty storage, vaccine contamination, lack of proper orientation of stuff, level of anti-Rotavirus antibodies in breast milk and enteric co-infections.

In a cohort study done in Philadelphia, Pennsylvania, it was proven that RotaTaq-immunised children have fewer episodes of acute gastroenteritis compared to non-immunised children. In a randomised double-blinded control study done in high income countries of Asia, Rotavirus vaccine (Rotarix) showed an efficacy of 96.1% against severe gastroenteritis.²¹ In a randomised, double-blinded, placebo-controlled phase III study in 10 Latin American countries Rotavirus vaccine efficacy was found

to be 82.1% against wild-type G1. The vaccine efficacy for hospital admission for Rotavirus gastroenteritis was shown to be 83.0%.²²

Various other studies done in Africa, Latin America, Asia and Europe proved that Rotavirus vaccine was very effective against severe Rotavirus gastroenteritis which occurred during the first 2 years of life.^{24,25} Rotavirus vaccine significantly reduced the infant mortality rate (IMR) in Sudan (Figure-2) while no significant decrease in IMR was seen in Ethiopia where Rotavirus vaccine was not introduced (Figure-3). According to another study, vaccination in Global Alliance for Vaccines and Immunisation (GAVI)-eligible countries would prevent 2.46 million childhood deaths and 83 million disability-adjusted life years (DALYs) from 2011 to 2030, with annual reductions of 180,000 childhood deaths at peak vaccine uptake.²⁶

Post-licensure studies of RotaTaq and Rotarix found evidence of porcine circoviruses (PCV) type 1 in Rotarix vaccines. However, there is no evidence of PCV disease in humans. Moreover, clinical trials did not detect PCV in the serum of vaccinated infants. It was suspected that PCV came from the growth of Rotavirus in vitro. After advisory meetings and evaluation of the available evidence, the FDA

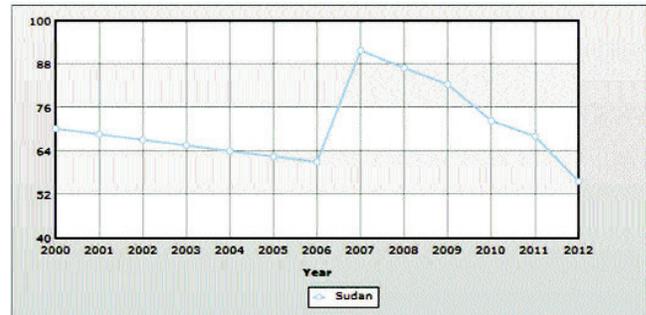


Figure-2: Infantile Mortality Rate in Sudan (Arrow shows the point at which Rotavirus vaccine was first Introduced in Sudan) (From Indexmundi.com).

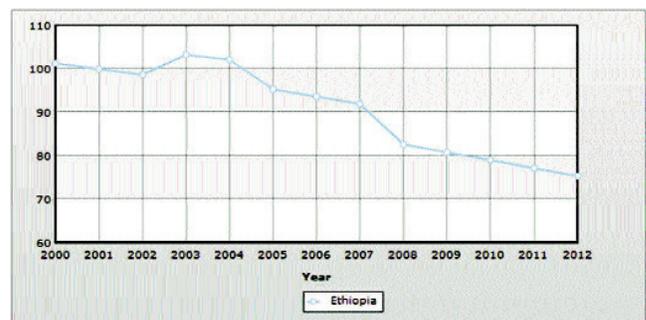


Figure-3: Infantile Mortality Rate in Ethiopia (From Indexmundi.com).

has approved both RotaTaq and Rotarix for use in the US.

A review of the use of Rotateq in Europe documents the benefits and efficacy of the vaccine in reducing the burden of Rotavirus gastroenteritis in the age group where the risk of Rotavirus gastroenteritis is the highest. It has effectively been able to reduce ED visits and hospitalisations and has early protective efficacy after the first and second doses.²⁷ Moreover, it is tolerated well orally. Both Rotateq and Rotarix can be administered concomitantly with other vaccines. According to the Centre for Disease Control and Prevention,²⁸ an increased risk of intussusception has not been reported by all studies conducted on the safety and efficacy of the vaccines. Analysis of the results of the studies which report an increased risk of intussusception yields that 40 to 120 vaccinated infants in the US may develop intussusception each year.²⁸

However, the CDC asserts that the benefits of the vaccine in terms of decreasing the morbidity due to Rotavirus vaccines are greater than the minimal risk of intussusception as the vaccine prevents over 65,000 hospitalisations from Rotavirus disease in the US. Therefore the CDC advocates the use of Rotavirus vaccines in the US.²⁸ Given the efficacy of the vaccines, UK has also included Rotavirus vaccine in its national immunisation programme, along with many other countries all over the globe.²⁹ It is important to highlight that Rotavirus vaccine is reported to have a reduced efficacy in developing countries which can be attributed to the improper handling and administration of the vaccine as well as the increased burden of disease.

Rotavirus Vaccine: its feasibility

Child health is an important national issue in developing countries. It is of particular importance in Pakistan because one child dies every minute as a result of diarrhoea and acute respiratory infection. Reducing under-5 mortality by gastroenteritis to less than one in 1,000 is one of the targets of Millennium Development Goal (MDG) 4. Insufficient health services, poverty and lack of timely access to medical facilities causes deaths from otherwise preventable diseases. In such a state of affairs, nipping the disease in the bud can go a long way in the prevention of morbidity and mortality.

An argument against the use of Rotavirus vaccination in developing countries is the dearth of resources and the economic impact of introducing, marketing and delivering a new vaccine. However, cost-benefit analysis shows that the costs of Rotavirus vaccine outweigh the economic burden due to disease-associated morbidity and mortality. In a study done on the cost effectiveness of

the rotavirus vaccine it was found out that \$188 million spent on treatment and \$243 million spent on societal costs could be saved because of the introduction of this vaccine. The same study concluded that because of the vaccine 58% of the costs spent on treatment can be saved.³⁰ According to analysis done on cost effectiveness of Rotavirus vaccine, the vaccine introduction in Pakistan will be very cost effective. Incremental cost per DALY averted was found to be \$42 assuming \$10 per vaccinated child for base case vaccine. The Rotavirus vaccination programme was found to be cost-effective in Pakistan when the result for the base case was compared with Pakistan per capita gross domestic product (GDP).³¹ Furthermore, as Pakistan is on GAVI-eligible country list, so it can seek the help from GAVI for the implementation of Rotavirus vaccine in Pakistan EPI schedule.

Future Implications

Data about effectiveness of Rotavirus vaccine in most developing countries is not available. Like all vaccinations, introduction of the Rotavirus vaccine can promote selective pressure on human Rotavirus. As a result, changes in the antigenicity and genome can decrease the efficacy of the vaccines. However, this is not an established consequence of widespread use of the vaccine and with the advent of sequence technologies and phylogenetic analyses, the strains affecting humans can be closely monitored.

Conclusion

Rotavirus vaccine is a very effective option in terms of efficacy, safety and cost against diarrhoea caused by Rotavirus all over the world. Rotavirus vaccination will decrease morbidity, reduce the number of hospitalisations and have a positive economic impact on healthcare. It is recommended that it should be included in the EPI programme of Pakistan.

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