**ROTAVIRUS VACCINES IN CLINICAL DEVELOPMENT: CURRENT PIPELINE AND STATE-OF-THE-ART**

**Sartorio Marco Ugo Andrea, MD1; Folgori Laura, MD2; Zuccotti Gianvincenzo, MD1 ; Mameli Chiara, MD1**

1Department of Pediatrics, V. Buzzi Children’s Hospital, University of Milan, Milan, Italy

2Paediatric Infectious Disease Unit, Department of Pediatrics, Luigi Sacco Hospital, University of Milan, Milan, Italy

**Corresponding Author:**

Chiara Mameli

Mailing address: V. Buzzi Hospital, Via Castelvetro 32, 20157 Milan - Italy

E-mail address: chiara.mameli@unimi.it

Telephone number: +39 0263635331

**Introduction**

Rotavirus is the most common pathogen responsible for severe diarrhoea in the <5 years children and has a major impact on childhood morbidity and mortality. The majority of deaths occurs in developing countries whereas in high-income countries Rotavirus disease accounts for nearly half of paediatric hospital admissions for diarrhoea.[1](#_ENREF_1) In 2006, the orally-administered live-attenuated Rotavirus vaccines RotaTeq® (pentavalent bovine-human reassortant vaccine, Merck & Co) and Rotarix® (monovalent human vaccine, GSK Biologicals) entered markets in the United States and Europe after the first licensed Rotavirus vaccine Rotashield® (withdrawn due to the association with intussusception). Since the introduction of RotaTeq®/Rotarix®, the virus-related mortality halved at a global level and a reductions of up to 90% in Rotavirus hospitalizations was reported in high-income countries.[2](#_ENREF_2) Also, herd immunity has been demonstrated in non-vaccinated neonates, young infants, older children and adults.[3](#_ENREF_3)

Though the outcome of vaccine introduction has been significant in low-income countries, a lower efficacy compared with the resource-rich countries has been registered, mainly due to underlying conditions such as malnourishment and comorbidities.[4](#_ENREF_4) Moreover, post-marketing safety monitoring showed that these vaccines have been also associated with a slight raise of intussusception incidence, especially in the first seven days after administration (around 20/100,000 children). [5](#_ENREF_5) However, since the benefits outweigh the risks, Rotavirus vaccination is still highly recommended in more than 90 countries worldwide.[1](#_ENREF_1)

Some barriers as age restrictions on vaccine use, safety issues, a reduced efficacy in low-income countries, the life-attenuated nature itself and the substantial vaccine costs currently restrict the full potential of disease prevention. Therefore, research is still ongoing to overcome these limits and is now focusing on the implementation of new oral vaccines and the development of parenteral vaccines.

The overall aim of this study was to provide a state-of-the-art of Rotavirus vaccines currently in clinical development. The specific objectives were (i) to assess the vaccine pipeline and (ii) to review the ongoing clinical trials on new Rotavirus vaccines in the paediatric age.

**Methods**

Medline (Ovid MEDLINE® without Revisions 1996) and Cochrane CENTRAL (Issue 4 of 12, April 2019) databases were searched, using a strategy combining MeSH and free-text terms that included “Rotavirus” AND “vaccine” in children (0–18 years). *Clinicaltrial.gov*, the Chinese Clinical Trial Registry (ChiCTR), the Australian New Zealand Clinical Trials Registry (ANZCTR), the Clinical Trials Registry - India (CTRI), and the Pan African Clinical Trials Registry (PACTR) were searched using the same strategy. We included studies recruiting children, whether adults were considered or not. Data on trial design, phase of the study, population, intervention, setting and evaluated outcomes were extracted. For completed trials, the publications reporting the results were also retrieved. Clinical studies conducted selectively on Rotateq® and Rotarix® were excluded.

**Results**

Our search identified nine new vaccines currently in clinical development (Table 1). The vaccine pipeline is diverse and includes both multiple live-attenuated oral vaccines and non-replicating candidates. Most of them are currently licensed at a national level, mainly in the private market, and aim to meet the performance of Rotarix®/Rotateq® while trying to minimise safety issues and costs. Among those licensed in national markets, there are a human-bovine reassortant vaccine (ROTAVAC®)[6](#_ENREF_6) and an oral bovine pentavalent vaccine (ROTASIIL®)[7](#_ENREF_7) licensed in India, a monovalent Lanzhou Lamb Rotavirus (LLR®) vaccine licensed in China,[8](#_ENREF_8) and the Rotavin-M1® licensed in Vietnam.[9](#_ENREF_9) Lastly, the oral RV3-BB was developed from the human neonatal Rotavirus strain, RV3 (G3P[6]), identified in the stool of asymptomatic infants.[10](#_ENREF_10) Several non-replicating parenteral candidates just entered the Rotavirus vaccine pipeline, most of which are still in the pre-clinical phase. At present, two candidates have being studied in clinical trials, the trivalent truncated VP8: P[4], P[6], P[8] (the major circulating human Rotavirus genotypes) and the new vaccine MT-5625.[11](#_ENREF_11)

Overall, 21 clinical trials fulfilled our inclusion and exclusion criteria (Table 2). Among them, only three studies involved the new non-replicating parenteral candidates. Thirteen trials were already completed whereas eight studies were still ongoing (four of which not yet recruiting patients). Results were available for 10 studies (Table 2). Of the 21 trials included, according to the 2019 World Bank Classification,[12](#_ENREF_12) two were carried out in high-income, 16 in middle-income, and two in low-income countries; one study was conducted in multiple settings. All but one trials involved infants between six and eight weeks of age, with the upper limit sometimes raised until 12 weeks; many studies included toddlers and five included neonates. With regards to the study outcome, most trials focused on both safety (rate of adverse events) and efficacy (anti-Rotavirus serum IgA titers and/or reduction in Rotavirus gastroenteritis rate) compared to placebo or worldwide licensed oral rotavirus vaccines.

**Discussion**

Our search identified nine new Rotavirus vaccines currently in clinical development, seven oral and two non-replicating candidates for intramuscular administration. At the moment, 21 clinical trials focuses on both safety and efficacy endpoints in infants, especially between six and eight weeks of age. As expected, considered the burden of Rotavirus disease in developing countries, the majority of studies was conducted in low and middle-income settings.

The development of new oral vaccines aims to reduce the vaccination costs for low-income countries and increase the efficacy in those settings were licensed vaccines have a great impact in reduction of Rotavirus burden.

Parenteral vaccines could potentially overcome safety and efficacy issues. Indeed, efficacy should not be affected by co-infections or concurrent illness as for oral vaccine, and also intussusception risk should be avoided since immune response is not dependent on vaccine viruses replicating in the gastrointestinal tract.[13](#_ENREF_13) Moreover, parenteral formulations provide the opportunity to be administered in combination with other routine childhood vaccines without a strict age restriction, and could be offered safely to children affected by primary and acquired immunodeficiency, as well as preterm infants expanding the Rotavirus vaccine protection and increasing the compliance to this vaccination.

Two parenteral vaccines are now under clinical development, and a clinical trial for Inactivated Rotavirus Vaccine strain CDC9 (IRV-CDC9) is expected to start in mid-2019, with promising pre-clinical results so far.14

This study has some limitations. First of all, the search was not conducted in a systematic way and the results could therefore be not comprehensive. Secondly, this review has not taken into account pre-clinical studies, therefore other potential candidates might be now available for clinical trials. Lastly, considered the heterogeneity of the interventions and the paucity of published data, it was not possible to run any statistical analysis on the available results.

In conclusion, in spite of the significant impact of the live-attenuated oral Rotavirus vaccine, there are still many issues hampering its global dissemination. Some new candidates showed promising results in terms of efficacy and safety and, at the same time, the cost per dose was reduced. If these results will be confirmed also in the real word settings, they could definitively facilitate the increase in the rate of global coverage, especially in high-burden low-income settings. Simplified strategies to speed up the paediatric vaccine labelling will need to be combined with enhanced methods of post-marketing pharmacovigilance for emerging adverse events in routine clinical care.

**REFERENCES**

1. Banyai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. *Lancet (London, England)* 2018; **392**(10142): 175-86.

2. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; **62 Suppl 2**: S96-s105.

3. Gastanaduy PA, Curns AT, Parashar UD, Lopman BA. Gastroenteritis hospitalizations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. *Jama* 2013; **310**(8): 851-3.

4. 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? *The Journal of infectious diseases* 2009; **200 Suppl 1**: S39-48.

5. Tate JE, Yen C, Steiner CA, Cortese MM, Parashar UD. Intussusception Rates Before and After the Introduction of Rotavirus Vaccine. *Pediatrics* 2016; **138**(3).

6. Chandola TR, Taneja S, Goyal N, et al. ROTAVAC((R)) does not interfere with the immune response to childhood vaccines in Indian infants: A randomized placebo controlled trial. *Heliyon* 2017; **3**(5): e00302.

7. Naik SP, Zade JK, Sabale RN, et al. Stability of heat stable, live attenuated Rotavirus vaccine (ROTASIIL(R)). *Vaccine* 2017; **35**(22): 2962-9.

8. Li D, Xu Z, Xie G, et al. [Genotype of Rotavirus Vaccine Strain LLR in China is G10P[15]]. *Bing du xue bao = Chinese journal of virology* 2015; **31**(2): 170-3.

9. Dang DA, Nguyen VT, Vu DT, et al. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. *Vaccine* 2012; **30 Suppl 1**: A114-21.

10. Bines JE, At Thobari J, Satria CD, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. *The New England journal of medicine* 2018; **378**(8): 719-30.

11. Groome MJ, Koen A, Fix A, et al. Safety and immunogenicity of a parenteral P2-VP8-P[8] subunit rotavirus vaccine in toddlers and infants in South Africa: a randomised, double-blind, placebo-controlled trial. *The Lancet Infectious diseases* 2017; **17**(8): 843-53.

12. World Bank Country and Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed 17 May 2019.

13. Glass RI, Jiang B, Parashar U. The future control of rotavirus disease: Can live oral vaccines alone solve the rotavirus problem? *Vaccine* 2018; **36**(17): 2233-6.

14. Velasquez DE, Wang Y, Jiang B. Inactivated human rotavirus vaccine induces heterotypic antibody response: correction and development of IgG avidity assay. *Human vaccines & immunotherapeutics* 2015; **11**(2): 531-3.

**Table 1: Rotavirus vaccines in clinical development**

|  |  |  |  |
| --- | --- | --- | --- |
| **Candidate** | **Producer** | **Strain** | **Route** |
| Oral human neonatal rotavirus vaccine (RV3-BB) | BioFarma, Indonesia | Human neonatal G3P[6] | Oral |
| Lamb rotavirus-based reassortants (LLR) | Lanzhou Institute of Biological Products, China | Lamb strain G10P[12] | Oral |
| Rotavin/Rotavin-M1 | PolyVac, Vietnam | Human G1P[8]; Human G2P[4] | Oral |
| Human-bovine reassortant vaccine (116E, ROTAVAC) | Bharat Biotech, India | Human G9P[11] | Oral |
| Bovine-human reassortants (BRV) | Shanta Biotechnic, India | Tetravalent combination (G1-G4)P[5] | Oral |
| Serum Institute of India & Institutu Butantan, Brazil | Pentavalent combination (G1-G4, G9)P[5] | Oral |
| Wuhan Institute of Biological Products, China | Hexavalent combination (G1-G4, G8, G9)P[5] | Oral |
| Rotashield | International Medica Foundation and PATH, USA | Tetravalent human-rhesus reassortant vaccine (RRV-TV) - G1 to G4 specificity | Oral |
| Heat-stable rotavirus vaccine (HSRV) | Hilleman, MSD, India | Pentavalent G1-G4 and P1[8] | Oral |
| Trivalent P2-VP8 subunit rotavirus | PATH, National Institutes of Health, USA | Trivalent Truncated VP8: P[4], P[6] and P[8] | Intramuscolar |
| MT-5625 | Mitsubishi Tanabe Pharma Corporation, Japan | Not known | Intramuscolar |