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REVIEW

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Diverse processes in rotavirus vaccine development

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ABSTRACT

Rotavirus is a major cause of severe diarrhea and mortality in children under five years of age, leading to approximately 128,500 deaths annually.[1–3] Vaccination is the most effective strategy for preventing rotavirus infection. While two widely used vaccines, Rotarix and RotaTeq, have shown good efficacy in high-income countries, their effectiveness is lower in low- and middle-income countries due to factors such as malnutrition and poor sanitation.[4–6] These challenges include complex vaccination schedules and high production costs. Researchers are working on novel vaccines, including inactivated virus and viral protein-based options, as well as virus-like particles and recombinant proteins.[7–9] Improving vaccine stability and applicability is crucial for resource-limited settings, and global vaccination strategies are expected to significantly reduce infection burdens, improve child health, and contribute to the achievement of global health goals.[10–14]

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Introduction

Rotavirus is one of the leading causes of diarrhea in children under five years of age worldwide, resulting in high hospitalization and mortality rates. According to estimates from the World Health Organization (WHO), approximately 128,500 children die each year from rotavirus infection, with the vast majority of these fatalities occurring in developing countries.[1–3] Rotaviruses are transmitted via the fecal-oral route, and infected individuals secrete large quantities of the virus that can survive for extended periods in contaminated water, food, and surfaces. Owing to its strong resistance to environmental conditions, the risk of rotavirus infection is particularly high in areas with poor sanitation and unsafe drinking water. Consequently, vaccination is considered the most effective preventive measure, significantly reducing the incidence of severe diarrhea and related deaths caused by rotavirus infection in children.[2,6,14]

Since the approval of the first rotavirus vaccine in 2006, numerous countries have gradually incorporated it into their routine immunization programs, especially in high-income countries, where vaccination coverage has significantly increased.[15] Vaccines primarily fall into two categories: monovalent (Rotarix, GSK) and pentavalent (RotaTeq, Merck) vaccines (Table 1), both of which have demonstrated good protective efficacy in multiple clinical trials and have significantly reduced the incidence of severe diarrhea.[10,16,17] Research indicates that in high-income countries, the effectiveness of the rotavirus vaccine can exceed 85%, leading to a substantial decrease in hospitalizations and deaths related to rotavirus.[17] For example, the introduction of the rotavirus vaccine in the United States has resulted in more than a 90% reduction in hospitalization rates for children under five years of age, greatly alleviating the healthcare burden and saving considerable resources for the healthcare system.[18] The success stories from these high-income countries illustrate that strong public health infrastructure, robust health policies, and high public trust in vaccines are critical for the success of vaccination campaigns.[19]

Traditional rotavirus vaccine: currently in use

Although, Rotarix and RotaTeq these two vaccines are widely used, there are significant differences in vaccination rates between countries and regions, especially in low- and middle-income countries, where more challenges have limited the extensive use of these two vaccines. One primary obstacle is economic constraints.[20–23] Although international organizations such as The Global Alliance for Vaccines and Immunization (GAVI） and the Vaccine Alliance provide funding and technical support to these countries, the high costs of vaccine procurement, transportation, and storage remain significant barriers. The cold chain requirements for vaccine transport are stringent, and many low-income countries have a weak infrastructure and lack a stable electricity supply and sufficient refrigeration equipment, making vaccines susceptible to failure during transportation and storage.[24–26]

In addition to economic challenges and inadequate health infrastructure, the protective effectiveness of rotavirus vaccines varies significantly across regions. Numerous studies have shown that in high-income countries, the effectiveness of the vaccine can reach over 85%, substantially reducing severe diarrhea and hospitalization caused by rotavirus.[17] However, in low- and middle-income countries, vaccine

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efficacy typically ranges from 50 to 70%, demonstrating a marked decrease in protective effects. Several factors have contributed to this disparity. Malnutrition is a major health issue for children in developing countries.[24,25] Malnourished children exhibit weaker immune responses to vaccines because of their underdeveloped immune system, thereby reducing their efficacy. Intestinal coinfections play a crucial role in many developing countries. Children often face infections from multiple intestinal pathogens, which can interfere with the immune response to vaccines and diminish their protective effects.[27–29] Poor sanitation is also a significant reason for the reduced effectiveness of the vaccines. In environments lacking clean drinking water and basic sanitation facilities, the lack of hygiene accelerates the transmission of rotavirus, leaving vaccinated children at higher risk of infection.[30,31] In response to these challenges, enhancing the coverage and effectiveness of vaccines in low-income and middle-income countries has become a global public health priority. As traditional rotavirus vaccines have been widely implemented and promoted, their limitations have become more evident.[32,33] In recent years, the predominant circulating genotypes of rotavirus in low- and middle-income countries have been G3P[8] (45.3%) and G1P[8] (32.1%), which partially match the strains targeted by existing vaccines such as Rotarix and RotaTeq. However, the transient surge of non-vaccine-targeted strains like G2P[4] (6.1%) may reduce vaccine effectiveness. Although no significant antigenic drift ($dN/dS < 1$) has been detected, genetic recombination events and high genetic diversity could still impact the long-term efficacy of vaccines. Research conducted in Bangladesh revealed that during the pandemic, the rotavirus positivity rate increased from 23% to 34%, potentially linked to the strained healthcare resources at the time. The study recommends continuous monitoring of genotype dynamics and the promotion of vaccination to address genetic diversity challenges and reduce severe cases and deaths.[34]

First, vaccination schedules are complex. Existing rotavirus vaccines require multiple doses (RotaTeq requires three doses, while Rotarix only requires two doses) (Table 1). This poses difficulties in economically disadvantaged and healthcare resources limited regions, where some families may struggle to make regular visits to healthcare facilities or lack a clear understanding of the vaccination timetable/schedules, leading to incomplete vaccination.[10,16] In addition, the production costs of traditional vaccines are relatively high. Organizations such as GAVI provide financial support to low-income countries, and ensuring a long-term and reliable vaccine supply remains a significant challenge because the high costs and complex management requirements associated with cold chain transportation hinder the promotion of vaccines.[2,18] To address these issues, the development and promotion of novel rotavirus vaccines are becoming important in the field of vaccination. Researchers are working on creating more adaptable rotavirus vaccines that can remain stable under various conditions, thereby reducing reliance on stringent cold chain transportation, such as improving access to vaccination and ultimately enhancing the effectiveness of rotavirus prevention efforts in resource-limited settings.[14,15]

Other approved and used rotavirus vaccines

Rotavac™ vaccine

Currently, in addition to the two widely used rotavirus vaccines worldwide (Rotarix and RotaTeq), three other oral rotavirus vaccines are available in specific countries and regions of India.[32,35,36] This vaccine is based on the 116E strain, isolated from a mother-and-child hospital at the All India Institute of Medical Sciences (AIIMS) in Delhi, and belongs to the G9P [11] serotype. Rotavac™ has been shown to effectively protects newborns from subsequent rotavirus infections (Table 2).[37–39] The development of this vaccine has benefited from strong support from the Indian government and aims to address the public health issue of the high rates of infant diarrhea in the region. It has been successfully incorporated into India's national immunization program. The launch of this vaccine not only fills a gap in the Indian rotavirus vaccine market but also signifies an enhancement in vaccine development capabilities in developing countries.[40] The ROTAVAC® rotavirus

Table 1. Description of currently in use traditional rotavirus vaccines.

Currently in Use			
Vaccine Name	Type	Developers/ Researchers	Key Information
Rotarix	Monovalent (Oral)	GSK	Widely used globally; effective against rotavirus infections.
RotaTeq	Pentavalent (Oral)	Merck	Covers multiple rotavirus strains; demonstrated high efficacy in clinical trials; widely adopted in high-income countries.

Table 2. Additional approved and used rotavirus vaccines.

Other approved and used rotavirus vaccines			
Vaccine Name	Type	Developers/Researchers	Key Information
ROTAVAC™	Monovalent (Oral)	AIIMS, India	Based on the 116E strain; developed for India; widely used in India and neighboring countries due to low cost and ease of production and storage.
LLR-85	Monovalent (Oral, Attenuated Lamb Strain)	Lanzhou Institute of Biological Products, China	Developed using lamb rotavirus strain; approved for use in China; cost-effective and used in rural areas.
Rotavin-M1	Monovalent (Oral, Live Attenuated)	POLYVAC, Vietnam	Developed in Vietnam; part of the country's self-sufficient vaccine policy; affordable and suitable for low-income regions.

vaccine has demonstrated good efficacy and safety in clinical trials. Phase II clinical trial results showed that the vaccine achieved a protective efficacy of 53.6% against severe rotavirus gastroenteritis, laying the foundation for its subsequent development.[41] Phase III trials further confirmed that its liquid formulations (ROTAVAC 5C and 5D) were non-inferior to the lyophilized formulation in terms of immunogenicity, and its protective efficacy against severe rotavirus gastroenteritis was comparable to that of mainstream vaccines, particularly showing significant effectiveness in resource-limited regions such as India. Additionally, the liquid formulation of ROTAVAC® can be stored at 2–8°C, addressing the reliance on cold chain logistics and improving accessibility in low-income countries. Although its efficacy may be influenced by environmental factors (e.g., sanitation conditions) and genetic diversity, studies support its role as a critical tool for rotavirus prevention, especially as no interference was observed when co-administered with other vaccines.[42] Future efforts should focus on expanding vaccination coverage and continuous genetic surveillance to further optimize its long-term protective efficacy.[43] Due to its low cost, ease of production, and storage characteristics, this vaccine is widely used in India and some neighboring countries, particularly playing a significant role among low-income populations.[44]

Lanzhou lamb rotavirus (LLR-85) vaccine

Second, the Lanzhou Institute of Biological Products in China developed a new rotavirus vaccine called the Lanzhou Lamb Rotavirus (LLR-85) vaccine, based on a live attenuated lamb rotavirus strain (Table 2).[45] This vaccine uses the G10P[12] monovalent lamb rotavirus strain, which was first isolated from primary calf kidney cells in 1984. After decades of research and optimization, the LLR-85 vaccine has been approved in China and has successfully entered the private market.[46] In the third phase of the clinical trials, 9,998 participants were included and divided into two groups: the LLR3 group and the placebo group, each with 4,999 participants. Under optimal conditions, 9,985 participants completed the first dose, including 4,992 from the LLR3 group and 4,993 from the placebo group; 9,755 participants received the second dose, followed by 9,580 who received the third dose.[47] At the end of the epidemic season, 4,582/4,359 participants from the LLR3 group and 4,611/4,422 from the placebo group entered the Per Protocol Set (PPS) dataset. In the immunogenicity evaluation subgroup, 630 participants were recruited, but only 543 completed serum collection, including 265 from the LLR3 group and 278 from the placebo group. Efficacy analysis of the vaccine showed 278 cases of severe rotavirus gastroenteritis (sRVGE), including 63 in the LLR3 group and 215 in the placebo group. The vaccine efficacy against sRVGE was 70.3%, whereas that against RVGE of any severity was 56.6%.[47] Vaccine efficacy during the first and second epidemic seasons also showed good results, with efficacies of 75.2% and 68.8% against sRVGE, and 59.3% and 55.1% against RVGE of any severity, respectively. Additionally, there were 98 cases of severe hospitalization, including 20 in the LLR3 group and 78 in the placebo group, indicating a protective efficacy against severe symptoms of 74.0%.The efficacy of the vaccine against G2, G3, and G4 rotaviruses was also evaluated, with an efficacy of 68.5% against RVGE of any severity caused by these types at the end of the second epidemic season, 75.2% in the first season, and 58.8% in the second season.[47] The efficacy against non-G2/G3/G4 RVGE types remained relatively stable in the second epidemic season, showing a slight decrease but above 54.0%, indicating an overall sustained vaccine efficacy. In particular, for G9-induced RVGE, the LLR3 vaccine demonstrated effective cross-protection, with an efficacy of 70.3% during the second epidemic season. Furthermore, owing to its relatively low price and good safety and efficacy, the vaccine has significantly contributed to reducing cases of infant diarrhea caused by rotavirus, especially after its launch in remote areas and rural communities. This not only showcases China's advancements in biotechnology but also reflects its potential for vaccine self-sufficiency. The unique antigenicity of the LLR-85 vaccine allows for higher protective efficacy against specific strains in certain regions, further invigorating China's child immunization efforts.[47]

Rotavin-M1

In Vietnam, the government has been promoting a self-sufficient vaccination policy that encourages the production and use of domestic vaccines (Table 2).[48] The Vietnam Vaccine and Biological Products Research Center (POLYVAC) developed an oral live attenuated human rotavirus vaccine called Rotavin-M1[36]. This vaccine is based on three candidate strains (G1P[8], G1P[4], and G4P[6]) isolated from hospitalized infants with diarrhea in Vietnam. After cell culture and subculturing, the KH0118–2003 strain (G1P[8]) was selected as the best vaccine candidate. The development of this vaccine adhered to vaccine production guidelines established by the World Health Organization (WHO). After years of clinical trials, it received production licensing and was launched in the market.[49] The introduction of the Rotavin-M1 vaccine is not only an important breakthrough in Vietnam's vaccine development field but also a part of its efforts to promote local vaccine self-sufficiency policies. This vaccine is inexpensive, making it particularly suitable for use in the impoverished areas of Vietnam and neighboring countries. Furthermore, the Vietnamese government actively promotes vaccination through various channels, striving to increase the coverage of rotavirus vaccines and reduce the hospitalization rates of children due to rotavirus diarrhea. The successful development of this vaccine demonstrates significant progress under Vietnam's self-sufficiency policy, and provides valuable experience and insights for other developing countries.[36,49]

Non-replicating, extravascular delivery of potential rotavirus vaccine candidates research

A team led by Li Hongjun at the Institute of Medical Biological Research of the Chinese Academy of Medical Sciences (IMBCAMS) is developing a non-replicating rotavirus vaccine aimed at delivery via the parenteral route (such as injection), and safely and effectively stimulating the immune response using inactivated viruses or viral proteins as antigens (Table 3).[8,50] This vaccine uses a human wild-type rotavirus strain, ZTR-68-A (G1P[8]), isolated from the feces of a child

Table 3. Description of candidate rota virus vaccines (under development).

Candidate (Under Development)			
Vaccine Name	Type	Developers/Researchers	Key Information
ZTR-68(Vero)	Inactivated (Extravascular)	Li Hongjun, IMBCAMS, China	Uses inactivated viruses or viral proteins; provides higher safety; suitable for low- and middle-income countries.
Inactivated rotavirus vaccine (IRV)	Inactivated (Extravascular)	Glass RI team, CDC, USA	Heat-inactivated rotavirus particles; induces high levels of antibodies; potential complement to live oral vaccines.
RV-VP6	Recombinant VP6 Protein	Blazevic V., Cincinnati Children's Hospital	VP6 protein enhances immunogenicity; used as an adjuvant for norovirus and rotavirus VLP vaccine candidates.
Rotavirus VLPs	Virus-like Particles (VLPs)	Estes MK., Baylor College of Medicine	Produced using insect cells; high levels of serum antibodies; potential as a subunit vaccine.
P2-VP8-P[4/6/8]	Trivalent Non-replicating (Subunit)	Cryz S., National Institutes of Health (NIH), USA	Composed of three VP8 subunit proteins; potential trivalent vaccine with enhanced stability and immunogenicity.
S60-VP8 PVNPs	Trivalent VLP (Pseudovirion Nanoparticles)	Tan M., USA	Trivalent nanoparticle vaccine; broad neutralizing activity and strong immune responses.
VP8-rotavirus + hAV-VP1*	Dual Vaccine (Rotavirus and Hepatitis A)	Bahramali G., USA	Fusion of VP8 protein of rotavirus and VP1 protein of hepatitis A virus; developed to address vaccination challenges in low-income countries.
mRNA Vaccine (VP7 Protein)	mRNA Vaccine (Lipid Nanoparticles)	Li H., China	Encodes VP7 protein of G1 rotavirus; encapsulated in lipid nanoparticles; strong immune response; developed as a novel mRNA-based vaccine.

with diarrhea in Zhaotong City, Yunnan Province, China. The genotype was G1-P[8]-I1-R1-C1-M1-A1-N1-T1-E1-H1.After multiple processing steps at IMBCAMS, the virus was cultured at a multiplicity of infection (MOI) of 0.1 in Vero cells in serum-free MEM medium, followed by centrifugation clarification, ultrafiltration concentration, and purification via ion exchange chromatography and molecular sieve chromatography.[51] The final vaccine formulation was obtained by formalin inactivation and adjuvanted with aluminum hydroxide to enhance the immune response.[52]

Initial preclinical studies indicated that this inactivated rotavirus vaccine effectively induced neutralizing antibodies in the serum and provided protection for animal models, demonstrating good immunogenicity, particularly in children from middle- and low-income countries, where traditional oral vaccines are less effective. This vaccine, presented as a milky white suspension, was designed to prevent gastrointestinal diseases caused by rotavirus in infants and children under five years of age.[52] Human rotavirus strain ZTR-68 undergoes strict culture, purification, and inactivation. The vaccine is available in three dosage forms: 80 EU, 160 EU, and 320 EU, each containing 0.5 milliliters, with a recommended dose of 0.5 milliliters. To determine the appropriate vaccination dosage, the research team conducted a randomized, double-blind, Phase I clinical trial focusing on the safety and immunogenicity in adult participants.[52] A total of 96 adults aged 18–49 years were enrolled in the safety analysis, and 84 adverse events were recorded, of which 42 were deemed to be related to vaccination. Compared with the placebo group, the incidence of adverse events among the different dosage groups did not show significant differences, with the main adverse events being elevated alanine aminotransferase levels, headaches, and fever, most of which were mild (grade 1).Although the incidence of adverse events was slightly higher in the high-dose group, no statistically significant differences were found compared with the placebo group, indicating good safety of the vaccine. All reported adverse events were grade 1 with no severe adverse reactions (grade ≥3).[52]

Neutralizing antibody titer tests showed that, in the low-dose group, the geometric mean titer (GMT) of neutralizing antibodies was 583.01, and the geometric mean increase (GMI) relative to the placebo group was 1.106 after full immunization at 28 days.[52] The GMT for the medium-dose group was 899.34, with a GMI of 1.543, compared to the low-dose group, whereas the high-dose group reached a GMT of 1055.24, with a GMI of 1.173, indicating that neutralizing antibody levels were dose-dependent.[52] The seroconversion rate of neutralizing antibodies in the placebo group was only 4.17%, while for the low-dose group it was 0.00%, the medium-dose group was 4.17%, and the high-dose group significantly increased to 20.83%. In terms of specific IgG testing, the IgG GMT for the low-dose group was 3444.26 with a GMI of 2.245; for the medium-dose group, it reached 6888.55, with a GMI of 2.000; and in the high-dose group, the IgG GMT was 7511.99 with a GMI of 1.091, showing that IgG levels significantly increased with dose. The seroconversion rates for IgG were 16.67% and 33.33%, and significantly increased to 79.17% in the placebo, low-, and high-dose groups, respectively.[52]

For specific IgA measurements, the low-dose group had an IgA GMT of 2332.14, with a GMI of 2.709; the medium-dose group had an IgA GMT of 4800.98, with a GMI of 2.059; and the high-dose group had an IgA GMT of 3204.30. Compared to pre-immunization, IgA antibodies showed significant increases across all dosage groups, with the high-dose group achieving an IgA seroconversion rate of 45.83%.Overall, the results indicated that, as the vaccination dose increased, all measured antibody levels exhibited a dose-dependent response, particularly in the high-dose group, which achieved significant increases in neutralizing antibodies and specific IgG and IgA levels, demonstrating that the vaccine is effective in enhancing the immune response.[52]

Therefore, this inactivated rotavirus vaccine shows excellent safety and tolerability and is expected to provide a scientific basis and effective immunization solutions for preventing rotavirus-associated gastrointestinal diseases, not only laying the foundation for further vaccine development but also offering strong support for future immunization planning and implementation in public health, ultimately contributing to the protection of children's health.[52]

The Baoming Jiang team at the Centers for Disease Control and Prevention (CDC) is actively developing a safe and effective inactivated rotavirus vaccine (IRV), owing to the challenges associated with the application of chemical inactivation techniques for rotavirus (Table 3).[7] This study explored a range of heat-treatment conditions, and the results showed that purified YK-1(G3P[3]) rotavirus in dilute buffer was completely inactivated after heat treatment, with no evidence of viral growth observed after two consecutive passages.[53] These findings indicate that heat-inactivated rotavirus particles maintain their structural and biochemical characteristics and immunogenicity, resembling the morphology of live natural virus particles, and almost all structural viral proteins, including VP1, VP2, VP4, VP6, and VP7, are retained. Western blot analysis revealed not only the detection of major proteins in heat-treated samples but also the presence of some high molecular weight bands, which may be heat-induced protein aggregates.[54,55] Despite retention of the dsRNA genome in inactivated particles, no viral growth was observed in Vero cells. Without the addition of an adjuvant, two doses (2 and 20 μg) of muscle-injected heat-inactivated YK-1 rotavirus effectively induced high titers of total and neutralizing antibodies in the mouse serum. Notably, significantly higher antibody titers were detected after using 20 μg of antigen for the two immunizations. The results from the micro-neutralization assays showed a dramatic increase in neutralizing antibody titers following booster immunization. Furthermore, the study found that the addition of an aluminum hydroxide adjuvant (Al(OH)3) significantly enhanced the total antibody titers and further improved the immune response, although its impact on neutralizing antibodies was relatively limited, which may be related to the design of a single immunization scheme. Therefore, research suggests that at least two doses of parenteral rotavirus vaccination should be administered to effectively activate both the innate and adaptive immune responses in the body, thereby enhancing antibody production.[7,53–55] Although a variety of inactivated viral vaccines have been approved and widely used, selecting safe and effective inactivation methods remains a challenge in the development of new vaccines. Many vaccines are inactivated using formaldehyde, but studies have shown that this may result in weaker neutralizing antibody responses and enhanced disease. In contrast, heat treatment has demonstrated advantages in the development of vaccines for multiple pathogens, effectively inducing neutralizing antibody responses. Compared to formaldehyde-inactivated vaccines, those treated with heat show weaker immune responses. Therefore, heat treatment holds promise as a new direction for developing safer and more effective vaccines.[7,53]

These findings indicate that heat inactivation technology could become a new method for producing a safe and effective rotavirus parenteral vaccine and may serve as an important complement to oral live vaccines for rotavirus. This study provides new insights and direction for the development of rotavirus vaccines. In summary, this study offers preliminary experimental evidence for the safety and efficacy of the vaccine, with the hope of providing better preventive measures for children's health in the future.[53]

Non-replicating vaccines include not only inactivated vaccines but also virus-like particles (VLPs) as an effective option. A team led by Blazevic V. at Cincinnati Children's Hospital investigated the effect of a tubular form of recombinant VP6 protein from rotavirus (RV) to enhance the immunogenicity of a norovirus (NoV) VLP vaccine candidate and found that it has an adjuvant effect in vivo (Table 3).[56] This study focused on analyzing the effect of VP6 on the activation and maturation of antigen-presenting cells (APCs) and its role in promoting the uptake of NoV VLPs by APCs. Experiments using the mouse macrophage cell line RAW 264.7 and dendritic cell line JAWSII showed that VP6 nanotubes could be effectively internalized by APCs and significantly upregulated the expression of co-stimulatory molecules such as CD40, CD80, and CD86, suggesting that VP6 may enhance immune responses by promoting the activation state of APCs.[56] VP6 treatment induced the production of pro-inflammatory cytokines, including tumor necrosis factor (TNF-α), interleukin (IL-6), and interferon (IFN), further confirming its important role in APC immune activation. The mechanism of action of VP6 is partially dependent on lipid raft-mediated endocytosis.[56] Moreover, the combination of VP6 and GII.4 VLP from norovirus significantly enhanced the specific immune response, including increased antibody production and cellular immune responses, particularly cross-reactivity against various norovirus strains, thereby demonstrating the potential of this combination for addressing norovirus variants. Notably, VP6 internalization efficiency was higher in RAW macrophages than in immature dendritic cells, whereas no significant uptake was detected in Caco-2 cells.[56,57]

In summary, VP6 shows potential as an adjuvant to enhance immune responses to norovirus vaccines by promoting maturation and activation of APCs and enhancing their capacity to take up VLPs, thereby laying a theoretical foundation for the design and optimization of future novel combination vaccines.[57] Additionally, a team led by Estes MK at Baylor College of Medicine conducted preliminary research on rotavirus vaccines using VLPs as vaccine candidates.[58,59] These VLPs were produced through the co-infection of insect cells with recombinant baculoviruses, demonstrating their potential for the development of rotavirus vaccines, which not only improves the production efficiency of the vaccine but may also enhance its immunogenicity, as it expresses VP2 from bovine rotavirus RIF and VP4, VP6, or VP7 from simian rotavirus SA11. Following non-oral administration of these VLPs, rabbits produced high levels of rotavirus-specific serum antibodies and fecal IgG but not fecal IgA, and the production of fecal IgG provided partial protection against oral challenges with ALA rotavirus. Additionally, mice vaccinated with G1 VP2/6/7 or VP2/4/6n VLPs also had neutralizing antibodies, and the immunogenicity of VLPs was significantly enhanced when QS21 adjuvant was used, indicating that VLPs are promising subunit vaccines.[58]

A team led by Cryz at the National Institutes of Health (NIH) developed a trivalent, non-replicating candidate vaccine against rotavirus (RV) consisting of three truncated VP8 subunits linked to the P2 CD4+ epitope of tetanus toxin (P2-VP8 -P[4/6/8]) (Table 3). This study compared the physicochemical properties of these three engineered protein fusions using various analytical techniques, and evaluated the stability and degradation pathways of the antigens under different

environmental stresses.[60] P2-VP8-P[4] and P2-VP8-P[6] exhibited comparable physical stability when subjected to variations in pH and temperature, whereas P2-VP8-P[8] showed a higher level of stability. Forced degradation studies have indicated similar chemical stability profiles across variations, with methionine 1 being particularly vulnerable to oxidation. Additionally, a single cysteine residue located at position 173/172 is prone to form intermolecular disulfide bonds. Among these variants, P2-VP8-P[6] is the most affected, exhibiting the highest degree of deamidation at asparagine 7.These results provide a structural model for nonreplicating RV antigens and lay the groundwork for the development of novel vaccines.[60]

Tan M and his team developed a candidate for a trivalent vaccine against rotaviruses based on pseudoviruses, using pseudovirus-like nanoparticles S60-VP8 (PVNP), which display the structural VP8 domain that binds to glycans in the rotavirus spike protein (Table 3). This study developed a scalable approach for the mass production of non-labeled S60-VP8* PVNP as a candidate parenteral vaccine, targeting four rotavirus P-types: P[8], P[4], P[6], and P[11]. The process consisted of two main steps: first, selective precipitation of the S-VP8 protein using ammonium sulfate, followed by further purification through anion-exchange chromatography. The resulting purified soluble protein self-assembles into PVNP. After intramuscular injection, the vaccine induced a strong immune response in mice, with sera from mice vaccinated with the trivalent vaccine displaying high levels of IgG and IgA antibodies, strong blocking abilities, and broad neutralizing activity. Trivalent S60-VP8* PVNP is a promising non-replicating parenteral vaccine against globally relevant rotaviruses.[61]

Jiang X and his team will focus their research on the P particles of the norovirus, which serve as a quasi-viral nanoparticle platform for developing vaccines against norovirus, rotavirus, and influenza virus (Table 3). Norovirus (NoV) causes acute gastroenteritis in millions of people worldwide. The P region of the norovirus capsid protein forms a quasi-viral structure composed of 24 subunits, known as P particles, which are characterized by excellent vaccine properties. P particles can be easily produced in Escherichia coli, are highly stable, and have strong immunogenicity. Each P region consists of three surface loops that effectively display foreign antigens, rendering P particles as a valuable platform for developing vaccines against other infectious diseases. This article summarizes the discovery, structure, development, and application of P particles, highlighting their potential as vaccines against norovirus and other pathogenic agents such as rotavirus and influenza virus.[62]

Bahramali G. and his team developed a new dual vaccine candidate by combining the VP8 protein from rotavirus with the VP1 protein from hepatitis A virus to address current issues faced by vaccines in low-income countries.[63] The recombinant protein VP8*-Rota + AAY + hAV-VP1, produced using an Escherichia coli-based expression system, had a molecular weight of approximately 45.5 kDa and was purified using size exclusion chromatography. Combined VP1 and VP8 proteins along with vaccines against both rotavirus and hepatitis A virus (with or without adjuvants ALUM and M720) were subcutaneously administered to BALB/c mice.[63] The results showed that the combined protein, when mixed with adjuvants, led to significantly higher IgG, IgG1, and IgG2 levels along with strong short-term IL-5 and IFN-γ responses, surpassing the long-term IL-5 response of single-component vaccines. Therefore, the combined VP8*-Rota + AAY + hAV-VP1 protein is considered a promising dual vaccine candidate for effective prevention of hepatitis A and rotavirus infections.[63]

mRNA vaccines represent a new type of vaccine technology that introduces messenger RNA (mRNA), which encodes the antigen protein, into human cells, allowing them to synthesize antigens and trigger an immune response (Table 3).[64] This technology has advantages such as rapid development and good safety profiles, playing an important role in the prevention and control of the COVID-19 pandemic and opening new pathways for future vaccine research and development.[64] Li H and his team developed a nucleotide-modified mRNA vaccine encapsulated in lipid nanoparticles (LNPs), encoding the VP7 protein of G1 rotavirus, and utilized the 5' untranslated region obtained from human rotavirus. After quality testing, the vaccine was administered to mice via subcutaneous or intramuscular injection, followed by three doses. In this study, The levels of IgG antibodies, neutralizing antibodies, and cellular immunity were assessed. The results indicated that IgG antibody levels in the non-adjuvant group were significantly elevated, with the highest antibody titers observed after intramuscular injection. The vaccine elicited a potent antiviral immune response and activated chemokine signaling pathways, demonstrating its potential for preventing rotavirus infections.[64]

Summary

New-generation non-replicating vaccines such as mRNA and viral vector vaccines demonstrate significant advantages over traditional vaccines, particularly in terms of design and application. Traditional vaccines primarily induce immune responses through attenuated or inactivated pathogens, bacteria, or portions of their proteins. While these methods are validated and effective, they present several drawbacks, including the potential for mild side effects such as fever and pain at the injection site. More critically, the immune protection provided by traditional vaccines can sometimes be short-lived, and the research and development timeline is protracted, typically spanning several years to a decade, to navigate complex clinical trials before they become widely available. In addition, traditional vaccines require strict production and storage conditions, particularly cold chain management, which complicates their distribution in resource-limited settings. Consequently, when faced with sudden public health crises, traditional vaccines often fail to provide rapid responses.

In contrast, new-generation non-replicating vaccines utilize genetic information to instruct host cells to synthesize antigens, effectively reducing reliance on live viruses and significantly enhancing safety. For example, mRNA vaccines do not contain live virus. Instead, they carry genetic instructions that encode specific antigens from pathogens, thereby enabling cells to autonomously produce these antigens and elicit a strong immune response. The successful application of this

technology has been particularly evident during the COVID-19 pandemic, demonstrating its ability to rapidly address emerging pathogens. More importantly, new-generation vaccines not only effectively stimulate humoral immunity, but also promote cellular immunity, achieving dual immune protection that bolsters defense against viral variants, an invaluable characteristic in an era of frequent viral mutations.

The flexibility and adaptability of these novel vaccines empower researchers to swiftly respond to emerging diseases and promptly address public health crises. Hence, they are playing an increasingly important role in the global public health response. As technology continues to advance, non-replicating vaccines offer new possibilities for safeguarding human health, and are poised to play an even more critical role in vaccine development and disease prevention in the future, protecting humanity against a wide array of infectious diseases. Therefore, strengthening research and promotion efforts for rotavirus vaccines is not only key to improving child health but also an essential component of global public health.

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Notes on contributor

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Clinical trial registration

The study, titled "A Phase I Clinical Trial for Inactivated Rotavirus Vaccine (Vero Cell)," is registered under the number ChiCTR2000039776. The study was approved by the ethics committee (reference number AF/SC-08/03.0). The study titled "Phase Three Clinical Trials of Trivalent Rotavirus Genetic Reassortment Vaccine," registered under the NCT number NCT01738074.

Literature retrieval and screening strategies

Databases used (such as PubMed, Web of Science, etc.), search keywords (e.g. 'rotavirus vaccine,' 'inactivated vaccine'), time range (1980–2024), and inclusion/exclusion criteria.

References

1. Li J, Wang H, Li D, Zhang Q, Liu N. Infection status and circulating strains of rotaviruses in Chinese children younger than 5-years old from 2011 to 2018: systematic review and meta-analysis. Hum Vaccin Immunother. 2021;17(6):1811–1817. doi: 10.1080/21645515.2020.1849519.
2. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD. Global, regional, and national estimates of rotavirus mortality in children < 5 years age, 2000–2013. Clin Infect Dis. 2016;62(suppl 2):S96–S105. doi: 10.1093/cid/civ1013.
3. Duan Z. Expert consensus on immunoprophylaxis of childhood rotavirus gastroenteritis (2024 version). Zhonghua yu fang yi xue za zhi [Chin J Preventative Med]. 2024;58:1–33.
4. Lepage P, Vergison A. Prevention of childhood rotavirus disease through the use of rotarix ™ and RotaTeq ™ vaccines. Expert Opin Biol Ther. 2007;7(12):1881–1892. doi: 10.1517/14712598.7.12.1881.
5. Weycker D, Sofrygin O, Kemner JE, Pelton SI, Oster G. Cost of routine immunization of young children against rotavirus infection with rotarix versus RotaTeq. Vaccine. 2009;27(36):4930–4937. doi: 10.1016/j.vaccine.2009.06.025.
6. Velasquez-Portocarrero DE, Wang X, Cortese MM, Snider CJ, Anand A, Costantini VP, Yunus M, Aziz AB, Haque W, Parashar U, et al. Head-to-head comparison of the immunogenicity of RotaTeq and rotarix rotavirus vaccines and factors associated with seroresponse in infants in Bangladesh: a randomised, controlled, open-label, parallel, phase 4 trial. Lancet Infect Dis. 2022;22(11):1606–1616. doi: 10.1016/S1473-3099(22)00368-1.
7. Jiang B, Wang Y, Saluzzo JF, Bargeron K, Frachette MJ, Glass RI. Immunogenicity of a thermally inactivated rotavirus vaccine in mice. Hum Vaccin. 2008;4(2):143–147. doi: 10.4161/hv.4.2.5263.
8. Zhang B, Yi S, Ma Y, Zhang G, Zhang Y, Xie T, Li H, Sun M. Immunogenicity of a scalable inactivated rotavirus vaccine in mice. Hum Vaccin. 2011;7(2):248–257. doi: 10.4161/hv.7.2.14121.
9. Mudur G. India to introduce rubella and rotavirus vaccines and inactivated polio vaccine. BMJ. 2014;349(12):g4844. doi: 10.1136/bmj.g4844.
10. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, Dallas MJ, Heyse JF, Goveia MG, Black SB, et al. Safety and efficacy of a pentavalent human–bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23–33. doi: 10.1056/NEJMoa052664.
11. Patel M, Shane AL, Parashar UD, Jiang B, Gentsch JR, Glass RI. Oral rotavirus vaccines: how well will they work where they are needed most? J Infect Dis. 2009;200(s1):S39–S48. doi: 10.1086/605035.
12. Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, Ngwira B, Victor JC, Gillard PH, Cheuvart BB, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med. 2010;362(4):289–298. doi: 10.1056/NEJMoa0904797.
13. Kirkwood CD, Boniface K, Barnes GL, Bishop RF. Distribution of rotavirus genotypes after introduction of rotavirus vaccines, Rotarix® and RotaTeq®, into the national immunization program of Australia. Pediatr Infect Disease J. 2011;30(1):S48–53. doi: 10.1097/INF.0b013e3181fefd90.
14. Rotavirus vaccines WHO position paper: January 2013 – recommendations. Vaccine. 2013;31(52):6170–6171. doi: 10.1016/j.vaccine.2013.05.037.
15. Agocs MM, Serhan F, Yen C, Mwenda JM, de Oliveira LH, Teleb N, Wasley A, Wijesinghe PR, Fox K, Tate JE, et al. WHO global rotavirus surveillance network: a strategic review of the first 5 years, 2008-2012. MMWR Morb Mortal Wkly Rep. 2014;63(29):634–637.

16. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, Cheuvart B, Espinoza F, Gillard P, Innis BL, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11–22. doi: 10.1056/NEJMoa052434.
17. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, Meurice F, Han HH, Damaso S, Bouckenooghe A. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007;370(9601):1757–1763. doi: 10.1016/S0140-6736(07)61744-9.
18. Kollaritsch H, Kundi M, Giaquinto C, Paulke-Korinek M. Rotavirus vaccines: a story of success. Clin Microbiol Infect. 2015;21(8):735–743. doi: 10.1016/j.cmi.2015.01.027.
19. Santos VS, Marques DP, Martins-Filho PR, Cuevas LE, Gurgel RQ. Effectiveness of rotavirus vaccines against rotavirus infection and hospitalization in Latin America: systematic review and meta-analysis. Infect Dis Poverty. 2016;5(1):83. doi: 10.1186/s40249-016-0173-2.
20. van Hoek AJ, Ngama M, Ismail A, Chuma J, Cheburet S, Mutonga D, Kamau T, Nokes DJ. A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: comparison between rotarix and RotaTeq vaccines. PLOS ONE. 2012;7(10):e47511. doi: 10.1371/journal.pone.0047511.
21. Zeller M, Patton JT, Heylen E, De Coster S, Ciarlet M, Van Ranst M, Matthijnssens J. Genetic analyses reveal differences in the VP7 and VP4 antigenic epitopes between human rotaviruses circulating in Belgium and rotaviruses in rotarix and RotaTeq. J Clin Microbiol. 2012;50(3):966–976. doi: 10.1128/JCM.05590-11.
22. Diller JR, Carter MH, Kanai Y, Sanchez SV, Kobayashi T, Ogden KM. Monoreassortant rotaviruses of multiple G types are differentially neutralized by sera from infants vaccinated with ROTARIX and RotaTeq. J Infect Dis. 2021;224(10):1720–1729. doi: 10.1093/infdis/jiab479.
23. Fallah T, Mansour Ghanaiee R, Karimi A, Zahraei SM, Mahmoudi S, Alebouyeh M. Comparative analysis of the RVA VP7 and VP4 antigenic epitopes circulating in Iran and the rotarix and RotaTeq vaccines. Heliyon. 2024;10(13):e33887. doi: 10.1016/j.heliyon.2024.e33887.
24. Bravo L, Chitraka A, Liu A, Choudhury J, Kumar K, Berezo L, Cimafranca L, Chatterjee P, Garg P, Siriwardene P, et al. Reactogenicity and safety of the human rotavirus vaccine, rotarix ™ in the Philippines, Sri Lanka, and India: a post-marketing surveillance study. Hum Vaccines & Immunotherapeut. 2014;10(8):2276–2283. doi: 10.4161/hv.29280.
25. Kulkarni R, Arora R, Arora R, Chitambar SD. Sequence analysis of VP7 and VP4 genes of G1P[8] rotaviruses circulating among diarrhoeic children in Pune, India: a comparison with rotarix and RotaTeq vaccine strains. Vaccine. 2014;32(1):A75–83. doi: 10.1016/j.vaccine.2014.03.080.
26. Morozova OV, Sashina TA, Fomina SG, Novikova NA. Comparative characteristics of the VP7 and VP4 antigenic epitopes of the rotaviruses circulating in Russia (Nizhny Novgorod) and the rotarix and RotaTeq vaccines. Arch Virol. 2015;160(7):1693–1703. doi: 10.1007/s00705-015-2439-6.
27. Wu D, Yen C, Yin ZD, Li YX, Liu N, Liu YM, Wang H-Q, Cui F-Q, Gregory CJ, Tate JE, et al. The public health burden of rotavirus disease in children younger than five years and considerations for rotavirus vaccine introduction in China. Pediatr Infect Dis J. 2016;35(12):e392–e398. doi: 10.1097/INF.0000000000001327.
28. Liu Y, Guo T, Yu Q, Zhang H, Du J, Zhang Y, Xia S, Yang H, Li Q. Association of human leukocyte antigen alleles and supertypes with immunogenicity of oral rotavirus vaccine given to infants in China. Medicine. 2018;97(40):e12706. doi: 10.1097/MD.0000000000012706.
29. Parker EPK, Praharaj I, Zekavati A, Lazarus RP, Giri S, Operario DJ, Liu J, Houpt E, Iturriza-Gómara M, Kampmann B, et al. Influence of the intestinal microbiota on the immunogenicity of oral rotavirus vaccine given to infants in south India. Vaccine. 2018;36(2):264–272. doi: 10.1016/j.vaccine.2017.11.031.
30. Gheorghita S, Birca L, Donos A, Wasley A, Birca I, Cojocaru R, Melnick A, Ciobanu S, Mosina L, Cortese MM, et al. Impact of rotavirus vaccine introduction and vaccine effectiveness in the Republic of Moldova. Clin Infect Dis. 2016;62(suppl 2):SS140–SS146. doi: 10.1093/cid/civ1209.
31. Reddy SN, Nair NP, Tate JE, Thiyagarajan V, Giri S, Praharaj I, Mohan VR, Babji S, Gupte MD, Arora R, et al. Intussusception after rotavirus vaccine introduction in India. N Engl J Med. 2020;383(20):1932–1940. doi: 10.1056/NEJMoa2002276.
32. Ella R, Bobba R, Muralidhar S, Babji S, Vadrevu KM, Bhan MK. A phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, attenuated, oral rotavirus vaccine (116E), ROTAVAC®, administered simultaneously with or without the buffering agent in healthy infants in India. Hum Vaccines Immunother. 2018;14(7):1791–1799. doi: 10.1080/21645515.2018.1450709.
33. Kumar CPG, N SR, Subramanian S, Shenoy A, Maniam R, Dorairaj P, Ramasubramaniam P, Thiyagarajan V, Kulandaivel M, Guruswamy R, et al. Epidemiology of intussusception hospitalizations in children under 2 years of age post rotavirus vaccine introduction in Tamil Nadu and Puducherry, India. Indian J Pediatr. 2021;88(S1):124–130. doi: 10.1007/s12098-020-03597-1.
34. Haque W, Talha M, Rahman S, Hasan M, Alam S, Hassan Z, Moni S, Khan SH, Hossain ME, Faruque ASG, et al. Rotavirus trends and distribution of genotypes before and during COVID-19 pandemic era: Bangladesh, 2017–2021. J Med Virol. 2024;96(5):e29681. doi: 10.1002/jmv.29681.
35. Mohan KV, Glass RI, Atreya CD. Comparative molecular characterization of gene segment 11-derived NSP6 from lamb rotavirus LLR strain used as a human vaccine in China. Biologicals: J Int Assoc Biol Standardization. 2006;34(4):265–272. doi: 10.1016/j.biologicals.2005.11.005.
36. Dang A, Van Trang N, Thiem VD, Anh TH, Mao ND, Wang Y, Jiang B, Hien ND, Luan LT. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (rotavin-M1) in Vietnamese children. Vaccine. 2012;30(1):A114–21. doi: 10.1016/j.vaccine.2011.07.118.
37. Ghoshal V, Nayak MK, Misra N, Kumar R, Reddy NS, Mohakud NK. Surveillance and molecular characterization of rotavirus strains circulating in Odisha, India after introduction of Rotavac. Indian J Pediatr. 2021;88(S1):41–46. doi: 10.1007/s12098-020-03622-3.
38. Skansberg A, Sauer M, Tan M, Santosham M, Jennings MC. Product review of the rotavirus vaccines ROTASIIL, ROTAVAC, and rotavin-M1. Hum Vaccines Immunother. 2021;17(4):1223–1234. doi: 10.1080/21645515.2020.1804245.
39. Chandola TR, Taneja S, Goyal N, Antony K, Bhatia K, More D, Bhandari N, Cho I, Mohan K, Prasad S, et al. ROTAVAC ® does not interfere with the immune response to childhood vaccines in Indian infants: a randomized placebo controlled trial. Heliyon. 2017;3(5):e00302. doi: 10.1016/j.heliyon.2017.e00302.
40. Jalilvand S, Latifi T, Kachooei A, Mirhoseinian M, Hoseini-Fakhr SS, Behnezhad F, Roohvand F, Shoja Z. Circulating rotavirus strains in children with acute gastroenteritis in Iran, 1986 to 2023 and their genetic/antigenic divergence compared to approved vaccines strains (rotarix, RotaTeq, ROTAVAC, ROTASIIL) before mass vaccination: clues for vaccination policy makers. Virus Res. 2024;346:199411. doi: 10.1016/j.virusres.2024.199411.
41. Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S, Goyal N, Kawade A, Kang G, Rathore SS, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2014;383(9935):2136–2143. doi: 10.1016/S0140-6736(13)62630-6.
42. KK, Chiteti SR, Aileni VK, Babji S, Blackwelder WC, Kumar A, Vagha J, Nayak U, Mitra M, D N, et al. Phase III randomized clinical studies to evaluate the immunogenicity, lot-to-lot consistency, and safety of ROTAVAC® liquid formulations (ROTAVAC 5C & 5D) and non-inferiority comparisons with licensed

ROTAVAC® (frozen formulation) in healthy infants. Hum Vaccin Immunother. 2023;19(3):2278346. doi: 10.1080/21645515.2023.2278346.
43. Ella R, Bobba R, Muralidhar S, Babji S, Vadrevu KM, Bhan MK. A phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, attenuated, oral rotavirus vaccine (116E), ROTAVAC®, administered simultaneously with or without the buffering agent in healthy infants in India. Hum Vaccin Immunother. 2018;14(7):1791–1799. doi: 10.1080/21645515.2018.1450709.
44. P KK, Chiteti SR, Aileni VK, Babji S, Blackwelder WC, Kumar A, Vagha J, Nayak U, Mitra M, D N, et al. Phase III randomized clinical studies to evaluate the immunogenicity, lot-to-lot consistency, and safety of ROTAVAC® liquid formulations (ROTAVAC 5C & 5D) and non-inferiority comparisons with licensed ROTAVAC® (frozen formulation) in healthy infants. Hum Vaccin Immunother. 2023;19(3):2278346. doi: 10.1080/21645515.2023.2278346.
45. Chang JT, Li X, Liu HJ, Yu L. Ovine rotavirus strain LLR-85-based bovine rotavirus candidate vaccines: construction, characterization and immunogenicity evaluation. Vet Microbiol. 2010;146(1–2):35–43. doi: 10.1016/j.vetmic.2010.04.016.
46. Liu Y, Yue CY, Li Y, Wang YM, Gao SR, Wang ZG, Xie X, Zhao HP, Wang D, Liang XF, et al. Analysis of vaccination situation of orial live attenuated rotavirus vaccine (LLR strain) among children in 6 provinces of China. Zhonghua yu fang yi xue za zhi [Chin J Preventative Med]. 2018;52(3):282–286. doi: 10.3760/cma.j.issn.0253-9624.2018.03.012.
47. Xia S, Du J, Su J, Liu Y, Huang L, Yu Q, Xie Z, Gao J, Xu B, Gao X, et al. Efficacy, immunogenicity and safety of a trivalent live human-lamb reassortant rotavirus vaccine (LLR3) in healthy Chinese infants: a randomized, double-blind, placebo-controlled trial. Vaccine. 2020;38(46):7393–7400. doi: 10.1016/j.vaccine.2020.04.038.
48. Luan T, Nguyen TV, Nguyen PM, Huong NT, Huong NT, Huong NTM, Hanh TB, Ha DN, Anh DD, Gentsch JR, et al. Development and characterization of candidate rotavirus vaccine strains derived from children with diarrhoea in Vietnam. Vaccine. 2009;27(5):F130–8. doi: 10.1016/j.vaccine.2009.08.086.
49. Van Trang N, Tate JE, Phuong Mai LT, Vu TD, Quyet NT, Thi LK, Thi Chu MN, Ngoc Tran MP, Thi Pham TP, Nguyen HT, et al. Impact and effectiveness of rotavin-M1 under conditions of routine use in two provinces in Vietnam, 2016–2021, an observational and case–control study. Lancet Reg Health - West Pac. 2023;37:100789. doi: 10.1016/j.lanwpc.2023.100789.
50. Wu JY, Zhou Y, Zhang GM, Mu GF, Yi S, Yin N, Xie Y-P, Lin X-C, Li H-J, Sun M-S. Isolation and characterization of a new candidate human inactivated rotavirus vaccine strain from hospitalized children in Yunnan, China: 2010-2013. World J Clin Cases. 2018;6(11):426–440. doi: 10.12998/wjcc.v6.i11.426.
51. Zhou Y, Wu J, Hu X, Chen R, Lin X, Yin N, Lu C, Ye J, Zhao Y, Song X, et al. Immunogenicity of inactivated rotavirus in rhesus monkey, and assessment of immunologic mechanisms. Hum Vaccin Immunother. 2023;19(1):2189598. doi: 10.1080/21645515.2023.2189598.
52. Wu JY, Zhang W, Pu J, Liu Y, Huang LL, Zhou Y, Gao J-M, Tan J-B, Liu X-L, Yang J, et al. A randomized, double-blind, placebo-controlled phase I clinical trial of rotavirus inactivated vaccine (vero cell) in a healthy adult population aged 18–49 years to assess safety and preliminary observation of immunogenicity. Vaccine. 2024;42(19):4030–4039. doi: 10.1016/j.vaccine.2024.05.014.
53. Jiang B, Gentsch JR, Glass RI. Inactivated rotavirus vaccines: a priority for accelerated vaccine development. Vaccine. 2008;26(52):6754–6758. doi: 10.1016/j.vaccine.2008.10.008.
54. Resch TK, Wang Y, Moon SS, Joyce J, Li S, Prausnitz M, Jiang B. Inactivated rotavirus vaccine by parenteral administration induces mucosal immunity in mice. Sci Rep. 2018;8(1):561. doi: 10.1038/s41598-017-18973-9.
55. Moon SS, Richter-Roche M, Resch TK, Wang Y, Foytich KR, Wang H, Mainou BA, Pewin W, Lee J, Henry S, et al. Microneedle patch as a new platform to effectively deliver inactivated polio vaccine and inactivated rotavirus vaccine. NPJ Vaccines. 2022;7(1):26. doi: 10.1038/s41541-022-00443-7.
56. Blazevic V, Lappalainen S, Nurminen K, Huhti L, Vesikari T. Norovirus VLPs and rotavirus VP6 protein as combined vaccine for childhood gastroenteritis. Vaccine. 2011;29(45):8126–8133. doi: 10.1016/j.vaccine.2011.08.026.
57. Malm M, Tamminen K, Lappalainen S, Vesikari T, Blazevic V. Rotavirus recombinant VP6 nanotubes act as an immunomodulator and delivery vehicle for norovirus virus-like particles. J Immunol Res. 2016;2016:1–13. doi: 10.1155/2016/9171632.
58. Conner ME, Zarley CD, Hu B, Parsons S, Drabinski D, Greiner S, Smith R, Jiang B, Corsaro B, Barniak, et al. Virus-like particles as a rotavirus subunit vaccine. J Infect Dis. 1996;174(Supplement 1):S88–92. doi: 10.1093/infdis/174.Supplement_1.S88.
59. Velázquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, Glass RI, Estes MK, Pickering LK, Ruiz-Palacios GM. Rotavirus infection in infants as protection against subsequent infections. N Engl J Med. 1996;335(14):1022–1028. doi: 10.1056/NEJM199610033351404.
60. Agarwal S, Hickey JM, Sahni N, Toth T, Robertson GA, Sitrin R, Cryz S, Joshi SB, Volkin DB. Recombinant subunit rotavirus trivalent vaccine candidate: physicochemical comparisons and stability evaluations of three protein antigens. J Pharm Sci. 2020;109(1):380–393. doi: 10.1016/j.xphs.2019.08.002.
61. Tan M, Jiang X. Histo-blood group antigens: a common niche for norovirus and rotavirus. Expert Rev Mol Med. 2014;16:e5. doi: 10.1017/erm.2014.2.
62. Tan M, Jiang X. Norovirus P particle: a subviral nanoparticle for vaccine development against norovirus, rotavirus and influenza virus. Nanomedicine. 2012;7(6):889–897. doi: 10.2217/nnm.12.62 .
63. Yarmohammadi H, Aghasadeghi M, Akhavan Sepahi A, Hamidi-Fard M, Bahramali G. Designing the fusion protein of rotavirus VP8 and hepatitis a virus VP1 and evaluating the immunological response in BALB/c mice. Iran J Microbiol. 2024;16:401–410. doi: 10.18502/ijm.v16i3.15797.
64. Lu C, Li Y, Chen R, Hu X, Leng Q, Song X, Lin X, Ye J, Wang J, Li J, et al. Safety, immunogenicity, and mechanism of a rotavirus mRNA-lnp vaccine in mice. Viruses. 2024;16(2):211. doi: 10.3390/v16020211.