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RELATING A CONCEPTUAL OVERVIEW OF VACCINES UTILIZATION FOR THE PREVENTION OF ROTAVIRUS IN CHILDREN

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Abstract

Rotavirus infection is an emphatic health concern that when left unabated elicits hospitalizations, and deaths of many children due to diarrhea, even in developed countries; let one in poor settings. Likewise, the virus can affect older youngsters and adults resulting in mild infection. The consequences of the rotavirus could not be unconnected with the levels of poor prevention ploys put in place, including the inability of the body of children to counteract the rotavirus with a substantial immunity due to earlier invasion. Thus, it is important to seek for vaccines, because vaccination use in disease prevention is becoming a forefront efficient and easiest way nowadays. This paper brings a conceptual overview of vaccines utilization for the prevention of rotavirus infection in children under the following headings: Introduction, rotavirus vaccines, replicating vaccines, non-replicating vaccines, subunit vaccines, virus like particles, encapsulation, rotavirus vaccination, and conclusion.

Keywords: Rotavirus, Vaccines, Children, Diarrhea, Hospitalizations, Deaths, Vaccination

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Introduction

Prior to the introduction of the rotavirus vaccine, rotavirus infection was responsible for 200,000 emergency room visits, 55,000 hospitalizations, and 60 to 65 deaths each year in the U.S. Worldwide, it is the leading cause of severe diarrhea among young children, leading to 2 million hospitalizations and more than 500,000 deaths of children ages 5 and under annually. Older children and adults can also be infected with the virus, but the illness is generally milder (Dan Brennan, 2020).

Four oral, live, attenuated rotavirus vaccines, Rotarix™ (derived from a single common strain of human rotavirus); RotaTeq™ (a reassorted bovine-human rotavirus); Rotavac™ (naturally occurring bovine-human reassortant neonatal G9P, also called 116E); and RotaSiil™ (bovine-human reassortant with human G1, G2, G3 and G4 bovine UK G6P backbone) are available internationally and WHO prequalified. All four vaccines are considered highly effective in preventing severe gastrointestinal disease. In low income countries, vaccine efficacy can be lower than in industrialized settings, similar to other live oral vaccines. Even with this lower efficacy, a greater reduction in absolute numbers of severe gastroenteritis and death was seen, due to the higher background rotavirus disease incidence (WHO, 2022).

WHO recommends that rotavirus vaccines should be included in all national immunization programmes and considered a priority particularly in countries in South and Southeast Asia and sub-Saharan Africa; WHO continues to recommend that the first dose of rotavirus vaccine be administered as soon as possible after 6 weeks of age along with DTP vaccination. Apart from a low risk of intussusception (up to 6 per 100 000 infants vaccinated), the current rotavirus vaccines are considered safe and well tolerated (WHO, 2022).

The public health impact of rotavirus vaccination has been demonstrated in several countries. For example, in the USA, a measurable decrease was seen in the number of rotavirus gastroenteritis hospitalizations accompanied by a suggested herd effect protecting older non-vaccinated children, while in Mexico a decline of up to 50% in diarrhoeal deaths in children under 5 years of age was attributed directly to the use of the vaccine (IVAC, 2020).

WHO reiterates that the use of rotavirus vaccines should be part of a comprehensive strategy to control diarrhoeal diseases with the scaling up of both prevention (promotion of

early and exclusive breastfeeding, hand-washing with soap, improved water and sanitation) and treatment packages (including low-osmolarity ORS and zinc) (WHO, 2O22).

Methods

Making research processes through relating them with the current knowledge is a paramount activity in scientific and academics. Thus, presently utilization of literature review in making conceptual reviews is evident. A literature review is dubbed to be a systematic process of collecting and synthesizing works (studies) from the old works (researches). It gives a good foundation for knowledge increase, development in theories, and making empirical works as well (Jaakkola, 2020). In an interdisciplinary study, literature and conceptual works are important in shading lights and making interrelationships and correlations. This method is of many uses including showing knowledge gaps, making hypothesis, and increasing in understanding (Raju & Phung, 2021). The conceptual design in research gives a plain path to restrict the researcher from being lost in the course of empirical or experimental work (Neupane, 2021). Thus, this study conceived a related literature review for prevention of rotavirus infection in children using vaccines and vaccination. This paper brings a conceptual overview of vaccines utilization for the prevention of rotavirus infection in children under the following headings: Introduction, rotavirus vaccines, replicating vaccines, non-replicating vaccines, subunit vaccines, virus like particles, encapsulation, rotavirus vaccination, and conclusion.

Rotavirus Vaccines

Rotavirus vaccines are licensed in over 100 countries, and more than 80 countries have introduced routine rotavirus vaccination including Nigeria, almost half with the support of Gavi, the Vaccine Alliance. To make rotavirus vaccines available, accessible, and affordable in all countries—particularly low- and middle-income countries in Africa and Asia where the majority of rotavirus deaths occur, PATH (formerly Program for Appropriate Technology in Health), the WHO, the U.S. Centers for Disease Control and Prevention, and Gavi have partnered with research institutions and governments to generate and disseminate evidence, lower prices, and accelerate introduction. (Burnett et al.,. 2017). The incidence and severity of rotavirus infections has declined significantly in countries that

have acted on this recommendation. Globally, vaccination has reduced hospital admissions and emergency department visits by a median of 67% (WHO, 2022).

Replicating Vaccines

Because natural infection with rotavirus does not efficiently protect against repeat infection and mild disease, the goal of vaccination is not to prevent rotavirus infection, but rather to reduce the incidence of severe diarrheal illness during the first 2 years of life. Natural rotavirus infection often provides only partial protection against disease upon subsequent reinfection (Simonsen *et al.,* 2001). Vaccination efforts are currently aimed at group A virus, as they represent the major cause of severe diarrheal illness. Group A viruses are subdivided into serotypes on the basis of their ability to be neutralized by antibodies to the two major outer capsid proteins, VP4 and VP7 (G serotypes), 8 of which are found in humans. Of these, serotypes G1-G4 represent 80 to 95% of the viruses that are found in the human population, and all four serotypes can be present at any given time and location, although serotype G1 tends to predominate in most parts of the world. In recent years G9 serotypes seem to be emerging as important human pathogens in various regions of the world (Dorsey *et al.,* 2017). Neutralization studies based on reactivity with VP4 (P serotype) have identified at least 13 distinct P serotypes, but serologic reagents are not as readily available for their identification. While 19 distinct P serotypes have been identified by DNA sequence analysis of VP4 sequences, serotype and genotype do not always correlate directly, and viruses are often characterized by VP4 genotype rather than P serotype (Cezard *et al.,* 2001).

Studies in animal models of rotavirus infection indicated that the most important correlate of protective immunity was a strong local antibody response, rather than a serum antibody response. To provide the best chance for presenting rotavirus antigens locally, a Jennerian vaccination strategy was proposed. In this strategy, humans would be inoculated with animal viruses that would present antigen to the gut but not be able to replicate sufficiently to induce clinical symptoms. At least three Jennerian vaccine strains have been tested: RIT 4237, a tissue culture-adapted bovine virus (G6); RRV, a virus isolated from a young rhesus monkey (G3); and WC3, a bovine virus displaying a lower degree of attenuation than RIT 4237. In clinical trials, results have been mixed but generally positive. Although RIT 4237 protected 50% of vaccines in Finland against infection and 80 to 80% against severe illness,

it had very little reported efficacy in other areas of the world (Africa, Arizona). The second bovine strain, WC3, was able to protect 100% of children in American trials from severe serotype 1 diarrhea, but efficacy in other countries ranged from 0 to 48%. The efficacy of the WC3 and RIT vaccines did, however, demonstrate that cross-serotypic protective responses could be generated. The RRV strain of virus induced a mild-to-moderate symptomatic temperature elevation in some vaccines and generated a highly serotype-specific G3 antibody response (Dorsey *et al.,* 2017).

Due to the random circulation of all four human serotypes and assuming that immunity was G serotype-specific, an effective vaccine would need to be able to generate a heterotypic or multiple serotype-specific response to protect against the major human strains. (G1-G4). To address this, a modified Jennerian approach was studied in which the gene coding for the VP7 protein in animal viruses (RRV or WC3) was exchanged (reasserted) with genes from three or four human serotypes (Ball *et al.,* 1996). The product of this study was the RRV-tetravalent vaccine (RRV-TV). This vaccine contains a mix of RRV (serotype G3) and RRV reassortants containing G1, G2, or G4 VP7 genes. This vaccine underwent clinical trials in the United States, Finland, and Venezuela. In the United States trials, the tetravalent vaccine sometimes induced a higher incidence of fever after vaccination than a serotype 1 monoreassortant (RRV-S1), although this was not always significant (Dorsey *et al.,* 2017). Significant diarrhea and vomiting were not reported, and shedding of the vaccine strain in the stool was detected at a low level. Children receiving RRV-TV displayed a measurable but relatively low type-specific response to serotypes 1 to 4, while RRV-S1 recipients had measurable responses to serotype 1 only. The tetravalent vaccine provided significant protection (65-77%) against disease induced by serotype 3 virus, whereas the monovalent vaccine provided variable protection (0-45%). Thus, although overall protection by the tetravalent vaccine against severe illness caused by all serotypes was only 57%, it provided consistent heterotypic protection that may be necessary for efficacy in areas where serotype prevalence varies. The most significant finding was that RRV-TV vaccination prevented approximately 80% of dehydrating illness associated with gastroenteritis relative to placebo recipients. Further studies in Finland and Venezuela with the RRV-based tetravalent vaccine confirmed its substantial efficacy against moderate-to-severe diarrhea (Doro *et al.,* 2014).

The RRV-TV vaccine was licensed in the United States as Rotashield in 1998. By 1999, reports of intussusception associated with the vaccine were noted in a passive reporting system (Abramson *et al.,* 1999). After these cases were publicized, many more cases were reported. Initial epidemiologic investigations estimated a 10 to 50 fold-increased risk of intussusception in the first week after immunization with Rotashield (Murphy *et al.,* 2001). The manufacturer removed the vaccine from the market. Subsequent population based and case-control studies have confirmed the association of intussusception with the administration of Rotashield with the highest risk period being in the first week after the first dose of vaccine. Interestingly, population-based ecological studies failed to find significant increases in the total incidence of intussusception in states with high usage of the vaccine. It is now estimated that the risk of intussusception with Rotashield was approximately 1 excess case per 10,000 doses of vaccine administered (Dorsey *et al.,* 2017).

Non-replicating Vaccines

With the application of molecular biology to the vaccine problem, a number of alternatives to live-attenuated vaccines have been developed. All of these alternative candidates are still experimental and have only been evaluated in animal models of disease (Charles, 2021).

The most advanced of the non-replicating candidates is a recombinant subunit parenteral rotavirus vaccine, developed as a truncated recombinant VP8* protein of human rotavirus genotypes P[8], P[4] or P[6] expressed in *Escherichia coli* at the US NIH (Wen *et al.,* 2012).

The vaccine constructs have been demonstrated to elicit serum neutralizing immune responses in animals, and the immunogenicity could be significantly enhanced when the constructs were fused with the P2 epitope of tetanus toxoid, which elicits a strong T-cell helper function (Fix *et al.,* 2015). PATH, Seattle has developed the vaccine construct further, including process optimization and adsorption of the P2-VP8* with aluminum hydroxide; clinical trial lots were produced at Walter Reed Army Institute for Research (WRAIR) for the human studies (Groome, 2016)

An initial Phase I clinical evaluation of a monovalent P2-VP8-P[8] vaccine construct in healthy US adults demonstrated the safety and immunogenicity of the construct(Fix *et al.,* 2015). This led to an age-descending, dose-escalating study in South Africa, where the same

monovalent vaccine construct was demonstrated to be well tolerated and immunogenic in children and infants in all subject age groups (Groome, 2016)

High levels of anti-P2-VP8* serum IgG and IgA antibody, and neutralizing antibody responses were identified in an expanded infant cohort. Interestingly, Rotarix® shedding was significantly diminished in immunized subjects versus the placebo group, suggesting that the vaccine may provide efficacy against rotavirus disease in the small intestine (Fix *et al.,* 2015).

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Figure 1. Rotavirus, Vaccines, Non-replicating (Carl *et al.,* 2019)

Subunit Vaccines

Rotavirus subunit vaccines are being evaluated for use in humans. The virus-like particles (VLPs) for these vaccines are produced in insect cells coinfected with combinations of baculovirus recombinants expressing bovine RIF VP2 and simian SA11, VP4, VP6, or VP7 rotavirus proteins. Currently, 4 WHO prequalified, live attenuated oral RV vaccines (RotaTeq®, Rotarix®, Rotavac®, Rotasil®) are commercially available and combined cover more than 100 countries. In general, widely used RV vaccines (RotaTeq® and Rotarix®) show good efficacy (>85%) in developed countries; however, efficacy is reduced (40%-60%) in the low-income countries where the need is most (Burnett *et al.,* 2018). Although the causes for their reduced efficacy are unknown, and are an active area of investigation, contributing factors possibly include lower viral titer

(transplacentally acquired RV antibodies, components of breast milk and stomach acid) and impaired immune response (malnutrition, interfering microbes, and other coinfections) (Lazarus *et al.,* 2018). From limited available data, lower efficacy in certain subpopulations of the developing world of other live, attenuated oral vaccines has also been observed against enteric pathogens such as poliovirus and *Vibrio cholera*. Thus, there is interest in developing recombinant subunit protein, injectable RV vaccine candidates to address some of the current deficiencies of live attenuated oral vaccination (Jiang *et al.,* 2010).

Using recombinant viral proteins to induce an anti-rotavirus immune response has focused on the VP4 and VP7 proteins. Expressin of recombinant VP7 on the surface of cells by use of a vaccinia virus construct has resulted in an immunogenic protein that can provide passive protection in suckling mice. VP4 is efficiently expressed in baculovirus, and immunization of mice with recombinant protein can provide lactogenic immunity to virus challenge (Dorsey *et al.,* 2017).

Virus like Particles

Virus-like particles (VLPs) are virus-derived structures made up of one or more different molecules with the ability to self-assemble, mimicking the form and size of a virus particle but lacking the genetic material so they are not capable of infecting the host cell. Expression and self-assembly of the viral structural proteins can take place in various living or cell-free expression systems after which the viral structures can be assembled and reconstructed. VLPs are gaining in popularity in the field of preventive medicine and to date, a wide range of VLP-based candidate vaccines have been developed for immunization against various infectious agents (Saghi *et al.,* 2021). VLPs are dispersed nanomaterials that can be produced in a variety of systems, including mammals, plants, insects, and bacteria. Virus like particles (VLPs) can be exploited as carriers for the delivery of bio- and nanomaterials, such as drugs, vaccines, quantum dots and imaging substances by virtue of the cavity within their structure (Wang *et al.,* 2015; Burnet e*t al.*, 2017; Burnet et al., 2018).

Virus like particles have been generated by simultaneous expression of viral structural proteins in insect cells, and their potential for vaccination tested in animal models. Virus-like particles are thought to display outer capsid proteins in more native-like conformations and are stable under a variety of physical conditions. In the mouse-model, vaccination with

rotavirus virus-like particles conferred significant protection to viral infection in mice (Charles, 2021).

Encapsulation

A third effort to enhance local immunity is to microencapsulate rotavirus proteins or whole viruses for more effective delivery to mucosal surfaces. Studies in mice have shown that microencapsulated virus is more efficiently absorbed and delivered to gut-associated lymphoid tissue after oral inoculation than free virus, and that the local immune response is greatly enhanced by this mode of presentation (Dorsey *et al.,* 2017).

Polylactide (PLA) and polylactide-co-glycolide (PLGA) particles entrapping rotavirus (strain SA11) were formulated using a solvent evaporation technique, to minimize denaturation of viral antigen during the emulsification process, serum albumin was used as a stabilizer. Use of NaHCO and sucrose during the primary emulsification step resulted in uniform stabilized particles entrapping rotavirus (Saghi *et al.,* 2021).

Sonication during the primary emulsion and homogenization during the secondary emulsion process resulted in particles of sizes 2-8 micrometer, whereas nanoparticles were formed when sonication was used during both primary and secondary emulsion processes. Scanning electron and atomic force microscopy showed uniform pores and roughness throughout the polymer particle surface. Single dose oral immunization with 20 microgram of antigen entrapped in PLA particles elicited improved and long-lasting IgA and IgG antibody titer in comparison to the soluble antigen (Charles, 2021).

Recently, a rotavirus vaccine derived from neonatal strain, 116E, which is naturally occurring P[11]G9 human bovine reassortant strain had induced a good immune response after a single dose oral immunization in infants (Ahmed *et al.* 2004). Nevertheless, more extensive trials of this vaccine are needed. Vaccines to prevent rotavirus disease evaluated in human trials over the past 20 years have all been live attenuated rotaviruses that were administrated orally to mimic natural infection. However, the protection achieved hasbeen highly variable and does not offer a complete

protection (Mohammed *et al*., 2016).

Rotavirus Vaccination

Rotavirus is a highly contagious, sometimes deadly, virus that commonly causes diarrhoea among infants and children under the age of five. Nigeria is particularly badly affected: approximately 50,000 Nigerian children under five die from the infection every year, 14% of the global total and the second highest number of deaths worldwide. With the recent launch and integration of the rotavirus vaccine into the routine immunisation schedule in Nigeria, the country expects to reduce at least 40% of morbidity and mortality associated with rotavirus infections amongst children (Ukazu, 2022)

Rotavirus spreads easily among infants and young children. The virus can cause severe watery diarrhea, vomiting, fever, and abdominal pain. Children who get rotavirus disease can become dehydrated and may need to be hospitalized. Good hygiene like hand-washing and cleanliness are important, but are not enough to control the spread of the disease. Rotavirus vaccine is the best way to protect your child against rotavirus disease. Most children (about 9 out of 10) who get the vaccine will be protected from severe rotavirus disease. About 7 out of 10 children will be protected from rotavirus disease of any severity. RotaTeq® (RV5) is given in 3 doses at ages 2 months, 4 months, and 6 months. Rotarix® (RV1) is given in 2 doses at ages 2 months and 4 months. The first dose of either vaccine should be given before a child is 15 weeks of age. Children should receive all doses of rotavirus vaccine before they turn 8 months old. Both vaccines are given by putting drops in the child's mouth (Dan Brennan, 2020)

Rotavirus vaccines are licensed in over 100 countries, and more than 108 countries have introduced routine rotavirus vaccination, almost half with the support of Gavi, the Vaccine Alliance. To make rotavirus vaccines available, accessible, and affordable in all countries—particularly low- and middle-income countries in Africa and Asia where the majority of rotavirus deaths occur, PATH (formerly Program for Appropriate Technology in Health), the WHO, the U.S. Centre for Disease Control and Prevention, and Gavi have partnered with research institutions and governments to generate and disseminate evidence, lower prices, and accelerate introduction (Ward and Bernstein, 2009).

Spread of rotaviruses can be minimized by hand washing, use of disinfectant and other sanitary measures. Children infected with rotavirus should be excluded from childcare, preschool and work until there has been no vomiting or diarrhea for at least 24 hours. If working as a food handler in a food business, the exclusion period should be until there has

been no vomiting or diarrhea for 48 hours. The rotavirus vaccine provides good protection against the most common types of rotavirus vaccine, in combination with other vaccines, is now recommended to be given at 6 weeks of age (Dorsey *et al.*, 2017)

It's important for immunization providers and parents to remember that there are upper age limits for the doses of vaccine (Saheri *et al.*, 2014).

The 2019 Institute for Health Metrics and Evaluation (IHME) statistics ranked Nigeria as the country with the highest rotavirus mortality globally (IHME, 2020). Nigeria is at the threshold of introducing the rotavirus vaccine to its national immunization programme, and the country's application for support from Gavi, the Vaccine Alliance was approved in early 2020. However, introduction of the vaccine remains pending as at the last quarter of 2020 (UNICEF, 2020). The country is currently in the accelerated transition phase2 stage based on Gavi's classification, which implies that Gavi's subsidy will be phased out soon. However, the Gavi board has approved the extension of the transition period for Nigeria until 2028(GAVI, 2020). Either RV5 or RV1 can be used to prevent rotavirus gastroenteritis. RV5 should be administered orally, as a three-dose series, at 2, 4, and 6 months of age. RV1 should be administered orally, as a two-dose series, at 2 and 4 months of age. For both rotavirus vaccines, the minimum age for dose 1 is 6 weeks, and the maximum age for dose 1 is 14 weeks and 6 days. The vaccination series should not be started at 15 weeks of age or older, because of the lack of safety data around administering dose 1 to older infants. The minimum interval between doses is 4 weeks. All doses should be administered by 8 months and 0 days of age. While the ACIP recommends that the vaccine series be completed with the same product (RV5 or RV1) used for the initial dose, if this is not possible, providers should complete the series with whichever product is available (UNICEF, 2020).



Figure 2: A baby receiving the rotavirus vaccine during the launch in Abuja. (Ukazu, 2022).

Conclusion

Rotavirus is a forefront microbe eliciting significant consequence of diarrhea in children, and in turn killing and hospitalizing thousands globally. The consequences of the rotavirus could only be efficiently and easily be abated through prevention with vaccination s a core cardinal principle. Therefore, this paper laid a conceptual overview of prevention of rotavirus infection in children using vaccines.

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