

New Generation Rotavirus Vaccines

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Abstract

Rotavirus gastroenteritis (RVGE) is a vaccine-preventable disease that causes hospitalization and deaths due to severe gastroenteritis in developing countries. The World Health Organization (WHO) reported that 801000 children die annually due to gastroenteritis. Improvement in hygienic conditions is insufficient for preventing rotavirus gastroenteritis due to transmission via droplets and resistance to disinfectants; therefore, vaccination is the most effective method for prevention. At present, there are two licensed rotavirus vaccines, monovalent rotavirus vaccine (RV1, Rotarix, GlaxoSmithKline) and pentavalent rotavirus vaccine (RV5, RotaTeq, Merck). The WHO offered to integrate the rotavirus vaccine to the national vaccination programs of all countries worldwide since 2009. Current licensed vaccines have since demonstrated efficacy against severe gastroenteritis and hospitalization in developed countries. In countries with low income and high disease vaccination rate is low because of difficulties in vaccine supply and high cost of the vaccine and consideration about diminished efficacy of the other oral vaccines. Therefore, several groups are led to develop around the world, new rotavirus vaccines. In this review, we provide a summary of the new licensed vaccines with ongoing clinical trials and the locally licensed vaccines. (*J Pediatr Inf 2016; 10: 22-7*)

Keywords: Rotavirus, rotavirus vaccine, new generation rotavirus vaccines

Introduction

Rotavirus (RV) infection is the most important cause of gastroenteritis in children under five, especially the cause of severe gastroenteritis resulting in morbidity and mortality (1). Rotavirus gastroenteritis (RVGE) has a severe course accompanied by diarrhea, vomiting and dehydration in infants aged 3-24 months and may cause morbidity or even mortality (2). RV infection is seen in early ages in children living in low-income countries due to causes such as malnutrition, co-infection and insufficient health-care services and the clinical symptoms are more severe. The World Health Organization (WHO) report that 10% of mortality in children under five is caused by diarrheal diseases and that nearly 801000 children die annually due to gastroenteritis (3). Gastroenteritis is the second most frequent cause of mortality in children under five after pneumonia. The World Health

Organization reports that the most important agents responsible for mortality are pneumonia for lower respiratory tract infections and rotaviruses for gastroenteritis (4). RV is responsible for half of the gastroenteritis mortality; RV-related mortality was reported to be 453000 death/year in 2008 and 197000 death/year in 2011 (5, 6). More than half of the rotavirus-related mortality is seen in developing countries such as India, Nigeria, Pakistan, Ethiopia and the Democratic Republic of Congo; 20% of mortality is in India (5). However, RV gastroenteritis is an important health problem not only in developing countries but also in developed countries. Although it may not cause mortality in developed countries, it is a significant cause of morbidity; it causes hospitalization and economic losses (7). Because of all these reasons, RV gastroenteritis is an infectious disease that should be protected from.

In protection against acute gastroenteritis, breast milk, hand-washing, disinfection of toys

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are crucially important. However, personal and social hygiene rules that are important in protection against gastroenteritis alone are not effective in preventing RV infections. Rotavirus is found in high concentrations in the feces of infected persons. During the acute disease period, it is known that in each gram of the feces, 100 billion virus particles keep spreading. Virus excretion through the feces starts before the disease develops. During the 2-3 day period before the onset of gastroenteritis, RV is usually detected in the feces. Excretion lasts nearly for 10 days; after the improvement of the symptoms, it continues for another 2-3 days. Rotavirus can spread not only through only the fecal oral route, contaminated food or water, but also through contact and droplet. Therefore, it is different from other viral, bacterial and parasites gastroenteritis; it has seasonal properties such as respiratory viruses (RSV, influenza).

Rotavirus is resistant to many chemical disinfectants and temperature changes. It was found that remained alive for 6 and 60 days on dry surfaces. Rotaviruses could not be inhibited by the existing antiviral drugs. For all these reasons, reduction/prevention of rotavirus morbidity and mortality that is difficult to protect against, can spread easily and has an important disease load will only be possible with efficient and reliable vaccines.

Current Rotavirus Vaccines

Today, two RV vaccines, monovalent rotavirus vaccine (RV1, Rotarix, and GlaxoSmithKline) and pentavalent rotavirus vaccine (RV5, RotaTeq, Merck) are commonly used all over the world. The World Health Organization approved both vaccines and they were recommended to be included into the national programs of all countries as of 2009 (8). However, both vaccines have some limitations such as their use in low-and middle-income countries regarding reliability, efficiency, serotype/scope of strain, procurement and supply, financial support, and lack of attention to the disease by the experts in endemic countries.

Rotavirus vaccine studies started in Australia in 1973 right after the detection of the virus as the most frequent cause of infant diarrheas (9). The first RV vaccine was bovine type vaccine RIT4237 manufactured by SmithKline-RIT. Although this vaccine was reported to have 80% protection against severe diarrhea in Finland, since it was proved to be ineffective in the studies carried out in Africa and Latin America, its production was discontinued. Afterwards, similarly bovine type vaccine WC3 (P7 [5] G6) and attenuated rhesus monkey MMU18006 vaccines were manufactured in the Philadelphian Pediatric Hospital. In a placebo-controlled study carried out with MMU18006 in Venezuela, it was found that the vaccine's protection was 68% and severe diarrhea was seen in the vaccine group (10). However, none of these vaccines were licensed. The

lamb type monovalent RV vaccine (LLR) in China was licensed in 200-2001; it was a live attenuated vaccine and recommended for infants aged 2-36 months and an annual booster dose was recommended; it was reported that nearly 10 million dose of this vaccine was administered on that year in China. However, the vaccine was not evaluated by the phase three studies; through a case-control study, 838 RV-related hospitalized children were evaluated and it was reported that against an RV infection requiring hospitalization with a single dose, 73% effectivity was found and in terms of age groups, the vaccine's protection for infants aged 12-23 months in comparison to those aged 2-11 months was higher (11).

Despite these unsuccessful experiments, the studies were continued and reassortant vaccines were developed by using the reassortant feature of rotaviruses (hybridization, it is the case of one gene segment passing from one to the other one during the process of two viruses infecting a cell). Despite these unsuccessful experiments, the studies were continued and reassortant vaccines were developed by using the reassortant feature of rotaviruses. The first reassortant RV vaccine was tetravalent monkey-human reassortant rotavirus vaccine (RRV-TV, Rotashield, Wyeth-Lederle). This is a reassortant vaccine with serotype 3 RRV (monkey rotavirus) and G1, 2 and 4 serotype protein genes. When it was first started to be administered, it was found that that its effectivity was 80-100%; despite this delightful development, it was claimed that invagination risk increased nearly 25 times due to an unknown mechanism within the 10 days after its administration, and CDC (Central Disease Committee) withdrew the RV vaccine recommendation after one the vaccine went into effect (12, 13). However, subsequent investigations proved that invagination risk was less than anticipated (14).

Pentavalent human-cattle reassortant rotavirus vaccine (RV5, RotaTeq) contains 5 live attenuated human-cattle (WC-3) reassortant virus. The human surface proteins available in the vaccine are G1-G4 and P1A (8). 5 reassortant RV included in the vaccine contains more than 85% of the strains isolated in the last two decades both in developed and developing countries (14). Therefore, in RV5, a response to G1-4 and P1A (8) antigens available in more than 85% of the RV strains isolated in the warm climates has been designed. Reassortant vaccine is naturally attenuated as the animal strain does not grow in humans; and it enables neutralization with the G and P serotypes available in human rotaviruses. In protection, it is based on the assumption that serotype-specific neutralizing antibodies (homotypic immunity) are significant. RV5 is administered orally for three doses. The intermission between two doses is recommended to be at least 4 weeks. In general, the recommended vaccine scheme is 3 doses on the 2nd, 4th and 6th months (15).

Monovalent human RV vaccine (RV1, Rotarix) is a monovalent attenuated live rotavirus vaccine inclusive of **G1P1A** [8] strain. The original strain of RV1 is the 89-2 strain obtained from an infant infected with RV in Cincinnati. The wild strain was attenuated by being passaged 12 times. It is based on the assumption that in protection, RV1 is homotypical antibody response is as important as heterotypical antibody response. Following the recurrent natural infections, observation of cross-protection the development is based on the symptoms demonstrating that there is cross-protection between the bovine and monkey RV-originated human reassortant vaccines (16). This vaccine is well-replicated in the intestines and similar to the natural infection, provides protection against other serotypes. It was demonstrated that protection was provided not only against homolog G1 infection, but also against all types of RV serotypes inclusive of G) serotype frequently seen in Turkey (17, 18).

Rotavirus virulence and the protection mechanisms have not been fully understood despite many previous studies and tests done on the vaccine candidates. Following the vaccine, antibodies grow both in the serum and in the intestinal mucosa. Disease protection of the antibodies detected in the serum should be debated. In animal tests and in humans, humoral immunity was proved to be effective in the passive transition of antibodies. It was proven that orally given RV-specific antibodies enabled improvement in infants through passive immunization and it was protective against infections when given to monkeys. The most important antibodies that have a role to play in the immunity developing through natural infection are VP7 and VP4; while homotopic neutralizing antibody is formed in the serum following the first RV infection, more extensive heterotypic immune response occurs as a result of subsequently developing infections (19).

In pediatric and adult studies, it was found that IgA, IgG and neutralizing antibody levels were correlated with the protection against RV infection (20). In the experimental animal studies, it was found that cytotoxic T lymphocytes were significant in protection against the disease; however, its effect on humans is unknown. However, no correlation has been found between today's licensed vaccines and protection. The most important role in vaccine immunogenicity is the formation of anti-RV serum IgA; even though it was correlated with its effectivity, it was revealed that more comprehensive studies needed to be carried out. There is a need to carry out placebo-controlled studies with the currently licensed vaccines; however, ethical regulations constrain these types of studies in many countries.

The protection of rotavirus vaccines has been assessed by effectiveness studies. In the effectiveness studies, the effectiveness of RV vaccines against RV gas-

troenteritis, their effectiveness against severe RV gastroenteritis was to provide protection against doctor-emergency unit admissions and hospitalizations, and severe gastroenteritis that can cause death. Therefore, effectivity studies against hospitalizations and severe RV gastroenteritis are significant. In the prosperous European and North American countries, and in the middle-income South American countries, it was proven that RV vaccines were provided effective and reliable protection against RVGE, especially against severe RVGE (21). However, the effectivity of the vaccine in developing countries is not as high in the industrialized countries. In a study done in Ghana, Kenya and Mali where severe diarrhea and mortality rates were high in children under five between 2007-2009 in 5468 infants with 2 and 3 doses RV1 vaccine, it was found that severe RVGE frequency in the placebo group was 4.9% and 1.9% in the RV1 group, and the effectivity of RV1 against severe RVGE was 49.5% (22). Similarly, in a study done with RV5, it was reported that while its effectivity against severe RVGE was 64.1% in African countries (Ghana, Kenya and Mali), it was 51% in Asian countries (Bangladesh) (23). These studies have demonstrated that the effectivity of RV vaccines in developing countries is less than the industrialized countries where it is reported to be as high as 90%. However, RV vaccines are more effective on mortality in developing countries. For instance, although its effectivity in Malawi (49.5%) is less compared to the developed South Africa (76.9%), 4.2 per 100 children in South Africa prevent severe RV attack, it prevents 6.7 attacks in Malawi. Therefore, although RV vaccine effectivity in low-income countries is lower than middle or high-income countries, its effect on public health is more significant (24).

In summary, the two RV vaccines in current use today are effective in reducing RV-related childhood mortality in low and middle-income countries; however, some limitations of the vaccine have brought up the issue of new vaccine studies.

Research and development studies with the new generation rotavirus vaccine

Experiencing problems regarding the cost and supply of the vaccine in low and middle-income countries where the disease burden is high has increased the need to develop new RV vaccine. Today, research studies in which new live-attenuated human-bovine reassortant vaccine or neonatal strains are used are being carried out all over the world. Phase studies related with RV vaccines are summarized in Table 1.

The causes aimed at the new vaccine research studies are thought of as: the failure to enable the expected effectivity in countries where disease load is high and the belief that the effectivity of other oral vaccines has proba-

Table 1. Candidate rotavirus vaccines, phase studies

Vaccine name / Researcher	Pre clinic	Phase I	Phase II	Phase III
RotaVac, monovalent neonatal G9P(10), 116-E rotavirus vaccine (Bharat Biotech, India)				Licensed in India, effectivity studies underway.
RV3_BB vaccine (Murdoch Children's Research Institute, Australia)			Phase 2 studies are underway.	
BRV Pentavalent rotavirus vaccine (Serum Institute of India)				Effectivity studies are underway.
G1,2,3,4 vaccine that takes Tetrav				
• ChengDu Institute of Biological Products (China)	X			
• Instituto Butantan (Brazil)		X		
• Shanto Biotech, (India)		X		
Rotavin-IM G1P[8] (Vietnam)				Reported to have been licensed.
Non-replicated rotavirus vaccine (NRRV)				
P2-VP8 recombinant subunit, developed by PATH ^x		The phase I studies in adults have been concluded; effectivity studies in children and infants are underway.		

x: Performance Assessment & Quality Improvement, Rotavirus (RV)

bly decreased. Moreover, its contact with the other viruses and bacteria that colonize the intestinal system, neutralization of maternal antibodies (breast milk or transplacental) the virus, immaturity of the intestinal immune system, and lack of knowledge of the secrets of the infant intestinal mucosa.

Another important cause of the new vaccine research studies is the cost of the vaccine and the financial difficulties involved in the procurement of the vaccine. Cost of the current vaccines is high for the low and middle-income countries where the disease burden is high and production level of the vaccine does not cover all the children. Because of all these reasons, for the countries where the disease burden is high, hopes been pinned on the new vaccine development studies.

Various studies demonstrated that maternal antibodies reduced vaccine effectivity; therefore, in the current application, vaccination starts on the 6th week the earliest. Although it may change depending on the type of the vaccine, in order to enhance vaccine immunity to the maximum level, at least two or three doses of vaccine administration is recommended. Its administration together with the OPV vaccine has eased off its introduction into the vaccination schedules; however, there are also studies demonstrating that simultaneous administration of the two vaccines has reduced the response of the OPV vaccine. Therefore, the studies aimed at increasing the immunogenicity through cross-protection between the serotypes

of RV vaccine, and reducing the interaction with maternal antibodies by introducing the vaccines from birth have been underway.

Although the invagination risk with the currently licensed vaccines is as low as 1-2/100000, concerns still continue and it affects the policy regarding the application age of the first dose of the RV vaccine. In many countries where disease load is high, due to the delays in the introduction of vaccination, important opportunities are missed in preventing the RV-related mortality in children who are not vaccinated in the first 15 weeks. However, the WHO states that this limitation can be ignored in countries where the disease load and RV-related mortality is high. Therefore, it is recommended that age limitation is not important for the vaccination targeted by the new vaccine development studies, especially for the low-income countries where the disease load is high, more appropriate vaccines should be developed.

Asymptomatic or mild course of the RV infection in the neonatal period has caused the neonatal strains to be re-searched in the new vaccine development studies. Two vaccines in which neonatal strains were used were developed; one these vaccines was licensed in India (monovalent neonatal G9P (10) containing the 116E strain developed by the support of PATH [Bharat Biotech International Limited (BBIL)]. In the study done by the Biotechnology Institute of India involving many academicians and BBIL, it was found that 4352 infants vaccinated by the 116-E RV

vaccine developed 1.6% severe gastroenteritis attacks, and 2360 infants given placebo developed 3.2% severe gastroenteritis attacks; it was demonstrated that the vaccine reduced severe gastroenteritis 56% in the first year (25). This vaccine was licensed by the label Rotavac in India. It is reported that the cost of the vaccine is about one American dollar and the vaccine will start to be used step by step all over the world.

While the other neonatal vaccine (the RV3 vaccine containing P[6]G3 strain) was developed in Australia and it was reported to be effective and well-tolerant, since its immunogenicity was found to be low, its formula was changed and more antibodies were added. In the phase 1 and 2 studies, it was found that the vaccine was reliable and had high immunogenicity; the phase 2 studies have still been underway. The other human RV vaccine strain, Rotavin-IM G1P [8] was developed in Vietnam and was licensed.

Multivalent reassortant vaccine development studies were developed by the hybridization of cattle strains and human strains. The five-valent bovine-human reassortant vaccine developed in India is the BRV Hu (pentavalent G1-4 and G9) and the phase 3 studies have still been underway in many parts of India with the collaboration of PATH (26). The tetravalent G1,2,3 and 4 vaccines in which the other bovine reassortant was used, were licensed by the national health institutes in Brazil (Instituto Butantan), in India (Shanta Biotech) and in China (ChengDu Institute of Biological Products). In an effectivity study done in Finland, this vaccine was proved to have high effectivity and was immunogenic and non- allergenic.

Since the effectivity of the oral vaccine is not at the desired level in the countries where the disease burden is high, academic and state-funded organizations (such as PATH) in many countries have been working on the RV vaccine to be applied parenterally. Vaccine development studies have been working on vaccines comprised of inactive RV strains or of the subunits of RV proteins. The third most noticeable vaccine candidate is the 3 or 2-level virus-like particle (VLP_s); inactive RV particles and recombinant subunit proteins. The Organization of Performance Assessment Tools (PATH, Performance Assessment & Quality Improvement) for Quality Improvement in Hospitals of the European Regional Office of World Health Organization developed the chimeric vaccine protein comprised by the expression of VP8 in the *E.coli*, the subunit of outer membrane VP4 that increases its immunogenicity by being tied to the P2 epitope of the tetanus toxin where most of the neutralizing epitope is located. In the reliability studies done with the adults, it was demonstrated that the

P2-VP8 vaccine was well-tolerable and constituted a definite neutralizing antibody response (27). If immunogenicity is proven in the ongoing studies with infants, they will guide the new effectivity studies.

In summary, various scientific institutions such as the WHO, CDC, ESPID (European Society of Pediatric Infectious Disease), and AAP (American Academy of Pediatrics) recommend all the countries in the world the inclusion of the RV vaccine into the routine schedule. It has been reported that in the vaccine recommendations, between both current RV1 and RV5, there is no specific difference with regards to effectiveness and protection and both vaccines are reliable; and in RV vaccines, there is no increase inclusive of invagination in the side effects (28). In addition to increasing the effectiveness of the vaccine with the new generation RV vaccines, the most important thing is to reduce the costs, thus, enabling the RV vaccines to be cheaper and more accessible for the low-income countries.

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