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ARTICLE

Product review of the rotavirus vaccines ROTASIIL, ROTAVAC, and Rotavin-M1

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ABSTRACT

Rotavirus is the leading cause of severe dehydrating gastroenteritis and death due to diarrhea among children under 5, causing over 180,000 under-5 deaths annually. Safe, effective rotavirus vaccines have been available for over a decade and are used in over 98 countries. In addition to the globally available, WHO-prequalified ROTARIX (GSK) and RotaTeq (Merck), several new rotavirus vaccines have attained national licensure – ROTAVAC (Bharat Biotech) and ROTASIIL (Serum Institute of India), licensed and manufactured in India and now WHO-prequalified, and Rotavin-M1 (PolyVac), licensed and manufactured in Vietnam. In this review, we summarize the available clinical trial and post-introduction evidence for these three new orally administered rotavirus vaccines. All three vaccines have demonstrated safety and efficacy against rotavirus diarrhea, although publicly available preclinical data are limited in some cases. This expanding product landscape presents a range of options to optimize immunization programs, and new presentations of each vaccine are currently under development.

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Diarrhea is a leading cause of child mortality around the world, annually responsible for over 400,000 deaths among children under five years of age[1]. Among this age group, rotavirus is one of the most common causes of diarrheal deaths, accounting for over 180,000 under-five diarrheal deaths each year,[2,3] and the most common cause of severe dehydrating gastroenteritis, with a particularly heavy burden in developing countries.[4–7] The virus is highly transmissible, with nearly all children in unvaccinated populations experiencing at least one rotavirus infection in the first five years of life.[8] Experts estimate that, globally, for each rotavirus death in 2017, an additional 12 patients were hospitalized and 2,000 patients contracted rotavirus diarrhea.[2]

Rotavirus, of the *Reoviridae* family, is a highly communicable double-stranded RNA virus with an incubation period typically lasting 48 hours, during which time virus can be shed in the stool of an asymptomatic patient.[4] The virus is primarily transmitted through the fecal-oral route, but person-to-person and fomite transmission are also important.[4] Many, but not all, settings see seasonal patterns in rotavirus infection.[4]

Rotavirus targets and damages enterocytes lining the small intestine, leading to symptoms ranging from mild watery diarrhea to more severe illness, with vomiting, fever, and dehydration.[9] Mild cases can be treated in the community with oral rehydration solution (ORS) and zinc supplements,[10] but access to these simple interventions is limited for the poorest children; severe cases require intravenous fluids and resuscitation and can lead to death.[11] Providing clean water and improving sanitation reduces overall diarrheal illness but, on its own, is insufficient to control rotavirus; rotavirus diarrhea continues to have a significant burden in populations without access to vaccination.[12,13]

In the community, the most commonly available diagnostic testing to confirm rotavirus infection is through enzyme immunoassay (EIA) of stool samples.[1] Culture and other techniques including reverse transcription-polymerase chain reaction (RT-PCR) are common in research settings.[14]

Vaccine background

Safe, effective rotavirus vaccines (RVVs) have been available for over a decade. Building upon its original 2007 RVV position paper, in 2009 the WHO recommended that all countries include RVV in their national programs and schedules;[15] to date, the vaccines are included in the national immunization programs of more than 98 countries worldwide.[16] RVVs promote the immune response to rotavirus infection by stimulating the production of neutralizing antibodies to viral protein (VP) antigens, VP7 (G-type) and VP4 (*P*-type),[4,17,18] which are common to multiple, diverse strains of rotavirus.[19,20] With studies demonstrating that the globally available vaccines have comparable efficacy despite different strain composition, questions have emerged about the mediating role of non-neutralizing antibodies against other VP antigens.[20–22] As an oral agent given in multiple doses, currently available RVVs are thought to selectively activate IgA production in the gastrointestinal tract, where infection occurs.[1]

Although vaccination clearly protects against rotavirus disease, protection has notbeen demonstrated to correspond to a given level of neutralizing antibodies, thus, no immune correlate of protection is defined for RVV;[20,23] however, rotavirus-specific IgA is the most frequently used metric in clinical evaluations of vaccines. Clinical trial efficacy is typically

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evaluated on the basis of clinical outcomes, such as gastroenteritis and its related signs and symptoms, hospitalization, or death.[20]

ROTARIX® (GlaxoSmithKline, licensed in 2004) and RotaTeq® (Merck, licensed in 2006) are 80–90% efficacious in preventing severe rotavirus diarrhea in settings with relatively high income and low or very low mortality (across Europe and Latin America),[24,25] and 40–60% efficacious in settings with relatively low income and high or very high mortality (particularly across Asia and Africa).[26] Various studies also show cross-protection against rotavirus strains not included in the vaccine.[27]

Common, short-term side effects of rotavirus vaccine include irritability and mild, short-lived diarrhea or vomiting.[28] Large, controlled trials of the first RVV global market entrants, ROTARIX and RotaTeq, both live attenuated vaccines, have shown no difference in serious adverse event rates between RVV and placebo.[24,25] However, some post-marketing studies have shown a small increased risk for intussusception – one to seven additional cases per 100,000 vaccinated infants – mainly after the first dose.[24,25,29-38] Intussusception is a rare, naturally occurring condition involving a "telescoping" of the intestines over themselves, which can damage the tissue; the mechanism of intussusception remains poorly understood.[39] The benefits of widespread RVV in preventing severe illness, hospitalizations, and deaths far outweigh the small risk of intussusception.[26] However, the WHO continues to conduct and review regional surveillance of intussusception among populations vaccinated with RVV.[40] Post-licensure studies of ROTARIX in Africa showed no increased risk of intussusception, confirmed with a recent analysis of active surveillance data from seven African countries.[38] Recent post-licensure analysis of surveillance data from India, specifically states that have introduced ROTAVAC, has also found no increased risk of intussusception; these reports are summarized below.[41,42]

Product characteristics

In addition to ROTARIX and RotaTeq, three newer RVV products are available nationally (Rotavin-M1) or internationally (ROTAVAC, ROTASIIL), with varying presentations (Table 1).

Rotavin-M1, a liquid-frozen, monovalent rotavirus vaccine manufactured by Polyvac in Vietnam, was licensed in Vietnam in 2012.[43] It is not currently prequalified by WHO. Rotavin-M1 contains a single, live attenuated human rotavirus G1P[8] strain (KH0118-2003) isolated from a child in Vietnam.[44] Rotavin-M1 is available in single-dose vials that can be stored at −25°C to −15°C for two years and then at 2–8°C for two months after it has been thawed.[9,43] Rotavin-M1 is administered orally in a two-dose schedule, with the first dose at 6 weeks or later and the second dose 60 d after the first.[44,45] Data on the cold chain footprint required for storage at central and peripheral levels have not yet been made publicly available. A non-inferiority trial is currently underway to assess the immunogenicity of a liquid, ready-to-use formulation of Rotavin against the currently licensed form.[46]

ROTAVAC ®, a liquid-frozen, monovalent rotavirus vaccine manufactured by Bharat Biotech in India, was licensed in India in 2014 and received WHO prequalification in January 2018.[45] ROTAVAC contains a single, live attenuated human rotavirus G9P[11] strain, isolated from asymptomatic neonates at the All India Institute of Medical Sciences, New Delhi.[45] Each glass vaccine vial contains either one, five, or ten doses of the frozen vaccine.[47] In the frozen form, it can be stored in central cold chain facilities at −20°C for up to five years, and can be refrigerated for up to 6 months between 2°C and 8°C; it can be thawed and refrozen up to six times.[47] ROTAVAC vials are labeled with VVM2 markers, a heat-sensitive visual marker that becomes darker when exposed to heat as the vaccine moves through the supply chain.[48] ROTAVAC is administered orally in a three-dose schedule with DTP-1, 2, and 3. The cold chain storage requirements for the three doses required to fully immunize one child range from 9.6 cm^3 for the 10-dose vial to 45 cm^3 for the 1-dose vial (Table 1).[9] ROTAVAC 5 CM (now ROTAVAC 5D), a liquid formulation of ROTAVAC, has completed clinical trials and is under consideration for WHO prequalification.

ROTASIIL®, a freeze-dried/lyophilized, pentavalent rotavirus vaccine manufactured by Serum Institute of India, Pvt. Ltd., was licensed in India in 2017 and received WHO prequalification in September 2018. ROTASIIL contains five live attenuated human-bovine rotavirus reassortant strains, G1, G2, G3, G4, and G9, produced in vero cells.[14] Each vaccine vial contains either one or two doses of the lyophilized vaccine; the diluent is stored in a separate vial that can withstand ambient temperature fluctuations.[47] In its freeze-dried form, the vaccine can be stored up to 30 months, refrigerated at 2–8°C; the antacid diluent may be stored up to 60 months at ambient temperature or 2–8°C.[47] Lyophilization reduces the risk of virus destabilization through aqueous processes, imparting ROTASIIL with a longer shelf-life over other forms of drying.[49] ROTASIIL has demonstrated thermostability at temperatures up to 25°C for up to 36 months, between 37°C and 40°C for 18 months, and for short time periods over 55°C.[50] However, the lyophilizing process can damage virus components, and there are limited measurement and analytic tools to accurately detect destabilization associated with this process.[49] ROTASIIL vials are labeled with a vaccine vial monitor (VVM30)[48,51] Once reconstituted, the vaccine can be stored up to 6 hours at 2–8°C.[47,52] ROTASIIL is administered orally in a three-dose schedule, with DTP-1, 2 and 3. Excluding the diluent, the cold chain footprint required for the three doses required to fully immunize one child is 52.7 cm^3 for one-dose vials and 31.6 cm^3 for two-dose vials.[9] A new liquid formulation of ROTASIIL has also been developed, with demonstrated immunological non-inferiority to lyophilized ROTASIIL and a similar safety profile. It is under consideration for WHO prequalification.[53,54]

Preclinical studies

Preclinical study results for Rotavin-M1 are publicly available on a limited basis (Table 2). Preclinical testing of Rotavin-M1 involved the development of in vitro and in vivo assays for the rotavirus working seed and master seed, consistent with WHO's guidelines for attenuated rotavirus vaccine development. Testing was approved by Vietnam's national regulatory

Table 1. Product characteristics of Rotavin-M1, ROTAVAC, and ROTASIIL [9, 47, 48, 50, 93–96].

Vaccine	Rotavin-M1	ROTAVAC	ROTASIIL
Manufacturer	Polyvac; Center for Research and Production of Vaccines	Bharat Biotech	Serum Institute of India
Dose schedule	2-dose (first dose from 6 weeks, second dose from 1–2 months; should be given before 6 months of age)	3-dose (with DTP 1, 2, and 3)	3-dose (with DTP 1, 2, and 3)
Dose volume	2.0 mL	0.5 mL	2.5 mL
Doses per container	1	5, 10	1, 2
Strains	Single, attenuated human rotavirus strain (G1P[8])	Single, attenuated human rotavirus strain (G9P[11])	5 human-bovine (UK) reassortant rotaviruses (G1, G2, G3, G4, G9)
Presentation	Liquid vaccine in glass vial	Liquid in glass vial	Lyophilized in glass vial; antacid diluent from separate vial used to reconstitute
Storage	Frozen (−20-5°C)	Refrigerated (2–8°C): 6 months Frozen (−20°C): 5 y*	Vaccine -Refrigerated (2–8°C): 30 months Diluent – Ambient temperature of refrigerated (2–8°C): 60 months†
Cold storage volume per course	*Not publicly available*	1-dose: 45 cm^3 5-dose:12.6 cm^3 10-dose: 9.6 cm^3	1-dose: 53 cm^3 2-dose: 32 cm^3 ‡
Vaccine vial monitor	No	Yes (VVM2)	Yes (VVM30)
Route of administration	Oral	Oral	Oral
UNICEF price per course (Gavi-supported countries, 2020) §	n/a	5- and 10-dose vials: 2.55 USD	1-dose vial: 4.65 USD 2-dose vial: 2.85 USD

*Can be frozen-thawed 6 times without losing potency
†Once reconstituted, can be refrigerated (2–8°C) for up to 6 hours
‡ Cold storage volume excludes diluent
§ USD, does not consider wastage

authority, and each working and master seed lot was tested for safety, toxicity, and immunogenicity in several animals. Immunogenicity was demonstrated by a three-fold increase of antibody titers in baby monkeys.[77]

Descriptions of the results of preclinical studies of ROTASIIL are likewise somewhat limited in availability. ROTASIIL was produced in compliance with India's current Good Manufacturing Practices (GMP), which provides quality assurance of pharmaceuticals manufactured in-country.[69] Clinical lot testing demonstrated both consistency and stability between lots.[69] Toxicity testing was performed in rabbits and rats for single and multiple oral doses, with no significant adverse effects observed in the test animals.[69] Immunogenicity data in the studied animals are not publically available.[69]

The authors were not able to identify any publicly available preclinical study results for ROTAVAC.

Clinical studies

The clinical studies described below consider immunogenicity, safety, and efficacy of the three new RVV products (Table 2).

Rotavin-M1

Phase I

A 2009 two-stage study conducted by the National Institute of Hygiene and Epidemiology in Vietnam evaluated the safety of Rotavin-M1 produced by the Center for Research and Production of Vaccines and Biologicals (POLYVAC).[55] The first stage enrolled 29 healthy adult volunteers ages 18–40 y and administered two doses of Rotavin-M1 with a one-month interval between doses; no adverse events were reported.[42,55] The second stage, a phase I and II adaptive trial, enrolled 200 healthy infants, assessing the reactogenicity of Rotavin-M1 by looking at immediate reactions (30 minutes) to administration of each dose and changes in blood cell counts, serum transaminase, and urea nitrogen concentration after vaccination.[42,55] Researchers found that Rotavin-M1 was immunogenic and safe, and did not lead to an increased rate of fever, diarrhea, vomiting, or irritability in comparison to ROTARIX.[44] They also found that the two-dose schedule given weeks apart performed better than the three-dose schedule in terms of reactogenicity and rates of seroconversion. Rates of seroconversion were similar to infants in the ROTARIX group, but infants receiving Rotavin-M1 had less shedding of vaccine strain after subsequent doses.[44] Later studies intend to assess the efficacy of Rotavin-M1 with a larger sample size.[44]

Phase II

A Phase II study conducted by the National Institute of Hygiene and Epidemiology in Vietnam in 2009 (completed in 2010) evaluated the safety and immunogenicity of Rotavin-M1 in infants.[56] Additionally, this study evaluated dosage and scheduling in order to determine the optimum regimen for the administration of Rotavin-M1.[56] This study enrolled 200 healthy infants ages 6–12 weeks at enrollment and randomly assigned them to either a 3-dose schedule with a 1-month interval between doses or a 2-dose schedule with a 2-month interval between doses.[56] This study also assessed the safety and reactogenicity of Rotavin-M1 compared to GSK's ROTARIX. The duration of the immune response was assessed by analyzing antibody titers after one year.[56] Finally, this study evaluated the presence and shedding of rotavirus in stool.[56] No elevation of levels of serum transaminase, blood urea, or blood cell counts were observed.[44] The highest rotavirus IgA seroconversion rate

Table 2. Summary of clinical trials for Rotavin-M1, ROTAVAC, and ROTASIIL.

Rotavin-M1					
Study	Phase	Date	Design	Participants	Primary Objective
NCT01375907[55] Dang, 2012[44]	I	Started: 2009 Completed: 2009	Single group assignment to experimental group	160 healthy adults	Evaluate safety
NCT01377571[56] Dang, 2012[44]	II	Started: 2009 Completed: 2010	Randomized parallel assignment to four experimental arms (varying dose schedule)	160 healthy infants (6–12 weeks at enrollment)	Evaluate safety and immunogenicity
NCT01502969[57]	II/III	Started: 2010 Completed: 2011	Randomized parallel assignment to two arms (placebo or experimental)	799 healthy infants (6–12 weeks at enrollment)	Evaluate safety and immunogenicity
NCT03703336[46]	III	Started: 2019 Still in progress	Randomized parallel assignment to two arms (frozen formulation or liquid formulation)	825 healthy infants (60–91 d at enrollment)	Demonstrate non-inferiority in the immunogenicity of the liquid formulation compared to the frozen formulation
ROTAVAC					
Study	Phase		Design	Participants	Primary Objective
Bhandari, 2006[58]	I/II	Started: 2005 Completed: 2005	Double-blind, randomized, controlled trial	369 healthy infants	Evaluate safety and immunogenicity
Bhandari, 2009[59]	I/II	Started: 2006 Completed: 2008	Double-blind, placebo controlled, dose-escalation trial	187 health infants (6 weeks at enrollment)	Evaluate safety
Appaiahgari, 2014[60]	I/II	Started 2006 Completed: 2008	Randomized, double-blind, placebo-controlled	369 healthy infants (6 week at enrollment)	Dose escalation safety and immunogenicity
NCT03602053[61]	II	Started: 2018 Completed: 2019	Single center, randomized, controlled, open label study	450 healthy infants (6–8 weeks at enrollment)	Compare immunogenicity, reactogenicity, and safety of frozen and liquid formulations
NCT01305109[62] Bhandari, 2014[29] Bhandari, 2014[63]	III	Started: 2011 Completed: 2014	Randomized, double-blind, placebo-controlled trial (placebo or experimental)	6799 healthy infants (6–7 weeks at enrollment)	Evaluate efficacy
NCT03367559[64]	III	Started: 2018 Completed: 2019	Open-label, single group assignment	360 healthy infants (6–8 weeks at enrollment)	Immunogenicity, safety, and reactogenicity
Chandola, 2017[65]	III	Started: 2014 Completed: 2015	Randomized, double-blind, placebo-controlled	1356 healthy infants (6 weeks at enrollment)	Effect of vaccine on other co-administered childhood vaccines
Praharaj, 2019[66]	III	Started: 2018 Completed: 2018	Double-blind, placebo-controlled	1169 healthy infants (6–8 weeks at enrollment)	Impact of coinfections on efficacy estimates
Ella, 2018[67]	IV	Started: 2014 Completed: 2014	Randomized, single-blind	900 healthy infants (6–8 weeks at enrollment)	Immunogenicity, reactogenicity, and safety when administered with or without buffering agent
Ella, 2019[68]	IV	Started: 2015 Completed: 2016	Open-label, randomized assignment (two experimental groups with different doses)	464 healthy infants (6–8 weeks at enrollment)	Antibody response of two different dosing schedules
ROTASIIL					
Study	Phase	Date	Design	Participants	Primary Objective
Zade, 2014[69]	I/II	Started: 2014 Completed: 2014	Randomized, double-blind, placebo controlled	60 healthy infants	Evaluate safety and immunogenicity
NCT03474055[70] Kawade, 2019[53]	II/III	Started: 2017 Completed: 2018	Randomized parallel assignment to four experimental arms (three liquid and one lyophilized)	1500 healthy infants (6–8 weeks at enrollment)	Compare liquid formulation to lyophilized formulation.
NCT02133690[71] Kulkarni, 2017[30]	III	Started: 2014 Completed: 2017	Randomized parallel assignment to two arms (placebo or experimental)	7500 healthy infants (6–8 weeks at enrollment)	Evaluate efficacy
NCT02145000[72] Isanaka, 2017[73] Coldiron, 2018[74]	III	Started: 2014 Completed: 2019	Randomized parallel assignment to two arms (placebo or experimental)	4092 healthy children (6 weeks to 2 years at enrollment)	Evaluate efficacy and safety
NCT02584816[75] Desai, 2018[76]	III	Started: 2015 Completed: 2017	Randomized parallel assignment to four arms (three experimental and one active comparator)	1500 healthy infants (9–8 weeks at enrollment)	Evaluate lot-to-lot consistency in manufacturing

(73%, 95% CI (58–88%)) was achieved in group 2 H (2 doses–10(6.3)FFU/dose, 2 months apart).[44] The 2-dose schedules performed slightly better than the three dose schedules and the higher titer doses performed slightly better than the lower titer doses.[44] These rates of seroconversion were similar to that of the ROTARIX group (58%, 95% CI (42–73%)).[44] However, more infants who received ROTARIX (65%) shed virus in their stool after the first dose than those who received Rotavin-M1 (44–48%) ($p < .05$), although the percent shedding decreased after subsequent doses of either vaccine.[44] These data demonstrate that Rotavin-M1 is safe and immunogenic in infants, and is not associated with an increased rate of fever, diarrhea, vomiting, or irritability in comparison to ROTARIX; no intussusception events were detected.[44] Beyond initial Phase II studies, there are no publicly available immunogenicity, safety, efficacy, or risk of intussusception data. Data also demonstrate that the two-dose schedule performed better than the three-dose schedule.[44]

Phase II/III

A 2010 Phase IIb study conducted by the National Institute of Hygiene and Epidemiology in Vietnam evaluated the safety and immunogenicity of Rotavin-M1, including an assessment of the vaccine schedule of 2 doses with a 2-month interval at two study sites, Thanh Son-Phu Tho and Thai Binh city.[57] Researchers enrolled 799 healthy infants, ages 6 to 12 weeks at time of enrollment.[57] Participants were randomized to either placebo (cell culture medium in absence of virus) or active (Rotavin-M1 vaccine) groups.[57] Primary outcome measures included anti-rotavirus IgA antibody responses one month after vaccination. Secondary outcome measures included RV-IgA antibody responses to Rotavin-M1 one year after first dose, anti-rotavirus IgG antibody responses one month after vaccination, safety, and reactogenicity of each dose, and anti-RV IgG responses one year after the first dose.[57] The results of this study have not yet been published.

Phase III

A Phase III study registered in 2019 will be conducted by the Center for Research and production of Vaccines and Biologicals in Vietnam, to examine the non-inferiority of the immunogenicity of the liquid form of Rotavin compared to the frozen formulation.[46] The study will also assess the reactogenicity and safety of the vaccine.[46] This study will recruit 825 healthy infants from ages 60 to 91 d, and participants will be randomized to either the liquid or frozen formulation of Rotavin-M1.[46] The study will compare geometric mean concentration (GMC) of serum anti-rotavirus IgA antibodies between the liquid and frozen formulations, after each vaccine dose.[46] The study will also examine seroconversion, seropositivity, immediate adverse events, solicited and unsolicited adverse and severe adverse events, including intussusception.[46] Enrollment for this study has not yet begun.

Phase IV

The authors did not identify any Phase IV Rotavin-M1 studies published in the literature.

New presentations

The 2019 Phase III study described above will provide data to compare a new liquid formulation versus the existing frozen formulation.

ROTAVAC

Phase I/II

A 2005 Phase I study assessed the safety and immunogenicity of ROTAVAC and I321 (a live attenuated Indian rotavirus vaccine candidate strain) in healthy infants, using a randomized design with a placebo comparison group.[58] The study recruited 90 healthy infants age 8 weeks at enrollment, who received a single dose of ROTASIIL, I321, or placebo.[58] The study found that ROTAVAC induced a more robust immune response than either I321 or placebo.[58] There was no significant difference in the number of adverse events between the experimental and placebo groups.[58] This study found that ROTAVAC is attenuated, safe, and immunogenic with a single dose.[58]

A 2006 (completed 2008) study assessed the safety of ROTAVAC in comparison to placebo in healthy infants.[59] The Phase I/II study was a double-blind, placebo-controlled, dose-escalation trial in India, in which 187 participants received a dose of 1×10^4 focus-forming units (ffu) while 182 received a dose of 1×10^5 ffu in a 1:1 randomization with placebo participants.[59] The study found no significant difference in adverse events or toxicity between groups; zero vaccine-related adverse events (including intussusception) were observed.[59] A significant difference in immunogenicity between the two experimental groups and the placebo group was observed; the study found that the 1×10^5 ffu dose resulted in a robust immune response, compared to the 1×10^4 ffu dose, and was selected for further trials.[59] The study also reported viral shedding in approximately 20% of enrolled infants; shedding rate was lower than with ROTARIX but greater than with RotaTeq.[59]

A 2014 study of data collected in 2006 (completed in 2008) assessed the immune response and seroconversion of ROTAVAC in healthy infants age 6 weeks at enrollment.[60] The Phase Ia/IIb study was randomized, double-blinded, and placebo-controlled, and enrolled 369 infants.[60] The study reported interference of maternal antibody on ROTAVAC vaccine immunogenicity in infants, noting that ROTAVAC is able to overcome this interference when administered at a higher dose.[60]

Phase III

A 2011 (completed 2014) study conducted by Bharat Biotech in India evaluated the efficacy of a three-dose schedule of ROTAVAC in comparison to placebo.[62] The primary outcome was efficacy against severe rotavirus gastroenteritis, defined as number of cases of non-vaccine rotavirus in subjects from 14 d after the third dose to age 2 y.[62] The secondary outcomes were efficacy at preventing hospitalization, use of supervised rehydration therapy, and safety compared to the placebo group. This study enrolled 6,800 healthy infants beginning in 2011, ages 6–7 weeks in 2011.[62] It used a double-blind, placebo-controlled

design and randomized participants in a 2 to 1 allocation to (1) oral ROTAVAC vaccine, or (2) placebo. Participants were given three doses at four-week intervals co-administered with other routine childhood vaccines.[62] ROTAVAC was effective in preventing cases of severe rotavirus gastroenteritis and was well tolerated in Indian infants; the study further noted that ROTAVAC offered protection against a range of commonly circulating genotypes, including G1P[8], G2P[4], G12P[6], G12P[8] and G9P[4].[29] Vaccine efficacy against severe rotavirus gastroenteritis was 53.6% (95% CI, 35.0–66.9%; $P < .001$) and 56.4% (95% CI, 36.6–70.1%; $P < .001$) in the first year of life.[29] Vaccine efficacy in the second year of life was 48.9% (95% CI 17.4 to 68.4; $p = .0056$).[63] Prevalence of immediate, solicited, and serious adverse events was similar in both groups.[29] In the initial period, there were six cases of intussusception in the vaccine group and two in the placebo group, and in the second year there were eight cases in the vaccine group and three in the placebo group; all intussusception cases in the vaccine group occurred more than 100 d after the third dose and were not associated with vaccination.[29] No deaths were found to be related to the study vaccine.[29,63]

A study completed in 2015 assessed possible ROTAVAC interference with the immune response to coadministered vaccines.[65] Healthy infants aged 6 weeks at enrollment were randomized to either a control or placebo ground (where they would also receive coadministered childhood vaccines).[65] Coadministered vaccines included oral polio vaccine, diptheria, pertussis, tetanus, hepatitis b, and *Haemophilus influenza* type b.[65] The study showed that ROTAVAC can be safely administered with childhood vaccines without interfering with the immune response to the antigens contained in these vaccines.[65]

A 2018 (completed 2019) study conducted by the Institute of Clinical Research and Clinical Trial Support for Vaccine and Biological Products in Thái Bình, Vietnam, evaluated the immunogenicity, safety, and reactogenicity of ROTAVAC as a three-dose series in 360 healthy infants, ages 6–8 weeks.[63] This study used an open-label, single-group assignment model and administered three doses of ROTAVAC at a four-week interval with the first dose given at age 6–8 weeks.[64] Primary outcome measures were the frequency and rate of adverse events after vaccination, including immediate adverse events within 30 minutes of vaccination, and adverse events 7 d and 28 d after each vaccination.[64] The results of this study have not been published at the time of writing.

A 2019 study evaluated the impact of coinfections on the efficacy of the ROTAVAC vaccine.[66] The study recruited 1,169 healthy infants who were tested for the presence of coinfections.[66] This study found that vaccine efficacy increased from 49.3% to 60.6% in the absence of coinfections (difference, 11.3%, 95% CI, −10.3% to 30.2%).[66] In other words, accounting for coinfections could help to explain variance in efficacy amongst populations; this nonsignificant difference may merit further evaluation in larger studies.

Phase IV

A 2014 Phase IV, multi-center, single-blind, randomized study assessed the immunogenicity and safety of ROTAVAC when administered to healthy infants with and without the buffering agent.[67] The study enrolled and randomized to three arms 900 infants 6–8 weeks of age: Group I received the buffer five minutes before receiving ROTAVAC, Group II received no buffer, and Group III received the buffer simultaneously with ROTAVAC.[67] Eighteen serious adverse events were reported, but none were attributable to the vaccine.[67] ROTAVAC administration without a buffer was shown to be well tolerated and immunogenic.[67]

A 2015 (completed 2016) Phase IV study assessed the antibody response of two different dosing schedules of ROTAVAC in healthy infants.[68] This study also assessed the non-inferiority of ROTAVAC to ROTARIX for GMC in infants.[68] The study was a multicenter, open-label, randomized design with two experimental groups (Group I, 3 doses; Group II, 2 doses).[68] It showed that the GMC ratio met the non-inferiority criteria (0.82; 95% CI: 0.64, 1.05) and that there was no substantive difference between ROTAVAC and Rotarix.[68]

Surveillance

From 2015 to 2019, passive surveillance was conducted at 35 health facilities across three Indian states – Himachal Pradesh, Maharashtra, and Tamil Nadu – to better understand and estimate the risk of intussusception among infants vaccinated with ROTAVAC.[41] A total of 151 intussusception cases meeting Brighton Level 1 criteria were identified; of these, 104 were vaccinated with ROTAVAC and 47 were unvaccinated.[41] Attributable risk 1–21 d after the first and second doses (combined) was 0.11 (95% CI: 0.0–0.25) per 100,000 doses, and 0.42 (95% CI: 0.0-.70) per 100,000 doses for all three doses combined; no clustering of cases was seen after any dose.[41] The analysis found no increased risk of intussusception during the first 21 d following any of the three doses of ROTAVAC or all three doses combined, compared to the control period (d 22–365).[41]

As reported at the December 2019 meeting of the Global Advisory Committee on Vaccine Safety, active sentinel site surveillance was conducted across 28 hospitals in nine states in India following the introduction of ROTAVAC, with analysis of cases meeting Brighton Level 1 criteria to assess possible association of ROTAVAC vaccination and intussusception.[42] A total of 589 children with known ROTAVAC vaccination status (0, 1, 2, or 3 doses) were included in the analysis; incidence rate ratios for seven d after the first, second, and third doses were compared to the period from 28 d to 1 year of age.[42] The incident rate ratios showed no statistically significant difference from no association for d 1–7, and no significant difference was found for the risk window of 8–21 d after vaccination, with any dose.[42]

New presentations

A 2019 Phase IIb, single-center, randomized, controlled, open-label immunogenicity study conducted by the Center for Infectious Disease Research in Zambia enrolled 450 healthy infant volunteers, comparing 3 doses with the frozen formulation of ROTAVAC, 3 doses with the liquid formulation of ROTAVAC 5 CM (now ROTAVAC 5D), and 2 doses of ROTARIX.[61] The study evaluated immunogenicity at 28 d post-dose-3, as well as the reactogenicity and safety of the

two ROTAVAC formulations compared against each other and compared against ROTARIX, at one week after each dose.[61] The primary outcome measure was GMC of serum-anti-rotavirus IgA antibodies.[61] This study has been completed, but results have not yet been published.

ROTASIIL

Phase I/II

A 2014 multi-phased study assessed the toxicity of ROTASIIL in adults, toddlers, and infants.[69] The Phase I component was a randomized, double-blind, placebo-controlled study that examined the safety, immunogenicity, and shedding of the ROTASIIL vaccine in healthy adults, toddlers, and infants.[69] ROTASIIL was found to be safe and well tolerated and there were no reports of severe adverse events.[69] There were a few adverse event reports, including nausea, loss of appetite, diarrhea, and vomiting, but none of these were severe.[69] No shedding was seen in stool samples.[69]

The Phase IIa component was a double-blind, placebo-controlled study that assessed the safety, immunogenicity, and shedding of the vaccine virus contained in ROTASIIL, in healthy infants.[69] Two cases of severe adverse events were reported in post-vaccination follow-up, one urinary tract infection, and one septicemia; both were found to be unrelated to the ROTASIIL vaccine.[69] The vaccine was found to be safe and well tolerated, and three doses of the vaccine were found to be immunogenic.[69] No shedding was seen in stool samples.[69]

A randomized, double-blind, placebo-controlled Phase IIb study examined the immunogenicity of ROTASIIL in healthy infants.[69] The main difference between the Phase IIa and Phase IIb trials was the dose: Phase IIa used a dose of 1×105.2 ffu/serotype while Phase IIb used a dose of 1×105.6 ffu/serotype.[69] Vaccine and placebo were administered as three doses with a minimum four-week gap between doses, administered in a 1:1 ratio.[69] The vaccine was found to be safe, immunogenic in infants, well tolerated, and no severe adverse events were reported.[69]

Phase III

A 2014 (completed 2017) study conducted by Serum Institute of India used a multicenter, randomized, double-blind, placebo-controlled design to examine efficacy and safety of a three-dose series of ROTASIIL, administered orally with a four-week interval to healthy Indian infants, ages 6–8 weeks at enrollment.[71] Seven thousand five hundred participants were randomized to either the experimental vaccine arm or the placebo group with a 1:1 allocation.[71] The primary outcome was the occurrence of severe rotavirus gastroenteritis up to two years of age.[71] Secondary outcomes were safety, including solicited post-vaccination reactions, severe adverse events, unsolicited adverse events, intussusception, and death.[71] At the time of primary analysis, vaccine efficacy against severe rotavirus gastroenteritis was 36% (95% CI 11.7, 53.6, $p = .0067$) for the per-protocol analysis and 41.9% (21.1, 57.3, $p = .0005$) for the intention-to-treat (ITT) analysis; at the end of the follow-up period (until two years of age), vaccine efficacy was 39.5% using a per-protocol analysis and 38.8% using ITT analysis.[30] Vaccine efficacy against very severe rotavirus cases was 60.5% (95% CI 17.7, 81, $p = .0131$) at the time of the primary analysis and 54.7% (95% CI 29.7, 70.8, $p = .0004$) over the complete follow-up period in the per-protocol analysis.[30] The incidence of solicited, unsolicited, and serious adverse events was comparable between vaccine and placebo groups.[30] ROTASIIL was found to be effective, safe, and well tolerated by Indian infants.[30]

A 2014 (completed 2017) double-blinded, randomized, placebo-controlled study conducted by Epicenter in Niger evaluated the efficacy and safety of ROTASIIL in infants followed until they were young children.[72,73]Researchers recruited 4,092 participants ages 6 weeks and followed participants out to 2 y.[72,73] Participants were randomized to experimental vaccine and placebo groups using a 1:1 allocation.[72,73]Three doses of the vaccine or placebo were administered at four-week intervals, with the first dose occurring at age 6–8 weeks.[72] The primary outcome measures were episodes of severe rotavirus gastroenteritis after the final dose.[72] Secondary outcome measures were rotavirus gastroenteritis, hospitalization due to rotavirus gastroenteritis, hospitalization of any cause (adverse effects or rotavirus gastroenteritis), serious adverse events, and anti-rotavirus IgA sero-response rates and geometric mean titers.[72–74] The study found an efficacy of 66.7% (95% CI: 49.9, 77.9) against severe rotavirus gastroenteritis.[73] Only one case of intussusception was reported, 542 d after receipt of the third dose.[74] The vaccine group experienced 395 serious adverse events, compared to 419 serious adverse events in the placebo group; this difference was not significant.[74] Adverse events between the two groups were comparable, with 1474 (72.1%) participants receiving ROTASIIL and 1456 (71.1%) participants receiving placebo experiencing at least one adverse event ($p = .49$) in the follow-up period; ROTASIIL was found to be safe.[74] Limitations of this study included the complexity of accurately diagnosing participants in a low-resource environment where overlapping clinical features and pathologies can complicate classification.[74]

A 2015 (completed 2017) open-label, randomized study conducted by the Serum Institute of India recruited 1,500 healthy volunteers, ages 6–8 weeks.[75] Participants were randomized to four experimental arms: (1) ROTASIIL Lot A; (2) ROTASIIL Lot B; (3) ROTASIIL Lot C; or (4) ROTARIX.[75] This study evaluated equivalence in specific anti-rotavirus IgA antibodies across the three production lots and examined potential interference of the vaccine with other standard infant vaccines given concurrently.[75] Primary outcome measures included immunogenicity of the rotavirus vaccine in each group at four weeks after the third dose, and immunogenicity of universal immunization program vaccines, four weeks after the third dose of vaccination. Secondary outcome measures included immediate, solicited, and unsolicited adverse events (reactogenicity), within 30 minutes after vaccination and seven d after each vaccination, respectively.[75] Antibody responses between ROTASIIL and ROTARIX were comparable.[76] ROTASIIL was not found to interfere with the immunogenicity of concurrently administered vaccines: more than 97% of participants demonstrated seroprotective antibodies against diphtheria, tetanus, hepatitis B, and polio type 1 and 3.[76]

Phase IV

The authors did not identify any Phase IV ROTASIIL studies in preparation, ongoing, or published in the literature.

New presentations

A 2017 (completed 2018) study conducted by the Serum Institute of India in New Delhi, India, evaluated the liquid formulation of ROTASIIL in comparison to the lyophilized, or freeze-dried, formulation.[70] This non-inferiority study compared the induction of anti-rotavirus IgA antibodies across three different production lots.[70] Researchers recruited 1,500 healthy infants, ages 6–8 weeks at enrollment.[70] This study also evaluated consistency in the manufacturing of ROTASIIL by comparing anti-rotavirus IgA antibodies across three different production lots.[70] Participants were randomized to four different study arms; (1) liquid formulation Lot A; (2) liquid formulation Lot B; (3) liquid formulation Lot C; and (4) lyophilized formulation.[70] The incidence of adverse events was similar across all four study arms.[53] There was only one vaccine-related serious adverse event of gastroenteritis in the ROTASIIL group.[53] The liquid formulation was found to be non-inferior from an immunologic and safety perspective compared to the lyophilized formulation, and the study demonstrated lot-to-lot consistency.[53]

Vaccine impact on circulating rotavirus strains

No published studies have yet focused on the impact of Rotavin-M1, ROTASIIL, or ROTAVAC on circulating rotavirus strains. However, multiple studies have documented genotype changes in circulating strains following the introduction of other licensed rotavirus vaccines. In a systematic review on circulating rotavirus strains in the Middle East region, studies saw elevated proportions of non-vaccine strains G9P [8], G2P[4], and G9P[4] in Yemen, Saudi Arabia, and Morocco in post-vaccination periods with RotaTeq (G1, G2, G3, G4, and P[8]) and ROTARIX (G1P[8]).[78] A systematic review of rotavirus strains at the global level six years after RotaTeq and ROTARIX licensure found no significant shifts in strain prevalence, but recommended continued monitoring of G2P[4] prevalence in regions using ROTARIX.[79] Despite this scholarly interest in detecting any shifts in prevalence after population-wide introduction of the vaccine, the potential clinical relevance of such a trend is incompletely understood, as currently available oral, live attenuated RVV products demonstrate cross-protection against non-vaccine strains.[80,81] Continuing regionally representative surveillance after wider-spread introduction of the three new products described in this review will be useful to detect the emergence of potentially pathogenic strains.[79]

Schedule and integration with routine infant vaccines

Strong safety data support the concurrent administration of both ROTARIX and RotaTeq with the routine infant DTP dosing schedule;[65,82] the schedule for ROTAVIN-M1 differs slightly, as described above. Although no published studies have assessed the impact on immunogenicity, safety, or efficacy of the simultaneous co-administration of Rotavin-M1 with other routine infant vaccines, there is no evidence of appreciable interference of ROTAVAC and ROTASIIL with other simultaneously administered routine childhood vaccines.

Cost-effectiveness

Some data have suggested greater cost-effectiveness of ROTARIX compared to ROTAVAC and ROTASIIL,[83] however, a model in the Palestinian setting suggests ROTAVAC is cost-saving compared to ROTARIX;[84] increasing scale of use and changes in other parameters can easily shift results of such modeling in the opposite direction.[85] Future economic and cost-effectiveness studies in low- and low-middle income countries may highlight further economic benefits of these three new vaccines.

Interchangeability

As more products become available, the likelihood increases that a child might receive a mixed schedule or be mid-series when a country switches from one product to another. The WHO recommends that children complete the vaccine product series on which they began, since no studies on interchangeability have been performed to demonstrate equivalent efficacy and immunogenicity with multiple vaccine products.[86] However, in settings where additional doses with the initial product are unavailable, substitution of other rotavirus vaccine products offers protection over an incomplete vaccine series.[86] A multicenter-randomized study of rotavirus vaccine schedules in children showed that mixed vaccine schedules (ROTARIX and RotaTeq) were noninferior in the induced immune response.[87] A retrospective study of children with gastrointestinal symptoms in the New Vaccine Surveillance Network found that a 3-dose regimen of mixed RotaTeq and ROTARIX vaccines showed 80% vaccine effectiveness against rotavirus infection.[88] Studies of interchangeability between ROTAVAC and ROTASIIL are underway in India, where the two vaccines have been introduced on a state-by-state basis.[89]

New formulations and future developments

While the liquid-frozen and lyophilized formulations of ROTAVAC and ROTASIIL, respectively, are now in use in several countries, and Rotavin-M1 is available on the private market, all three manufacturers continue to develop new formulations to better meet the needs of a range of settings and markets. These aim to mitigate potential barriers to use of the current presentations in some settings – for example, a fully liquid ROTAVAC will eliminate the need for freezer (−20°C) storage for the vaccine – and improve their suitability for immunization programs by shifting toward ready-to-use presentations, while also gathering additional clinical trial and post-licensure data.

Studies are underway to elicit necessary, more widely applicable clinical trial data for Rotavin-M1. Once these additional clinical trials are complete and data available, it is anticipated that Rotavin-M1 will be eligible for consideration for licensure

by other national regulatory authorities, beyond Vietnam's private market, and potentially for WHO prequalification.

New formulations of both ROTAVAC and ROTASIIL have also been prioritized by manufacturers and are expected to be considered for WHO prequalification. ROTAVAC 5D – a fully liquid, ready-to-use version of the WHO-prequalified liquid-frozen ROTAVAC – is available in single- and multi-dose vials with VVM7, and can be stored at 2–8°C for up to 24 months.[90] It was commercially licensed in India in mid-2019; as discussed above, clinical trials for ROTAVAC 5D are completed and the vaccine will likely receive WHO prequalification status soon. A fully liquid formulation of ROTASIIL – which is currently available only as a lyophilized vaccine, requiring reconstitution – was launched in early 2020 and is undergoing clinical trials. A heat-stable presentation of ROTASIIL using a VVM250 is also anticipated; prior studies have demonstrated the current, lyophilized formulation of ROTASIIL retains its stability at temperatures up to 25°C for up to 36 months, between 37°C and 40°C for 18 months, and for short time periods over 55°C.[50] Using the newly WHO-approved VVM250 will ensure accurate tracking of ROTASIIL excursions from viable temperature ranges when storing the product outside the cold chain.

Market context

The global market for rotavirus vaccines has expanded significantly over the last 10 y, and demand is expected to continue increasing over the coming decade.[91] To reach the global market, ROTAVAC and ROTASIIL must be exported from India.[48] Given their WHO prequalification status, both can be procured by UN agencies for use in Gavi-eligible countries.[52,92-94] Rotavin-M1 would also require exportation from Vietnam to reach the global market, and pre-qualification to be eligible for UN agency procurement.

Conclusion

Data supports the safety and efficacy of these three new products – Rotavin-M1, ROTAVAC, and ROTASIIL – for preventing severe rotavirus disease. Post-licensure data on current formulations and clinical trial data on new formulations will be critical to inform country introduction decisions and market uptake. Continued research also is needed to understand the individual clinical, epidemiologic, and programmatic implications of using two RVV products simultaneously in the same population or switching from one product to another. Likewise, little is known about the potential implications of using a 'mixed' schedule for the individual child.

Economic questions remain as well. Although ROTAVAC and ROTASIIL are available for global procurement, exportation and shipment from India may incur additional costs. Operational research is needed to understand the feasibility of technology transfer agreements and similar mechanisms to allow localized manufacturing. Likewise, implementation research is needed to evaluate the implications of product characteristics on real-world access and uptake of vaccine. Frozen vaccines may offer lower cost and longer shelf life, but require an investment in cold chain expansion; lyophilized vaccines offer thermostability, but the requirement for reconstitution may introduce human error, or present complicated storage considerations. Further study should consider if the health workforce and training program can adequately prepare for complicated reconstitution workflows, as well as if projected vaccination costs are representative of the total cost of procuring and delivering one of these new vaccines. As the evidence continues to accumulate for these three products, studies answering these programmatic and implementation questions will be of similar importance as studies providing post-marketing safety and impact data. As Rotavin-M1, ROTAVAC, and ROTASIIL become more widely used, it will be important to consider global and national policies regarding their use, and how these policies can best reflect the body of emerging evidence to guarantee widespread vaccine access and high-quality program implementation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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