Control Strategies of Rotavirus Infection

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ABSTRACT

Rotavirus is major cause of gastroenteritis particularly in young and newborn children. The main way that the virus spreads is by the fecal-oral route, however, contaminated food, drink, and surfaces can also pose a significant risk of transmission. Due to inadequate sanitation and medical facilities, low- and middle-income nations are disproportionately affected by RV infections, which cause severe morbidity and mortality on a global scale. Various animals are affected by RV infections in addition to people, resulting in a variety of types. Infection of host cells, virus replication, assembly, and release of new virus particles are all phases of the RV life cycle. Personal contact, contaminated objects, and airborne routes are the three ways the disease spreads. According to epidemiology, childhood RV infections are common, vary seasonally, and are more severe in low-income countries. RV vaccinations, such as RotaTeq and Rotarix have successfully avoided severe gastroenteritis. Passive immunization is the main focus of animal vaccines; however, RV Virus-like Particles (RV-VLPs) promise to be a more broadly serotype-covered vaccine in the future. RV continues to be a major public health concern, and developments like RV-VLPs, as well as the development and execution of efficient immunization programs, are essential for the prevention and management of disease worldwide.

CITATION

Kanwal A, Faraz A, Arif S, Arshad M, Tahir I, Rameen, Yousaf S, Qasim S, Tahir S and Tahir H, 2023. Control strategies of rotavirus infection. In: Aguilar-Marcelino L, Zafar MA, Abbas RZ and Khan A (eds), Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, Vol 3: 477-487. https://doi.org/10.47278/book.zoon/2023.117

CHAPTER HISTORY Received: 19-March-2023 Revised: 27-May-2023 Accepted: 10-July-2023

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1. INTRODUCTION

Rotavirus (RV) belongs to the family Reoviridae and wheel-shaped, triple-layered virion with a diameter of about 100 nm (Nirmal and Gangar 2023). They have an 11-segment genome that codes for 5 nonstructural proteins (NSP1, NSP2, NSP3, NSP4, and NSP5) and 6 structural viral proteins (VP1, VP2, VP3, VP4, VP6 and VP7) (Azevedo et al. 2023). RV strains are categorized based on the differences between two outside proteins on the virus surface known as VP4 (P-type) and VP7 (G-type) (McDonald et al. 2009). These proteins greatly influence the specific RA strain and its antigenic characteristics. These proteins play an important role in the antigenic and strain properties of viruses. This is involved in entry into host cells, viral attachment, and the target of the host immune system. RVA, RVB, and RVC are the most prevalent infecting groups in humans and animals, with RVA strains being the most prevalent (Molinari et al. 2016). Birds like chickens and turkeys have RVD, RVG, and RVF. Some mammals like cows, horses, and pigs have RVI, RVB, RVH, RVC, and RVE (Vlasova et al. 2020). Bovine RV was the first group of RV separate in cell culture and was confirmed as a cause of diarrhea in calves in 1969 (Vlasova et al. 2017). In 1973 human RV was discovered by Bishop and his colleagues. The rotavirus mainly causes gastroenteritis, inflammation in the digestive system (Sadiq et al. 2018).

The virus has a significant risk of spreading from person to person. They can contract rotavirus through contaminated food, water, objects, or surfaces. This is primarily because it is transmitted through the fecal-oral route (Sánchez and Bosch 2016). The virus is very resilient and can persist on surfaces for extended periods. In temperate climates, RV infections occur more commonly in the winter but may occur in every season (Chao et al. 2019). The risk of infection is greater in infants and young children, and symptoms usually occur two to three days after contact. The most typical signs and symptoms include vomiting, fever, watery diarrhea, and pain in the abdomen (Fig. 1) (Reust and Williams 2016).

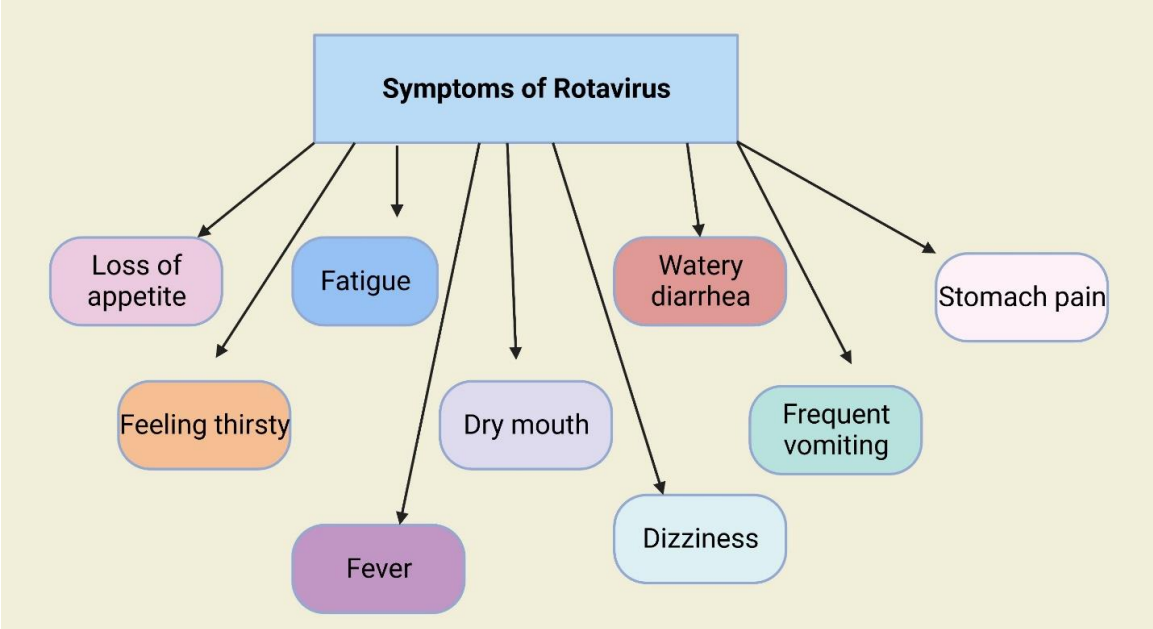

Fig. 1: Symptoms of Rotavirus (Retrieved from Biorender).

WHO estimates 200,000 deaths and millions of hospitalizations annually due to RA, primarily in areas with limited resources. Geographical differences affect the severity of rotavirus infection. Severe rotavirus sickness and death are more predominant in low and middle-income countries, mainly in Africa and Asia

(Varghese et al. 2022). The higher effect in these areas is due to limited healthcare access, clean water, and sanitation facilities (Watson et al. 2007).

2. ROTAVIRUS TRANSMISSION

RV spreads from person to person orally through feces (Yekta et al. 2021). In developing nations, RV can also spread through water that feces have polluted. RV may also transfer from child to child if caretakers' hands come into contact with contaminated objects or surfaces (Brady 2005). The rapid incubation period and frequent outbreaks suggest RV gastroenteritis is airborne. RV can be spread through the air in healthcare places (Koo et al. 2010). Children with RV infection pass 100 billion virus particles per gram of feces (Boone and Gerba 2007). These viruses can live from days to weeks on environmental surfaces, on hands for at least 4 hours, and in drinking or recreational water for weeks (Weber et al. 2010). Asymptomatic RV infections

3. EPIDEMIOLOGY OF ROTAVIRUS

RV is common and affects almost all children between the ages of three and five. Worldwide, 114 million instances of RV infection in children below 5 years old have been recorded in 2003 (Nair et al. 2010). By 2013, RV had caused more than 200,000 mortalities in children under the age of five around the world (Zhou et al. 2023). RV infections are common (about 30–50%) in hospitalized children with diarrhea worldwide. Over 90 percent of fatal RV infections happen in low-income nations (Tanaka et al. 2007). RV causes comorbid diseases like hunger, restricted access to healthcare, and a lack of availability of hydration therapy (Ren et al. 2021). Poor countries experience more cases of rotavirus caused by uncommon strains like G9P, and it affects kids at an earlier age than in rich countries. In Africa, almost 43% of all children hospitalized for RV are infants under 8 months, while in Europe, only 27% (Sadiq et al. 2018). Hospitalized patients (30-50%) and outpatient treatment patients (15-20%) are more likely to get RV-caused diarrhea than those who need home care (5-10%). Diarrhea induced by RV infection is more severe than typical (Parashar et al. 2003). RV detection rates were highest in children aged 6-23 months (41.8%) and lowest in children aged 6 months (24.7%). Of the 21,421 children enrolled during the four years of surveillance, 36.3 percent were positive for RV (Patel et al. 2013). The eastern region had the highest percentage of RV-associated diarrhea (39.8%), and the southern region had the lowest (33.8%) (Tate et al. 2016).

4. EPIDEMIOLOGY OF ROTAVIRUS IN ANIMALS

RV infections with symptoms are often more frequently found in birds and mammals. Animal RVs' molecular epidemiology is similar to that of humans in several respects (Rajendran and Kang 2014). RV diseases affect pigs, cattle, horses, and, to a lesser extent, sheep, goats, and camelids. In cattle, RV strains have been classified into 11 P types (P1, P3, P5, P6, P7, P11, P14, P17, P21, P29, and P33) and 12 G types (G1-G3, G5, G6, G8, G10, G11, G15, G17, and G24) (Matthijnssens et al. 2011). Out of 20 P and G combinations, G6P [5], G10P [11], and G6P [11] are most common in many parts of the world, making up 40% of cases (Uddin Ahmed et al. 2022). Pigs have been found at least 13 P categories (P6 or P7, P5, P8, P11, P13, P14, P19, P23, P26, P27, and P32) and 12 G (G1, G2, G3, G4, G5, G9, G6, G8, G10, G11, G12, and G26) (Papp et al. 2014: Daykin et al. 2019). However, the P and G genotypes of rotaviruses found in camelids, goats, and lambs frequently match those discovered in cattle. Canine RVs have the G3P [3] antigen combination in the majority of cases, whereas feline RVs have the G6P [9], G3P [9], and G3P [3], and genotypes (Doro et al. 2015).

5. EPIDEMIOLOGY OF ROTAVIRUS IN HUMANS

Young kids and infants between the ages of four months and three years are more prone to experience extreme clinical symptoms of RV (Khemani et al. 2017). Most kids are infected with RV by age five, although the rates vary by region (Page et al. 2016). RV infections frequently exhibit seasonal trends in temperate zone states, with the epidemic peaks more pronounced during wintertime (Shaman and Kohn 2009). In industrialized nations, one genotype dominates in a geographic location during a season. However, minority strains can still have distinct genotypes. In some years, no single dominant strain can be discovered in underdeveloped nations, and illnesses caused by many RV genotypes, that is, mixed infections, are common.17 P types (P1 to P11, P14, P15, P19, P24, and P28) and 14 G types (G1, G2, G3, G4, G5, G6, G8, G9, G10, G11, G12, G13, G14, G20 and G26), as well as almost 90 RVA antigen mixtures have been detected in youngster around the world through surveillance studies (Amimo et al. 2013). G12P [8] and G9P [8] strains have recently become widespread worldwide from 1990 to onward. G2P [8] and G1P [4] strains are frequently observed to co-circulate with G2P [4] and G1P [8] (Hungerford 2019). G2P [4] strains became more prevalent over successive seasons in regions where the national immunization strategy used the G1P [8] Rotarix vaccine (Bibera et al., 2020). The G8P [6] and G5P [8] viruses, which are found in various regions of Sub-Saharan Africa and South America, respectively, are historical instances of regionally prevalent strains (Linhares 2011). Porcine-like G4P [6] strains and G3P [9] strains are two examples that have been found in humans over the past 20 years in many countries all over the world (Wang et al. 2014).

6. LIFE CYCLE

The RV involves infecting host cells, replicating, assembling, and releasing new virus particles (Ravindran et al. 2016). In the small intestine, the RV first binds to certain receptors on the surface of host cells. A sugar molecule known as Salic acid serves as the main receptor. Following attachment, the virus enters the host cell through a process known as endocytosis, in which the cell engulfs the viral particle and produces an endosome (Abdelhakim et al. 2014). After the viral particle is engulfed by the host cell, it enters the endosome, where the outer covering is broken down, and the inner core is released. The acidic surroundings of the endosome, which lead to structural changes in the virus particle, initiate this process (Louten 2016). Eleven double-stranded RNA sections comprising the viral genetic makeup are present in the released viral core (Christiaens et al. 2020). Viral enzymes subsequently perform transcription and replication of the viral RNA inside the host cell. As a result, additional viral genome copies and messenger RNA (mRNA) is produced (Te Velthuis et al. 2010). The machinery of the host cell translates the viral mRNA into viral proteins. The structural proteins that comprise the virus particle, the non-structural proteins required for virus replication, and the enzymes involved in RNA replication belong to these proteins (Malone et al. 2022). In the host cells cytoplasm, replicated viral RNA segments and newly synthesized viral proteins generate new virus particles (Chou et al. 2013). The pre-structural of the viral genome forms a full virus particle newly constructed virus particles undergo maturate undergoing which the virus particle's exterior protein layer is changed, and it acquires infectious properties (Novoa et al. 2005). The host cell allows the virus particles to release. This can occur through several methods, such as cell lysis, in which the host cell is ruptured, or a process known as budding, in which the virus particle is encapsulated by the host cell membrane and discharged without resulting in cell death (Fig. 2) (Nanbo et al. 2018).

The released virus particles infecting additional host cells can continue the infectious cycle. Typically, the RV life cycle lasts ten to twelve hours, during which plenty of newly formed virus particles are produced. The sickness's large viral load and quick spread are attributed to this virus generation that occurs quickly.

7. DIFFERENT STRATEGIES TO CONTROL ROTAVIRUS

Strategies for controlling and preventing RV infections are being developed. Vaccination is the major method of lessening the social and financial costs of RV infections.

8. ROTAVIRUS VACCINES IN HUMAN USE

Animal virus strains induce cross-neutralizing antibodies against human strains, whereas heterologous virus strains are greatly attenuated for humans (Schwartz et al. 2007). Some were selected because they are common in neonatal units, while others were weakened through repeated cell culture passages. Live vaccines are given orally in doses to imitate RV infections and promote immunity against different variations of antigens (Azevedo et al. 2013). Non-replicating vaccines are made up of sub-unit and inactivated vaccines. The monovalent, two-dose vaccine Rotarix is made by GlaxoSmithKline (Belgium) (Braeckman et al. 2012). A single G1P [8] strain was repeatedly transmitted on cell culture to reduce it. The vaccine is widely accessible and is recommended in 70% of countries where routine RA vaccination is practiced (Danziger-Isakov et al. 2019). Table 1 shows the names of available vaccines, host and the efficacy.

RotaTeq is a pentavalent 3-dose vaccine developed by Merck (USA). Each of the 5 resistant strains in the vaccine represents a different human neutralization antigen (Matthijnssens et al. 2012). Each resistant's backbone genes are mostly provided by the parental strain, the bovine WC3, and its original neutralizing

Table 1: Vaccine names, host, strain, and efficacy against Rotavirus

Vaccine Name	Administration	Strains	Hosts	Efficacy	References
RotaTeq	Oral (liquid)	G1, G2, G3, G4, P[8]	Human-bovine	Approximately 85-98% against severe rotavirus gastroenteritis,	Cortese and Parashar 2009; Nayak et al. 2019
RotaShield	Oral (liquid)	G1, G2, G3, G4, G9, G10, P[8]	Human-bovine	Approximately 49-68% against severe rotavirus gastroenteritis	Glass et al. 2021
BRV-PV (BRVAX)	Oral (tablet)	G1P[8]	Human	Approximately 67-87% against severe rotavirus gastroenteritis	World Health Organization, 2020
Rotarix	Oral (liquid)	G1P[8]	Human	Approximately 85-98% against severe rotavirus gastroenteritis	Grimwood and Bines 2007; Ella et al. 2019
Rotavac	Oral (liquid)	G1P[8]	Human-bovine	Approximately 55-64% against severe rotavirus gastroenteritis	Burke et al. 2021
Rotavin-M1	Oral (liquid)	G1P[8]	Human	Approximately 53-67% against severe rotavirus gastroenteritis	Castellucci, 2017; Skansberg et al. 2021
Ervebo	Intramuscular	N/A	Hamster	Approximately 97.5-100% in preventing Ebola virus infection	Woolsey et al. 2022
RIX4414	Oral (liquid)	G1P[8]	Human-bovine	Approximately 85-98% against severe rotavirus gastroenteritis	Grimwood and Bines 2007
Lanzhou lamb-2 rotavirus vaccine	Oral (liquid)	G10P[15]	Lamb	Approximately 80-85% against severe rotavirus gastroenteritis	Carvalho and Gill 2018
Rotasiil	Oral (liquid)	G9P[11]	Cow	Approximately 53-67% against severe rotavirus gastroenteritis	Castellucci 2017
BRV-PV	Oral (liquid or suspension)	G1, G2, G3, G4 and G9	Human	66.7% efficacy	Folorunso and Sebolai 2020

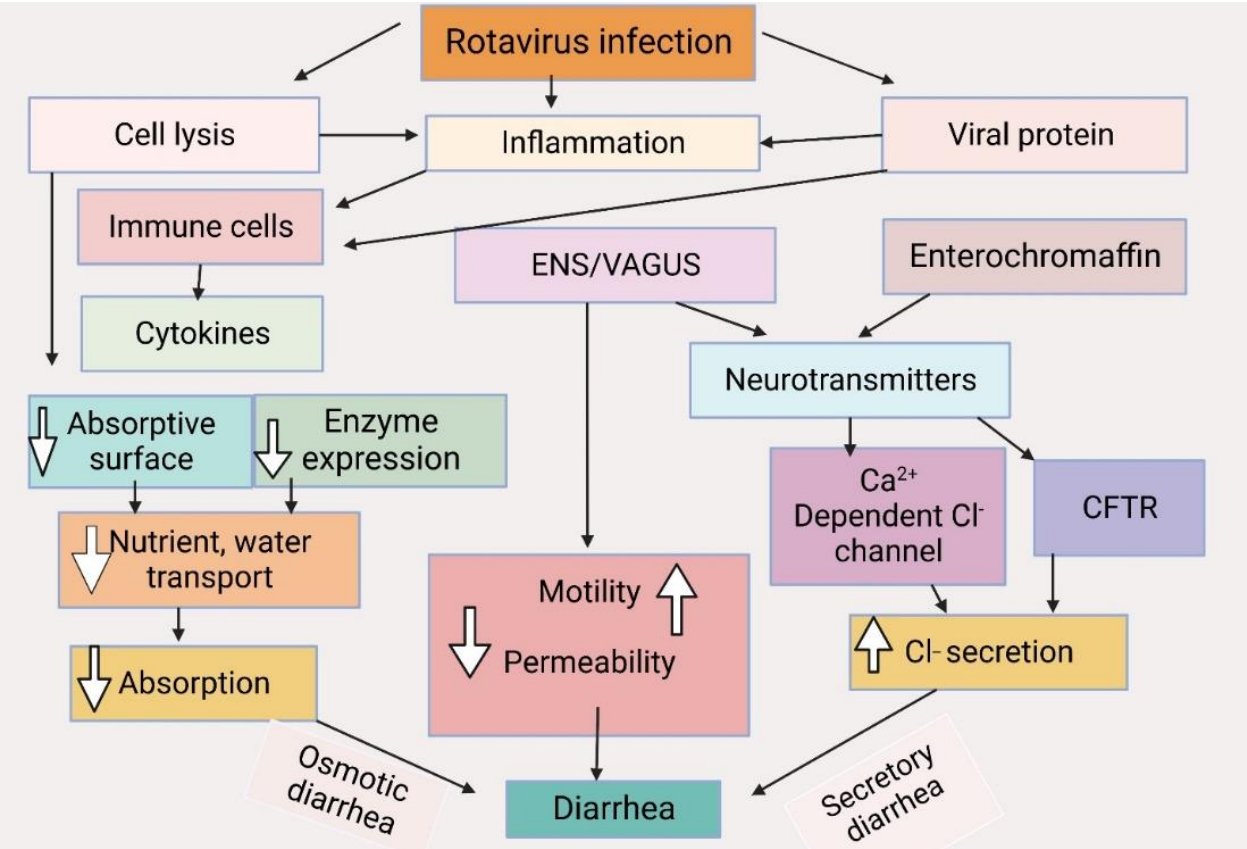

Fig. 2: Mechanism of Rotavirus Disease (Retrieved from Biorender).

antigens. The VP4 and VP7 are also detected (Doro et al. 2015). The Lanzhou Lamb RV vaccine was produced by Lanzhou Institute in China. This vaccine is monovalent and carries a G10P [15] rotavirus strain of an ovine origin (Li et al. 2018). Rotavac is a monovalent 3-dose vaccine and produced by Bharat Biotech in India. The vaccine contains a single human G9P [11] strain, which was discovered in an Indian youngster who was asymptomatic (Skansberg et al. 2021). After a Phase 3 trial showed a positive safety and efficacy profile, the vaccines were commercialized in 2014. A monovalent vaccine called Rotavin-M1 was developed at the center for research and production of vaccines and granted a license for Vietnam in 2007 (Kirkwood et al. 2019).

9. ROTAVIRUS VACCINES IN ANIMAL USE

Animal immunization strategies differ from those used to prevent rotavirus infections in infants and young children (Dhama et al. 2009). In humans, the main goal is to prolong the active immunity induced by vaccination during the first few years of a child's life, when the risk of extreme infections is at its highest after the parental antibody level has decreased by the age of four to six months (Kinyanjui et al. 2015). RV primarily affects the offspring of animals and passive vaccination is the major treatment for animals. This principle of passive vaccination is based on parental antibodies that can cross the placenta or be released in colostrum and give kids temporary protective immunity against clinically evident RV infection (Vojtek et al. 2018). Both inactivated and live attenuated vaccinations can raise the antibody concentration in pregnant animals. These vaccinations are given late in pregnancy, and RA antigens are frequently included

in polyvalent vaccines containing antigens from other significant intestinal infections (Obaro et al. 2014). The USA has access to a live modified vaccine used to vaccinate young piglets (Tizard 2020) actively.

10. RV VIRUS-LIKE PARTICLES

Production of rotavirus virus-like particles (RV-VLPs) was 1st reported in 1980. The formation of VLPs that can be easily isolated was subsequently achieved by co-expressing the VP6 and VP2 proteins in insect and mammalian cells (Kushnir et al. 2012). The expression of VP2 itself has been demonstrated to produce pseudo-core-like particles. RV- VLPs can significantly increase immune responses regardless of the method of vaccination used (intraperitoneal, intramuscular, intranasal, parenteral, intrarectal, and oral) (Marashi et al. 2014). The following factors make rotavirus VLPs a promising candidate and an alternative to conventional vaccines, they are effective immunogens and cannot transform into infectious forms because they lack genetic material, handling is risk-free, the viral proteins remain in their natural approval, they can be combined with an adjuvant to increase immunogenicity and large-scale recombinant vaccines for new serotype can be produced (Jere et al. 2014). Furthermore, a lower antigen can elicit the same immune response compared to subunit vaccinations since VLPs are similar to the parent virus (Noad and Roy 2003).

11. RECENT DEVELOPMENTS IN RV VIRUS-LIKE PARTICLES TECHNOLOGY

Several groups are currently focusing on developing combinatorial vaccines to improve their immunogenicity against different infections following the success of RV-VLP manufacturing systems (Changotra and Vij 2017). A potential combination vaccination against acute adolescent gastroenteritis that combines recombinant polymeric RV VP6 protein and norovirus VLPs generated in baculovirus-insect cell production systems (Blazevic et al. 2016). Additionally, it has been demonstrated that the RV VP6 protein affects the activation and maturation of antigen-presenting cells in vitro and has an adjuvant impact on norovirus-specific antibody reactions in vivo (Malm et al. 2017). None of the RV-VLPs have been tried on humans. However, gnotobiotic pigs, mice, and rabbits have been used to assess the RV-VLPs' immunogenicity, effectiveness, and safety (Yuan et al. 2000). Two VLP-based RV subunit vaccines, however, are made up of truncated VP8 in norovirus P particles and VP 2/6/7 and VP 2/4/6/7 in VP-based vaccines that are now in the preclinical stage of development (Heinimäki et al. 2020).

12. OTHER STRATEGIES

The challenges of removing rotaviruses from hands or infected surfaces must be addressed by rotavirus control techniques (Greenberg and Estes 2009). Rotaviruses are not easily destroyed by the chemical antiseptics and disinfectants frequently employed in hospitals and other institutions (Todd et al. 2010). Effective disinfectants should be used to clean environmental surfaces. Quaternary ammonium compounds and chlorhexidine gluconate, the active component of Hibiclens, should be used in formulations with a high alcohol content to become active against rotavirus (Dennehy, 2000). Rotavirus becomes inactive by quarternary ammonium compounds that contain >40% isopropyl alcohol by volume or formulations of chlorhexidine gluconate 0.5% w/v in 70% ethanol by volume (Hibitane in ethanol) (Rotter 2004). When applied to inanimate surfaces that had been experimentally contaminated with an infectious form of the RV, Lysol Brand Disinfectant Spray (79% ethyl alcohol, 0.1% o-phenyl phenol) effectively prevented the spread of rotavirus infection to humans (Boussettine et al. 2020). RV cannot be removed from hands using regular soap, and handwashing increases the risk of the virus spreading to more skin surfaces. Use a waterless hand cleaner with alcohol when washing your hands before and after coming into touch with sick kids (Bloomfield et al. 2007).

13. CONCLUSION

It is concluded that reducing the significant negative effects of rotavirus infection on public health, particularly in infants and young children, depends on controlling the infection. Vaccination remains the basis of prevention with multiple efficient vaccinations, including RotaTeq and Rotarix. The production of RV-VLPs shows promise as a candidate for a future vaccine. RV-VLPs greater serotype coverage and viral mimicry stimulate humoral and cellular immune responses. To further control and lessen the effects of RV infection globally, a multifaceted strategy involving vaccination, better hygiene habits, and continued research into new vaccine technologies like RV-VLPs is crucial.

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