Rotavirus Vaccines

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Abstract

Rotaviruses are the most common cause of severe gastroenteritis in infants and children. Rotaviruses are responsible for approximately 40% of all diarrheal hospitalizations among children under 5 years of age worldwide. Rotavirus, which is known as democratic virus, occurs with similar frequency in both developed and developing countries regardless of the hygiene conditions. Almost all children up to 5 years of age are infected with rotavirus at least once. But the majority of death cases towing to rotaviruses occur in children from resource-poor countries. Many investigators have reported that previous rotavirus infections protect against severe disease associated with reinfection. For this reason, vaccination in the early period of infancy is the most important method for protection against severe rotavirus infections and death. World Health Organization recommends rotavirus vaccination. After the introduction of rotavirus vaccines, significant reduction has been seen in morbidity and mortality because of rotaviruses. Rotavirus vaccine administration is particularly important in developing countries where majority of death cases are observed.

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Introduction

In a systematic analysis about the child mortality under 5 year of age, it was reported that 7,6 million children died due to preventable and treatable diseases in 2010. Diarrhea was responsible for 9.9% of those deaths (1). Despite the global improvements in child healthcare in the last three decades, diarrhea still constitutes the second most frequent cause of mortality in children under five years old. Across the globe, rotavirus is the most frequent cause of gastroenteritis in this age group. Rotavirus-related diarrhea is responsible for 36% of hospitalizations (2). In multi-centre study carried out in Turkey involving four centers between 2005-2006, it was revealed that the cause of hospitalisation in under 5 years of old-children hospitalised due to gastroenteritis was rotavirus in the ratio of 32.4%-67.4% (3).

In the pre-vaccination period, the number of annual rotavirus-related hospitalisation in small children in the United States of America was 55,000-70,000, and emergency service admission was 205,000-272,000. 20-60 mortality occurred annually in this age group. It is reported that the cost of rotavirus-related mortality and morbidity to the health system of USA is 319 million dollars and 893 million dollars to the public at large (4).

After a 1-3-day incubation period, the rotavirus infection causes a clinic picture characterized by watery diarrhea followed by fever and vomiting. It causes more severe gastroenteritis than the other viral agents. The disease has a severe course especially in children under two. Dehydration, acidosis and electrolyte imbalances are responsible for the complications and mortality (4).

The rotavirus which is known as democratic virus has a similar morbidity in the industrialised and developing countries. This, in turn, demonstrates that clean water source and improving the hygiene conditions are insufficient in preventing the disease. Regardless of the socio-economic development levels of societies and the regional differences, rotavirus infections makes 1/5 of 5-year-old children to need medical assistance and 1/50-1/70 of them to need hospitalisation. These infections result in mortality in one of every 205 children (5). More than 80% of rotavirus-related mortality is seen in the developing countries (Figure 1) (2, 6).

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The fact that rotavirus infections are seen frequently and that sequential infections have a milder course so that the patient is protected against severe infections has led the vaccination activities to be commenced. This fact was first evidenced by Bishop et al. (7). In a cohort study done in Mexico, it was revealed that previous rotavirus infections prevented the subsequent attacks by 77% and medium-heavy attacks 87% (8). Therefore, vaccination in the early period of life, similar to the first natural infection of the child, is the most effective prevention method against severe rotavirus infection attacks and related mortality.

Virology

Rotavirus was first detected in 1963 in the intestinal tissues of mice and monkeys (9). Due to their wheel-like structure, it was termed as rotavirus (In Latin, rota means wheel) (10). It was revealed that rotavirus was an agent of gastroenteritis as a result of the examination of duodenal biopsy of severe gastroenteritis infants by Bishop *et al*. in 1973 (11). Rotavirus is about 70 nm long, non-enveloped, double helical RNA virus belonging to the reoviridae family. It is composed of three sections of external capsid, internal capsid and core (Figure 2) (12, 13). The RNA genome in the core has 11 segments and encodes 6 structural proteins (Viral proteins; VP1-4, VP6, VP7) and 6 non-structural proteins (Non-structural proteins; NSP1-6). The viral genome, VP1 and VP3 are found in the core, and VP2 frames them. The VP6 that is synthesised in large quantities constitutes the structure of the internal capsid and virus grouping is implemented according to the VP6 protein. VP7, which is a glycoprotein (type G) VP4, which is a protease active protein (type P) constitute the external capsid layer. VP4 is responsible for linking to the cell, penetration, hemagglutination, neutralisation and virulence. VP7 modulates VP4 throughout the process of linking to the cell and penetration, and interacts with surface molecules of the cell following the linking of VP4 (14). These proteins which are the targets of neutralised antibodies determine the virus serotypes and are critically important for the vaccination activities. Rotaviruses are generally divided into groups and serotypes. The seven rotavirus groups have been defined as A, B, C, D, E, F and G. As was mentioned above, these groupings are implemented according to genetic and antigenic differences of VP6. Only the group A, B and C rotaviruses cause infections in humans. Group A rotaviruses are the most important causes of severe gastroenteritis in infants and children across the world. Group A rotaviruses are divided into serotypes based on VP7 (type G) and VP4 (type P) proteins. VP7 glycoprotein has at least 14 serotypes. VP7 (type G) can be detected by both specific enzyme immunoassay method (EIA) where monoclonal antibodies are used and by the molecular method where reserve transcription polymerase chain reaction (RT-PCR) is used. There is no serotype-genotype difference in the type G. Type P proteins, on the other hand, can only be detected by RT-PCR or the sequencing methods. Therefore, unlike the type G proteins, P genotypes are specified in square brackets (15). Although it may theoretically have more than 110 P and G combinations due to the assortment characteristics (penetration of a gene into another segment during the infection of two viruses the same cell simultaneously) of rotavirus, it has only few clinically common PG serotypes. Despite differences by years and regions, P[8]G1, P[4]G2, P[8]G3, P[8]G4 and P[8]G9 serotypes are responsible for more than 90% of the rotavirus diarrhea all over the world (16). In a Turkish study in 2006, in hospitalised rotavirus gastroenteritis cases, P[8]G1 was found as the most frequent serotype with 76% (3). Public Health Agency of Turkey, as a result of rotavirus study carried out using the stool samples taken from 2102 children under five within the framework of Turkish Rotavirus Surveillance Network (TRSN) reported that the most frequent genotypes were G1-G4 and G9 [G9P[8] (40,5 %) and G1P[8] (21,6 %) the most frequent two

Figure 1. Distribution of rotavirus-related mortality across the world, 2008 (2, 6)

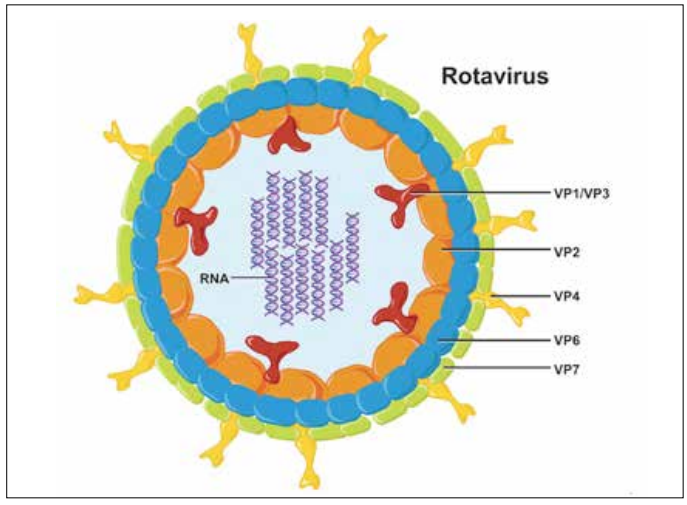

Figure 2. Structure of rotavirus (12, 13)

genotypes] and that a high coverage was obtained through the existing clinically used rotavirus vaccines. This study revealed that G9 genotype increased dramatically in our country (17).

Epidemiology

Transmission is believed to be by the fecal-oral route. While this transmission can be human to human, it can occur through objects. As much as 10^{10} -10^{12}/mL infectious particles are present in the stools of infected people, and as many as 1-10 particles are sufficient for this infection to contaminate. Almost all children are infected at least once by the rotavirus within the first five years (10). Rotavirus infections reach their peak in the 6-24 month-period of infants' lives. The fact that they are not frequently seen in the three-month infants may be due to the protective characteristics of breast milk, the antibodies passed on from the mother and the structure of immature intestinal epithelium. The protective nature of the first infection for the sequential infections causes the rotavirus infections to be rarely and asymptomatically seen in children older than five years old (7, 8).

Rotavirus infections reach their peak in winter months in mild climates. In countries, on the other hand, where there is tropical climate, despite briefly reaching their peak in winters, the infection has spread all over the year. One of the epidemiological differences in the industrialized and developing countries is the serotype diversity. Certain serotypes are seen in developed countries and mixed infections where more than one serotypes is present are rare. The increased infection risk during the winter season and the spread of a single strain make us think that the airborne or droplet contamination in the industrialised countries, and infection in developing countries have spread over the whole year, and serotype diversity is responsible for faecal oral contamination. Table 1 demonstrates the epidemiologic differences between the developing and industrialised countries (10).

Vaccine Development Studies

Demonstration of the protection effect of the previous infections in laboratory animals with the human rotaviruses strain has led to the creation of the idea that naturally weakened live animal rotavirus strains can create an immunological response in humans similar to the natural one and can protect children against diseases (18).

Immune response against rotavirus infection initially occurs in the intestinal mucosal epithelium exposed to the rotavirus and recognition continues increasingly. Therefore, the vaccines to be discovered against rotavirus disease should be oral vaccines with decreased virulence. Oral vaccines provide the best protection in the infection site; that is the place where pathology occurs in the intestinal mucosa. Rotavirus vaccines are designed in a way to cause protective response by copying the natural infection. Even if the first rotavirus infection prevents the severe re-infections, as it does not provide total protection, at least two-dose vaccines are recommended (7). In a multi-centre vaccination study in the USA, it was revealed that the previous rotavirus infection had 93% protection against the symptomatic re-infection in the second year. Even though the isolates in the second year are 66% in accord with serotype that causes the first infection, this high level of protection continues. This particular situation makes us think that the strains that cause infection lead to a VP7-based (type G) heterotypic protection. Symptomatic, serotype re-infection except G1 is not found in those people who suffer from natural rotavirus in the first year. It was demonstrated that the severe second attack occurred as a result of re-infection with different serotypes rather than re-infection with the same serotypes (19). Vaccine-dependent protection occurs through the antibodies caused by the VP7 or VP4 neutralised epitopes, non-neutralised IgA and IgG antibodies or T-cell-mediated mechanisms (18, 20).

The studies aimed at developing reliable and efficient vaccines against rotavirus started with a '*Jennerian*' approach in mid 1970s. In this approach, different animal rotaviruses were weakened in various passages in the cell cultures and manufactured in a way suitable for human use. An important reason of this is the difficulty of growing human rotaviruses in cell cultures. In this approach, 2 cattle and 1 rhesus monkey-based, live, non-human rotavirus vaccine demonstrated different effectiveness in wide range experimental studies. However, the results of effectiveness and reliability studies especially in the developing countries resulted in disappointment. In the end, the first generation vaccines prepared with the '*Jennerian*' vaccine development technique were abandoned (18).

Table 1. Differences in the rotavirus infection epidemiology between the developing and industrialised countries (10)

	Developing countries	**Industrialised countries**
Seasonality	All year	Winter
Case mortality rate	High	Low
Infection age		
Median	6-9 months	9-15 months
By 1 year of age	80%	65%
Rotavirus strain	Mixed	Single
Serotypes	± More diverse	4 common types
Transmission	Multiple routes	Single route
Inoculum	Larger	Small

Reassortant Rotavirus Vaccines (Modified Jennerian Vaccines)

Second generation vaccines were designed in 1990s for the purpose of including more than one G serotype in order to provide more immunity. All the second generation vaccines were the ones that were live, orally administered, and ensured protection similar to the one provided by the natural rotavirus infections. The vaccines were designed not for mild rotavirus infections, but for the severe rotavirus diarrhea.

The ability of two rotaviruses infecting the same cell during the mixed infections in the cell cultures in a laboratory environment (reassortman- re-match-up) and the ability of a one type of rotavirus interacting genetic materials with the other type of rotaviruses enabled *reassortant* vaccine manufacturing. In re-matching (*reassortant*) viruses, some genes come from the main animal rotaviruses and some others from the main human rotaviruses. Human rotavirus genome segment contains the gene segments that codify VP4 and VP7 proteins that are crucial in protection (4, 18).

***Simian-Human Reassortant* Rotavirus Vaccine: Rotashield®**

The first licensed rotavirus vaccine in the USA, Tetravalent Rhesus based Rotavirus Vaccine (RRV-TV) went into use in August 1998 under the commercial name Rotashield® (Wheyth, Madison, New Jersey). Rotashield® is a tetravalent reassortant vaccine composed of 3 simian-human reassortant rotavirus and 1 simian RRV strain (18).

Before it was licensed, Rotashield® was tested in 11.000 children in five comprehensive multi-centre studies. The vaccine was applied orally to infants at 2nd, 4th and 6th months. However, following the report of 600.000 doses vaccines and 15 invagination cases, its use was abolished (18). This particular side effect of the first licensed rotavirus vaccine ended up being the most important criteria in the future vaccines in terms of risk-benefit analysis. When the Rotashield® vaccine and invagination relationship was analysed in detail, it was found that this side effect was seen in healthy infants. The invagination risk is the highest in infants older than three months on the 3-7th days after the 1st and 2nd doses of vaccination. Therefore, it was decided that later rotavirus vaccines would be started in the first 3 months (14, 21, 22).

***Bovine-Human Reassortant* Rotavirus Vaccine: RotaTeq®**

The second licensed rotavirus vaccine in the USA, Pentavalent Rotavirus Vaccine (PRV went into use under the trading name RotaTeq® (Merck, Whitehouse Station, New jersey) in February, 2006. This vaccine was a reassortant vaccines composed of bovine-human reassortant rotavirus strains (18, 23).

RotaTeq® was comprised of the match-up of the genes of the human serotype G1, G2, G3 and G4 codifying VP7 and at the same time codifying P1A [8] together with VP4, with the main bovine (WC3) strain. It is the bovine (cattle) rotavirus strain that constitutes the main frame of the vaccine. This strain was purified from a calf (WC3) in Pennsylvania in 1980. The reason why human VP7 and VP4 genes were included into the vaccine was to constitute a comprehensive reactive antibody response against the two neutralised serotypes commonly seen in humans (18, 23, 24).

Before the vaccine was included into the vaccination calendar in the USA, it was tested in a total of 70.301 infants, 80% of whom were mainly in the USA and Finland (24). In this phase 3 study, following the 3-dose vaccination of RotaTeq®, it was revealed that the vaccine prevented gastroenteritis 74% and severe gastroenteritis and hospitalisation 95%. The effectivity was against G1-4 and G9 serotypes. However, the non-G1 rotavirus strains were relatively lower. After vaccination, 68.038 people were followed up for two years, and it was found that the vaccine reduced outpatient visits 86%, emergency admissions 94% and hospitalisations 96%. The vaccine reduced other-agent-related gastroenteritis hospitalisations 59%. After vaccination, the vaccine effectivity in the 2nd rotavirus season was that it reduced any severity of rotavirus gastroenteritis 63% and severe rotavirus gastroenteritis 88% (24).

If the relationship between antibody response against rotavirus vaccine and protection against the rotavirus gastroenteritis is not clear, the IgA level in the clinical studies was used as the criteria of vaccine immunogenicity. Similarly, before vaccination and two weeks after the 3-dose vaccination in the phase 3 study, seroconversion development characterised by 3 times or more antibody increase in comparison to pre-vaccination basal values was detected in the serum samples. While seroconversion ratio for the IgA antibody against rotavirus in the 349 vaccinated groups was 93-100%, it was 12-20% in the placebo group.

RotaTeq® is a pentavalent live vaccine composed of 5 human-bovine reassortant viruses, buffered by sodium citrate and phosphate with 24 months shelf life that needs to be refrigerated in 2-8°C. The 2 ml live vaccine ready for oral use includes G1 ($2.2x10^6$), G2 ($2.8x10^6$), G3 ($2.2x10^6$), G4 ($2.x10^6$) and P1 ($2.3x10^6$) infectious units.

Bovine rotaviruses, unlike the simian rotaviruses do not multiply in the infant small intestines. In this particular situation, the side effects with invagination leading the way, observed in the first doses after the oral inoculation vaccines composed of simian rotaviruses should not be seen in the vaccines composed of bovine rotaviruses. If viral replication and a large quantity of virus inoculations play a significant role in invagination, the same side effects should not be seen in bovine-human reassortant

vaccines. Following the RotaTeq® vaccine, 70,000 children were evaluated with regards to invagination risk, and within 42 days after vaccination, 6 cases in the RotaTeq® group and 5 cases in the placebo group were detected. After vaccination, it was found that RRV-TV vaccine-related (Rotashield) invagination risk was high and no mass clustering was observed on the 7th-14th days. After the first dose, during the one-year-long follow-up period, in the 13 invagination cases were detected in the vaccine group, and 15 cases in the placebo group (24).

No difference was found in the vaccine group in comparison to the placebo group in terms of sudden infant mortality, a life threatening event, pneumonia and seizures. In a 11,711 case study where the other side effects were investigated, in comparison to placebo group, 1 % more vomiting, 3% more diarrhea, 2% more otitis media, and 0.4% more bronchospasm were found that in the vaccine group. No difference was between the groups with regards to fever. After vaccination, virus spread via stool occurred in the first dose the most on the 1st-15th day (24).

***Bovine-Human Reassortant* Rotavirus Vaccine: Rotavac, 116E**

This vaccine obtained in India includes the G9P[11] strain. This vaccine contains 1 bovine gene and 10 human genes. The vaccine whose phase 3 investigations were completed in June, 2014, it was observed that it prevented severe gastroenteritis in the ration of 54%. However, the vaccine has not yet been licensed (12).

***Live Attenuated Human* Rotavirus Vaccine: Rotarix®**

Human rotavirus vaccine, Rotarix® (Glaxo-SmithKline, Rixensart, Belgium), contains the 89-12 (G1P[8]) strain obtained in the rotavirus epidemic in Cincinnati in 1989. This strain was weakened in the African monkey kidney cell by passaging 39 times. Adaptation of the virus grown in series passages into the infant bowels is less than the wild virus. Although the manufactured human rotavirus vaccine contains only one strain (G1, P1A [8]), it is effective against the other serotypes as well. It is simply because G3 and G4 strains almost always contain P1A. Therefore, P1A content of the vaccine provides protection against other strains apart from G1. It was demonstrated that the natural infections recurring by a single type G provided protection against other G types as well. While more than 90% serotype specific protection was provided against infections caused by G1P1A [8] after vaccination, 85% protection occurred against G3P1A[8] and G9P1A[8] infections.

Rotarix®, is a live attenuated, monovalent oral human rotavirus vaccine containing the G1P1A[8] strain, representing the VP7 and VP4 antibodies commonly present in human rotaviruses (18).

The effectivity of this vaccine was investigated in clinical tests involving more than 70.000 infants in Europe, USA, Latin America and Asian countries. Protection effectivity of Rotarix® against severe rotavirus gastroenteritis and hospitalisation was 85% and its effectivity against severe gastroenteritis due to any reason and hospitalisation 40%. These studies proved that Rotarix® was effective, reliable and well-tolerated vaccine. In comprehensive reliability tests carried out in the Central and South America, no relationship was detected of the vaccine with invagination.

Post Vaccination Surveillance Studies

The World Health Organisation recommended all the countries in the world in 2009 and 2013 to include rotavirus vaccine into their national vaccination calendars (25). It is especially emphasised that the countries where diarrhea is responsible for more than 10% of mortality in children under 5 years old should act urgently. Rotavirus vaccines today have been licensed in more than 100 countries and as of January 2015, they were included into the national vaccination calendars of 75 countries (26).

In the USA, the pentavalent vaccine (RotaTeq®) was licensed in February 2006 and monovalent vaccine (Rotarix®) in April 2008. In a study in which 2009-2010 rotavirus seasons was compared with the pre-vaccination season, it was seen that post rotavirus season was shortened and delayed; in addition, the investigated antibody positivity was visibly reduced (27). After routine rotavirus vaccination in the USA, rotavirus gastroenteritis-related doctor visits, hospitalisation and emergency admissions in children under 5 years old obviously reduced (28-31). With help of vaccination, in rotavirus gastroenteritis-related hospitalisations in children under 5 years old, 40,000-60,000 reduction was detected throughout the season of 2008 (30). Proving that rotavirus-relation hospitalisations in unvaccinated children under 3 years old in the USA were less than the pre-vaccination period made us think that vaccination enabled collective immunity as well (32). It was observed that mortality and morbidity decreased in most of the Latin American countries where rotavirus vaccination was included into the national immunisation programme in 2006-2007. When monovalent vaccine with 70% coverage in 2008 was compared with the pre-vaccination period in Mexico, it was demonstrated that diarrhea-related mortality in infants aged 0-11 months reduced 41% (33, 34).

In the post-licensing studies carried out in the USA, it was demonstrated that no increased was recorded in the invagination risk or other undesirable effects. However, the studies carried out in Mexico, Brazil and Australia concluded that monovalent and pentavalent vaccines, not as much as Rotashield® (Tetravalent Rhesus based Rotavirus Vaccine, RRV-TV), increased the invagination

risk (35, 36). Despite very low level of invagination risk (1-2/100,000), these two vaccines continue to be recommended in routine vaccination due to their benefits.

Porcine circovirus 1 (PCV1) was found in monovalent vaccine in March 2010, and porcine circovirus 1 and 2 (PCV1-2) in pentavalent vaccine in May 2010. Although PCV2 is a source of infection in pigs, it does not cause any infection in humans. PCV1, on the other hand, is not a source of infection for neither animals nor humans (12).

Although there were some cases that developed Kawasaki disease after the vaccination, no cause and effect relationship was found between the vaccination and the disease. In a study in America where a 1-year post-vaccination period was retrospectively investigated, it was found that there was a 20% reduction in the number of infants that were presented with an emergency or hospitalised due to convulsion (37, 38).

The most important problem, on the other hand, regarding the effectivity of rotavirus vaccines all over the world is the fact that vaccine effectiveness in the developing countries where more 80% mortality occurs is lower (50-60% on average) (5, 11). Figure 3 illustrates the distribution of the effectiveness of both monovalent and pentavalent vaccines against severe rotavirus gastroenteritis around the world. Vaccine effectivity decreases as the socioeconomic levels decrease (5). This particular situation may have to do with high level antibody transmission from the mother during pregnancy or in the postnatal period through breast milk, with high malnutrition levels, environmental enteropathy, the differences in the microflora and intestinal villus structures, and prevention of the antibody response through simultaneous other viral infections or simultaneous oral polio virus vaccine. Although rotavirus vaccine effectivity is lower in comparison to developed countries, given the frequency of rotavirus infections and their high number, vaccination is vitally important for these countries in preventing mortality and severe gastroenteritis. Especially for developing countries, the effort to discover a cheaper and more effective vaccine has been under investigation (11, 39). In this sense, apart from the licensed monovalent (P[12]G10,

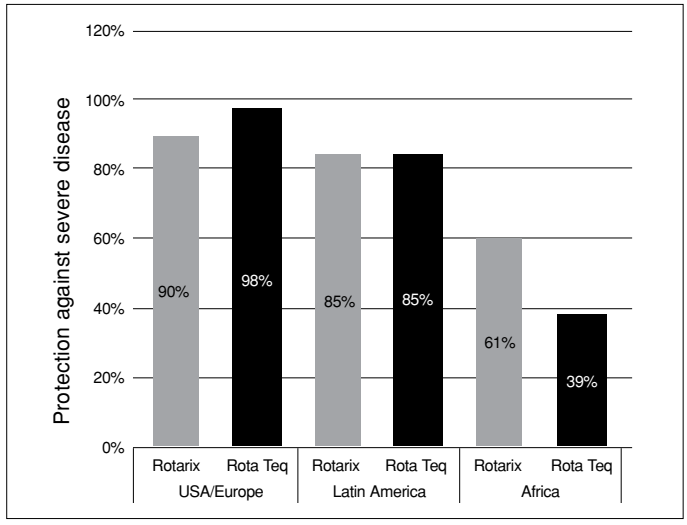

Figure 3. Relationship of the effectivity of rotavirus vaccines over the serious rotavirus gastroenteritis with the level of socioeconomic level across the world (4, 24)

Table 2. Comparison of licensed rotavirus vaccines (12)

	Pentavalent human-bovine reassortant rotavirus vaccine (PRV, RV5)	**Live attenuated human rotavirus vaccine (HRV, RV1)**
Trade name	RotaTeq	Rotarix
Serotypes contained	G1, G2, G3, G4, P1[8]	G1P[8]
Dose	2 mL	1 mL
Administration	Ready to use	Requires reconstitution
Number of dose	3	2
Recommended schedule	2, 4, 6 months	2, 4 months
Minimum age first dose	6 weeks	6 weeks
Maximum age first dose		
USA	14 weeks, 6 days	14 weeks, 6 days
Europe	12 weeks	12 weeks
Minimal interval between doses	4 weeks	4 weeks
Maximum age last dose		
USA	8 months, 0 day	8 months, 0 day
Europe	6 months	6 months
Oral applicator	Latex-free	Contains latex
Contains thimerosal	No	No

live, attenuated, Lanzhou lamb rotavirus vaccine (LLR) obtained from oral lamb rotavirus strain in China, and the monovalent Retain-IM vaccine obtained from the licensed human G1P[8] strain, there are also ongoing vaccines studies in the 1-2-3- phases (40). Besides, rotavirus serotypes vary by years and regions. It is crucially important to continue the post-vaccination surveillance investigations.

Vaccine Practices

Today there are two licensed live oral rotavirus vaccines in use all over the world. The World Health Organisation recommends infants to be routinely administered the rotavirus vaccine and do not differentiate between five valent RotaTeq® (RV5) and monovalent Rotarix® (RV1). RotaTeq® should be shot in three doses on the 2nd, 4th, and 6th months. The first dose can be administered from 6th week onwards, but should be shot before the 15th week (14 weeks, 6 days maximum). The infants who were vaccinated the first dose on the 15th week and later by mistake should continue according to the routine vaccination schedule. The timing of the first dose does not affect the reliability of the subsequent doses. There should be minimum 4-week breaks between the doses. The last dose should be administered before the 8th month (25, 41).

The first dose is administered between the 6th and 12th weeks in the European countries. The last dose is administered before the 6th month (33).

Rotarix® should be shot in two doses on the 2nd and 4th weeks. Similarly in the USA, the vaccination is commenced on the 6-15th weeks and two doses are administered before the 8th month (23). In European countries, just like with RotaTeq®, the first dose is administered on the 6-12th weeks, and the last dose is shot before the 6th month (12). There is no maximum time gap between the doses. Table 2 illustrates the comparative characteristics of RotaTeq® and Rotarix® vaccines (12).

The infants who have not yet completed their two or three exact dose vaccination schema are recommended to complete the schema even if they have had rotavirus gastroenteritis. It is because protection is limited after the natural infections. In the case of infants who have been vaccinated by a different brand of vaccine before, if the same brand vaccine is unable to be obtained, the vaccination should continue with existing brand. If the previous brand of vaccine is unknown, it should be completed as the 3-dose vaccine series (12, 23, 41).

Vaccination in Special Circumstances

Cases with mild gastroenteritis and mild fever could be vaccinated. However, vaccination of infants with moderate-severe gastroenteritis or inflammatory disease has to be postponed until the infection improves. It was demonstrated that breast milk did not reduce the vaccine effectivity (24). Re-vaccination of the infant who have previously had serious allergic reaction in the previous dose is contraindicated. Similarly, those who have serious allergy against the content of the vaccine should not be vaccinated either. As the applicator contains latex, Rotarix® should not be administered to those who have latex allergy. In these circumstances, RotaTeq® that does not contain latex, should be preferred. Similarly, in cases with spina bifida or extrophia vesicalis, there are some opinions suggesting that RotaTeq® should be preferred as those cases have the risk of developing latex allergy (12, 23).

The premature babies who are clinically stable should be chronologically vaccinated according to the normal schema from six week onwards. The hospitalised premature babies can be commenced to be vaccinated starting with the day of discharge from the hospital (23).

If the rotavirus-vaccinated infants need to be hospitalised, standard isolation measures are sufficient. However, they are not recommended to be hospitalised together with the patients who have immunodeficiency (41).

There is no time limitation between the blood products inclusive of immunoglobulin and rotavirus vaccines (12, 23).

The vaccine should not be administered to the infants who have an invagination story. However, it is thought that the vaccine will be useful for those who have any chronic gastrointestinal disease except invagination (12).

In severe combined immunodeficiencies, the vaccine is definitely contraindicated. Even though some experts suggest that rotavirus vaccine should be used in HIV-positive infants, a dominant argument prevails that the vaccine should not be administered the in primary and secondary immunodeficiencies like in severe combined immunodeficiencies (41).

Rotavirus vaccination can be administered to the infants with immunodeficiency or with a pregnant individual in the household. However, those with combined immunodeficiencies, receiving chemotherapy, and those in the first a two-month period following solid organ transplantation, those with the CD4 level 15%, and those receiving high dose steroid should not come into contact with nappies of rotavirus-vaccinated infants for a month (12, 23, 41).

Rotavirus vaccines can be administered simultaneously with the nasal or parenteral vaccines. While the American Advisory Committee on Immunization (ACIP) states that no specific time gap is required with the oral polio vaccine, the Institution of European Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and European Association of Paediatric Infection (ESPID) suggest that the vaccine should not be administered

simultaneously with the oral polio vaccine (12, 41). In order for us to be able to say precisely that the protection of rotavirus vaccines does not change when it is administered simultaneously with the oral polio vaccine, there is a need for comprehensive rotavirus studies in the countries that continue the oral polio vaccination in their vaccination schedules.

Conclusion

Vaccination is the most effective method in preventing the rotavirus gastroenteritis-related mortality and morbidity. Effectivity of the 2 oral rotavirus vaccines recommended by the World Health Organisation is lower in the countries where most of the rotavirus-related mortality is seen. Efforts to produce cheaper and more effective vaccines especially for these countries should continue. Since rotavirus serotypes change together with vaccination, it is crucially important to continue the post-vaccination surveillance investigations. At the same time, the vaccinated infants should be closely followed up with regards to non-specified invagination relationship and other side effects.

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