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Review Article

Rotavirus in Calves: Cutting-Edge Insights and Emerging Challenges

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Abstract

In calves, Rotavirus is the main cause of diarrheal disease, which significantly reduces productivity and economy. Since their discovery in the 1970s, the human rotaviruses have been recognized as the most important cause of acute infectious gastroenteritis among infants and children worldwide. Rotavirus has been found to infect almost all mammalian and avian species tested, and is primarily a disease of the young. In humans, rotavirus is the most frequent gastrointestinal pathogen in infants and children less than 2 years of age. Although rotavirus causes diarrheal disease in calves and humans around the world, many of its aspects are not fully understood, considering that it is one of the most significant health problems in calves, interrupting invention remunerations with decreased weight gain besides increased mortality, and having the probability to spread zoonotic diseases. In almost all cases, rotavirus causes pathological changes that lead to diarrhea in the small intestine. The species is widely distributed in the environment and has been extensively studied. There is a wide range of hosts for Rotaviruses, including animals in addition to humans. Several animal strains of rotavirus have antigenic similarities to some human strains, which might indicate that animals might be sources of human rotavirus infection. It has been found that both humans and animals can become infected with groups A to C. G2, G3, G4, and G9, P strains are the most frequently detected in humans and animals. Therefore, the purpose of this review was to get a better picture of the epidemiology, prevalence status, zoonotic significance, and ways to cope with bovine rotavirus.

Keywords: Rotavirus, Calves, Zoonotic, Prevalence, Human Strains

1. Introduction

When calves are younger than one month old, rotavirus is a frequent infection that causes severe diarrhea. Both humans and animals are susceptible to diarrhea caused by this pathogen. A rotavirus of the Reoviridae family causes diarrhea most commonly in farm animals [1, 2]. When an infection spreads rapidly, there is severe damage to the intestinal lining, which causes dehydration and fast fluid loss [3]. Rotaviruses have evolved largely due to genetic reassortment, which contributes heavily to genetic diversity. In spite of the lack of an effective treatment for BRV, early detection and confirmation are important for determining effective preventative and control measures. These measures might prevent excessive losses for livestock farmers [4].

Among all the enteric pathogens associated with diarrheal calves, 8 percent were positive for at least one pathogen other than bovine coronavirus, bovine rotavirus, and bovine norovirus [5]. Calves between the ages of 0 and 4 weeks are most likely to experience diarrhea. For dairy and beef farms to operate successfully, they need to wean a large number of healthy calves each year. As the calf enters weaning, it is essential for its immunity to be maximized and its exposure to infectious agents to be minimized. Among the major obstacles to the dairy and beef industries' success has been calves' morbidity and mortality. Death and morbidity are substantial financial losses in the global dairy industry. In wealthy countries, the morbidity and death rates of dairy and beef

calves remain un-acceptably high, despite advancements in husbandry techniques, clinical medicine, and diagnostic tool [6]. There are several risk factors that contribute to dairy in addition to beef calf morbidity and mortality, and identifying these factors is essential for designing and implementing prevention measures.

There has been extensive study of Rotavirus, one of the most widely distributed disease agents worldwide [7]. A rate of 20–60% infection with (Bovine Rota Virus) BRV has been reported in diarrhea samples in different studies [8]. According to a recent study, 11.8% to 26.8% of diarrheal calves in India had rotavirus infection [9]. Rotavirus infection was also extensively studied in European countries. The estimated prevalence in Sweden between 1993 and 2006 was 24–47%, in the UK 42%, and in France, Prevalence exists between 37 to 47.4%. Between 0 and 7% of rotavirus infections were detected in calf feces in Asian countries such as Bangladesh. It has been reported that 16.7% of Ethiopian children have rotavirus [10]. For calves to be controlled and prevented from becoming infected with rotavirus, it is essential to understand its epidemiology, zoonotic significance, and other relevant facts. Aim of the review is to offer an overview of the epidemiological status plus zoonotic significance of bovine rotavirus. An effective control and prevention plan in the country requires this information.

2. Structure and classification of rotavirus

RV particles (virions) consist of Rotavirus virions consist of three protein layers, making them triple-layered particles (TLPs).. Electron microscopy reveals that TLPs (proteins or viral particles) exhibit a wheel-like appearance, resembling a latin. rota, which is why Rotavirus is named for its distinctive structure. Cryo-electron microscopy combined with image reconstruction data has enabled the identification of its icosahedral symmetry [11]. 120 molecules of viral protein 2 (VP2) are arranged as 60 dimers in a T = 1 symmetry to form the single-layered particle (SLP = core shell). Approximately five dimers form each decamer around the fivefold symmetry axis, and 12 decamers form the core protein layer [12]. As early as 2010, the N-terminus of VP2 was believed to contribute to the 'fivefold hub' (density) in the core interior along the fivefold axis [12], but more recently, VP1 was recognized to be responsible [13]. At the axis of fivefold symmetry, replication enzyme complexes are located inside the core) opposite the class I channels [14] and they are in close contact with a particular genomic dsRNA segment via VP1 [15]. There are 11 segments of dsRNA in the viral genome as well as RNA dependent RNA polymerase (RdRp), VP1, and capping enzyme, VP3. In addition to their non-enveloped nature, rotaviruses contain a complex architecture consisting of three concentric capsids enclosing 11 segments of dsRNA genomes. NSP1, NSP2, NSP3, NSP4, NSP5 and NSP6 are among the non-structural proteins encoded by the RNA segments (VP1, VP2, VP3, VP4, VP6 and VP7). An epitope on the surface of a matured virus particles determines specificity of host, entry in the cell, and the function of enzymatic enzymes essential for the production of viral transcripts. Among non-structural proteins, NSP1 participates in genome replication, inhibits the innate immune system, and contains viral enterotoxins as well [16] (Figure 1).

There are 15 genera within the Reoviridae family, and *Rotaviruses* form one of the fifteen genera. The *Sedoreovirinae* subfamilies include the *Cardoreovirus,* the *Mimoreovirus,* the *Orbivirus,* the *Phytoreovirus,* the Rotavirus and the *Seadornavirus.* There are also several subfamilies under Spinareovirinae (Aquareoviruses, Coltiviruses, Cypoviruses, *Dinovernaviruses, Fijivirus, Idnoreoviruses, Mycoreoviruses, Orthoreoviruses,* and *Oryzaviruses).* There are at least eight different groups, also called species, of VP6 based on their serological reactivity and genetic variability [17]. At least 27 G types belong to RVA species (based on VP7 nucleotide sequence) and 37 P types belong to RVA species [18] (Rotavirus Classification Working Group, 2013). Genotypes and serotypes are synonymous for G types, e.g. G1, G2, etc. The number of P genotypes exceeds the number of reference sera used to determine P serotypes. As a result, a double nomenclature system has been introduced, such as PS1A [8], where 'P genotype 8' corresponds to 'P serotype 1A'. RVAs have been classed using the complete genome based on the

sequences, in which the genotypes VP7–VP4–VP6–VP1–VP2–VP3–NSP1–NSP2–NSP3–NSP4–NSP5/6 can be recognized and distinguished based on specific sequence identity cut-off points [19] (Table 1).

3. Epidemiology of bovine rotavirus

Rotavirus diarrhea causes severe problems in calves, leading to significant mortality, increased medical costs, and slower growth rates. Epidemiological studies indicate that animal rotaviruses affect cattle, swine, and horses, while also partially affecting goats, sheep, and camelids. The prevalence of different rotavirus genotypes varies depending on disease severity. Globally, the most common genotypes are G1, G2, G3, and G4, whereas G8 is more frequently reported in Africa. Providing specific data or recent studies would strengthen these claims [20]

3.1. Mode of transmission

In addition to interspecies transmission, cross-species transmission is possible. Rotavirus diversity is driven by interspecies transmission and subsequent reassortments, which allow for the introduction of novel pathogenic microorganisms possessing modified pathogenicity [21]. A fecal-oral route and direct contact are also possible routes of transmission [22]. Although the exact details of rotavirus entry into host cells are still being investigated, its infection mechanism is well understood. Rotavirus primarily infects enterocytes in the small intestine, leading to villous atrophy and impaired absorption of salts and water. This results in increased fluid secretion and diarrhea. The infection occurs mainly at the brush border and within the villous epithelium, where villous lactase activity decreases due to the rapid replacement of mature enterocytes with undifferentiated crypt cells. Calcium-dependent endocytosis and the role of VP4 in viral entry should be referenced with relevant molecular studies for accuracy (Figure 2). The term **"enterocytes"** refers to specialized epithelial cells that line the small intestine and play a key role in absorbing nutrients, water, and electrolytes. These cells are particularly important in maintaining gut homeostasis [23].

Report Shows that rotavirus could be spread via airborne and waterborne transmissions [24], although rotavirus transmission is primarily fecal-oral. Ingestion of rotavirus particles causes structural changes to the intestinal epithelium after infection by adult, differentiated enterocytes in the villi's middle and upper regions [25]. Enterocytes of small intestinal villi that produce enzymes and are able to absorb nutrients replicate the virus in their cytoplasm. As a result of the damage of mature entrecotes in the villi, the enterocytes rupture and slough, allowing virus to spread to adjacent cells. Villous crypt cells and colonic enterocytes cannot be infected by rotavirus like parvovirus. The VP4 protein attaches rotavirus to its cellular receptors (sialo glycoprotein and integrins). It is thought that the virus enters target cells via direct entry or fusion with enterocytes, or via Ca^{2+}-dependent endocytosis [26].

Rotavirus diarrhea can be caused by three different mechanisms. Enterocytes remain intact 12 to 24 hours after infection, but their brush-border disaccharidases (sucrase, maltase, and lactase) are greatly reduced. Osmotic diarrhea is caused by the inability of disaccharides in the diet to hydrolyze to monosaccharides; therefore, disaccharides cannot be absorbed by the body [27]. Additionally, NSP4 increases calcium channel opening within enterocytes. This results in sodium and water being effluxes from the body, resulting in secretory diarrhea [11]. In addition, high intra-enterocyte calcium concentration leads to oncolysis, which causes cells to die. It has been hypothesized that mature villous tip enterocytes die more quickly than immature enterocytes originating from stem cells within the crypt, resulting in villous blunting and mal-absorption [28]. Infection ends after the generation of an immune response and exhaustion of mature enterocytes [25].

Serotonin (5-hydroxytryptamine, 5-HT) causes emesis, a hallmark of rotavirus disease. In humans, enterochromaffin cells (EC) secrete 5-HT in response to rotavirus infection and replication. As a result of 5-HT, vagal afferent nerves connected to the solitary tract nucleus and the brainstem area postrema are activated [29].

3.2. Replication of rotavirus:

During rotavirus replication, the virus interacts with its host at multiple stages, including attachment, entry via receptor-

mediated endocytosis, transcription and translation within viroplasms, genome synthesis, packaging of viral RNA, and virion assembly. The mature virus is then released through cell lysis or a non-lytic pathway. These interactions disrupt cellular functions, contributing to pathogenesis [30].

Cells infected with Rotavirus replicate in their cytoplasm, in viroplasms, and in electron-dense structures near their nuclei [31]. By binding to NSP4 on the ER transmembrane, newly made viruses enter ER from viroplasms. It is important to note that rotavirus replication does not involve the Golgi apparatus, even though glycoproteins are synthesized and transported there. It is instead intracellular calcium concentrations that regulate rotavirus replication, morphogenesis, and pathogenesis). As early as 4 hours after infection, rotavirus toxin NSP4 is released from infected cells, first as a cleavage product including the toxic region and then as a fully glycosylated form during infection.VP4, the spike protein of rotavirus, plays a crucial role in host cell attachment and entry. It undergoes protease-dependent activation, where trypsin cleaves VP4 into two functional subunits: VP8 and VP5. VP8 primarily mediates binding to host cell receptors, while VP5 facilitates membrane penetration, allowing the virus to enter the cell via endocytosis. This cleavage enhances viral infectivity by promoting efficient interaction with the host cell membrane [33].

There are several receptors that are involved in the binding of Rotavirus in vivo, including sialic acid, integrins, histo-blood group antigens [32], TLRs (toll-like receptors) had also been implicated. Through receptor-mediated endocytosis, VP5 is required for cell entry, suggesting that VP4 needs to be divided into VP5 and VP8. There has also been evidence of calcium-dependent endocytosis. The virion enters the initial endosome via clathrin-independent non-caveolin endocytosis [33].

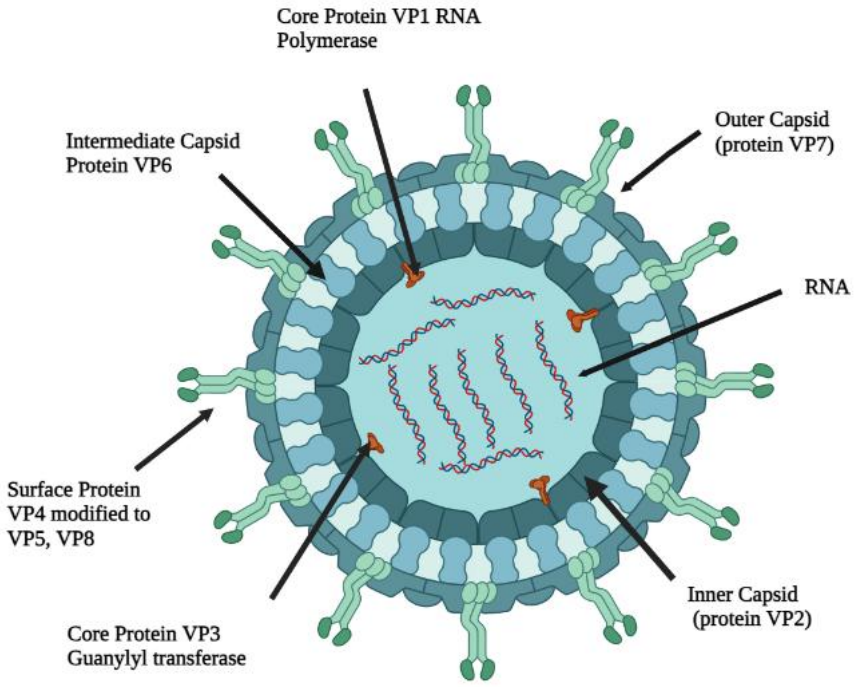

Figure 1. Structure of Rotavirus: Depicts the triple-layered architecture of the rotavirus, highlighting its key structural and functional proteins. The outer capsid contains VP7 and surface spike protein VP4 (cleaved into VP5 and VP8 for infectivity). Beneath lies the intermediate capsid protein VP6, and the inner capsid (VP2) encases the viral double-stranded RNA genome. Core proteins VP1 (RNA polymerase) and VP3 (guanylyl transferase) are essential for viral replication and capping of viral RNA..

A direct entry or fusion can also be suggested as a method by which the rotavirus enters the cell. The decrease in Ca+ concentration in the endosome and the uncoating of the TLP lead to the uncoating of VP7 and the loss of the outer capsids (VP7, VP5, and VP8). A single-layered particle (DLP) (core proteins and inner capsid VP6) is released into the cytosol [34]. The cytoplasm of the cell is the site of transcription and translation. Transcription of capped (+) RNAs from each of the 11 dsRNA segments begins with the internal polymerase complex (VP1 and VP3). (+) RNA functions either as a mRNA for translation, as a ribosome template for viral protein production, or as a template to replicate viral genomes. In viroplasms, there is viral replication and sub-particle assembly when NSP2 and NSP5 interact. The viroplasms form DLPs. Neither the outer capsid assembly process nor the assembly of DLPs and VP4 is not entirely grasped, however it is believed that DLPs are recruited to Membrane heaving cytosolic side by NSP4 [35]. A multifaceted of NSP4/VP4/DLP buds into the ER. As a result of the interaction between ER-resident VP7 and ER membrane, the final TLP is formed by the removal of the ER membrane and NSP4 [36]. Nonclassical vesicular transport or cell lysis is the method by which viruses are liberated from contaminated cells [38, 39]. As the virion enters the GIT, it would expose to trypsin-like proteases that might break down the protease-sensitive VP4 into VP5 and VP8, resulting in an infectious virion [37]. (Figure 3)

3.3. Prevalence in calves: global and regional variations

In calves, diarrhea is usually caused by the bovine rotavirus (BRoV) < 3 week of age [38]. Clinical signs are non-specific as is characteristic of NCD. Usually, pale yellow, non-bloody, there is widespread diarrhea that frequently has a lot of mucus in it. Typically, diarrhea lasts four to eight days. Fever can be present and the calves are usually dull and reluctant to drink. More than 8.0 million rural families get their income from livestock raising in developing countries like Pakistan (Economic Survey of Pakistan 2014-2015) [39]. Further, the unhygienic conditions and insufficient resources lead to food shortages for animals. In Pakistan 6% prevalence is observed in Punjab [40]. The infection's typical incidence and prevalence are 30 - 40% . Approximately 30% of rotavirus-related deaths occur in three subcontinental countries (India, Bangladesh, Pakistan) [41].

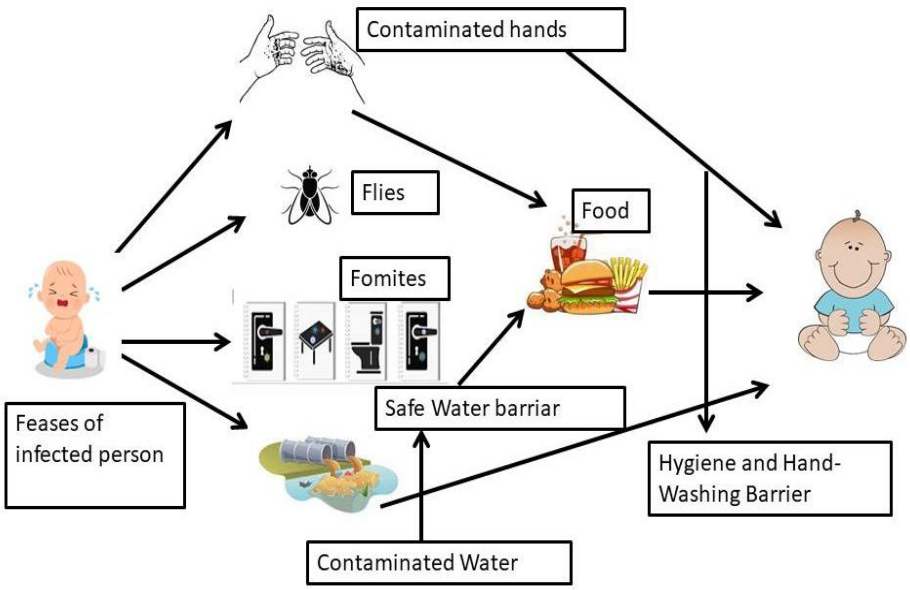

Figure 2. Transmission of Rota Virus: Pathways of Fecal-Oral Disease Transmission and Key Barriers for Prevention – How feces from an infected individual can contaminate hands, food, water, and surfaces (fomites), leading to the spread of disease to healthy individuals.

Table 1. Number of mammalian and/or avian species have been found to carry rotaviruses.

Groups of Rotavirus	Species of hosts
Group A	Various mammalian and avian species
Group B	Pigs, Sheep, Rats, Cattle, Goat and Humans
Group C	Ferrets, Juvenile, Pigs Dogs, Cattle, Goats and Humans
Group D	Turkey and Chicken
Group E	Pigs
Group F	Hens
Group G	Hens
Group H	Pigs + Humans
Reference	[42, 43]

In Pakistan, the total rate of bovine rotavirus infection is 2.6%. Rawalpindi and Okara have higher rates of infection, but Lahore only has a rate of 2% [44]. The prevalence of BRoV shedding by diarrheic calves has been reported at 7% to 80% in some studies [45]. Two case-control studies from Brazil and the USA detected BRoV in feces of 11% and 30% of diarrheic calves, respectively, compared to 0% in healthy calves [5]. However, other studies have demonstrated that BRoV can be detected in both healthy and diarrheic calves, including reports of BRoV in 2% to 12% of non-diarrheic and 7% to 30% of diarrheic fecal samples from dairy calves in Europe and Central America [46]. One study from France also reported BRoV in 49% of diarrheic and 45% of healthy beef calves. A recent study from Brazil also determined that BRoV was detected at significantly higher ($P < 0.0001$) frequency in the feces of dairy calves with diarrhea compared with the feces of non-diarrheic calves [46, 47]. Differences among studies include the age of the calves sampled, geographic location, management practices, experimental design, and assays to detect BRoV [e.g., polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and chromatographic lateral flow immunoassay] (Table 2). Additionally, most of these studies were cross-sectional in design and the health status of the control (healthy) group was not followed up to determine if calves that were shedding BRoV developed diarrhea after the time of sampling [48]. Overall, these results make it difficult to determine the clinical relevance of BRoV as a primary pathogen or a potential co-infection agent. Similarly, determination of the impact of BRoV is challenging since its role in disease is unclear[46, 49]. Mortality rates from 5% to 80% have been reported but whether mortality was attributable to BRoV is difficult to discern. As with most causes of NCD (neonatal calf diarrhea), the prognosis is good if supportive care is administered promptly. Regardless of the role of BRoV in diarrhea, this virus is predominantly found in young calves. After 3 months of age, calves are not usually susceptible to infection [46, 50].

3.4. The zoonotic potential of rotavirus

Rotaviruses exhibit a broad spectrum of host specificity, demonstrating the capability to infect a diverse array of animal species alongside the human population [51]. The identification of shared antigenic characteristics between specific animal-derived rotavirus strains and select human strains has

precipitated heightened conjecture concerning the potential involvement of animals as reservoirs for the transmission of rotavirus infections to humans [52]. An alternative perspective posits the potential cross-species infection of humans by animal rotaviruses, resulting in pathogenic manifestations whenever conducive circumstances arise. This perspective derives support from the discernment of atypical rotavirus genotypes exhibiting characteristics akin to those predominant in animal reservoirs. These distinctive human rotavirus variants could have materialized either as intact virions or through genetic reassortment events involving co-infecting human and animal strains within a singular cellular milieu [53]. The segmented architecture of the genome implies that analogous to other viruses characterized by segmented genomes, such as the influenza virus, the capacity for generating novel strains in rotaviruses is facilitated through a process termed reassortment. Reassortment transpires upon concurrent infection of a singular cell by two distinct rotaviral strains, wherein the exchange of genomic segments transpires concomitantly with replication and encapsulation events [54]. The 11 distinct genome segments inherent to the parental virus strains possess the potential to undergo reassortment in a random manner, thereby yielding a theoretical aggregate of 2048 conceivable genome constellations, as elucidated by Ramig, [55].

The rotaviruses are thought to exist as mixed populations of reassortants, and Gouvea and Brantly contend that reassortment is what gives rise to variety [56]. Diversity is dependent on the cocirculation of several different rotavirus types within a population. The most diverse strains, as well as uncommon strains, are seen in years with the most cocirculating strains [57].

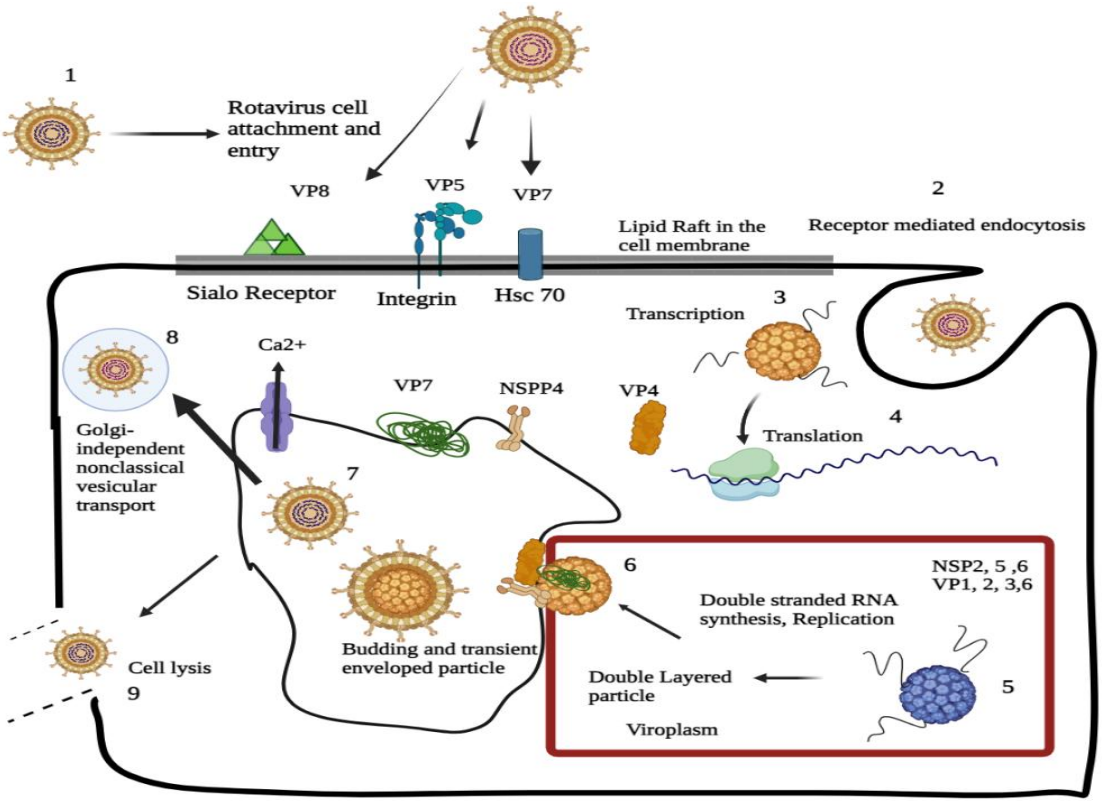

Figure 3. Replication of Rotavirus: The step-by-step process of rotavirus infection and replication within a host cell. Starting with viral attachment and entry via receptor-mediated endocytosis (1–2), the virus undergoes transcription (3) and translation (4), leading to the formation of viroplasms for RNA synthesis and replication (5–6). Newly formed viral particles bud through the endoplasmic reticulum (7), undergo non-classical Golgi-independent transport (8), and are finally released via cell lysis (9), completing the viral life cycle.

Table 2. Rotavirus prevalence in animals.

Country	Prevalence	Reference
Australia	79.9%	[45]
Spain	42.7%	[58]
England	42%	[59]
Algeria	21.84%	[60]
Tunisia	22.8%	[61]
India	15. 68%	[62]
Pakistan	2. 6%	[44]

According to Gouvea and Brandtly [56], the perpetual spread of mixed rotavirus populations in humans and animals leads to the emergence of novel and varied progeny rotaviruses [56]. Concerning the genesis of novel rotavirus strains through the process of reassortment, a notion of zoonotic genes could be formulated. Zoonotic genes are herein defined as genetic elements deriving from rotaviruses present in animal hosts, capable of engaging in molecular interactions with genes from human rotaviruses. This molecular interplay culminates in the assembly of infectious rotavirus particles, which subsequently undergo serial propagation within the human population [63]. Until recently, specific rotavirus genotypes had been closely associated with distinct animal species. For instance, human rotaviruses predominantly fell within the G types 1–4 and P types [3, 7]. Conversely, bovine rotaviruses were primarily attributed to G types 6, 8, and 10, as well as P types [64]. The demarcation of host species specificity concerning P and G types in rotaviruses has exhibited a diminishing demarcation. Notably, human group A rotavirus strains harboring genetic elements commonly encountered in rotaviruses of animal origin have been identified in afflicted pediatric populations, both in industrialized and developing nations. Noteworthy examples encompass G3 (frequently observed in species such as felines, canines, primates, swine, rodents, lagomorphs, and equines), G5 (detected in swine and equines), G6 and G8 (associated with bovine species), G9 (found in swine and ovine), and G10 (characteristic of bovine species). These strains have been isolated within the global human populace [65].

Humans and animals can be infected with groups A to C [66]. Members of There are two types of Rotavirus Group A: those defined by the glycoprotein (G) structures, such as G1 (G1, G2, G3, ..., Gn), as well as those defined by the protein cleavage (P), such as P1 (P1, P2, P3, ..., P1) genotypes [67]. The number of G genotypes in humans and animals has reached 36, while the number of P genotypes has reached 51 [68]. Animal species have also been found to exhibit G and P-type combinations found in humans. American and Canadian cattle were found to contain the G10P gene by Lucchelli et al [69]. There is a possibility that strains 26–28 of the G9 virus have been transferred from animals into humans [70].

Epidemiologically, substantive evidence substantiates the zoonotic transmission potential of rotaviruses. Human Group A rotavirus strains, harboring genetic elements conventionally encountered in rotaviruses of animal origin, have been successfully identified within afflicted pediatric populations across both developed and developing nations. Notably, strains encompassing specific G genotypes such as G3 (prevalent in diverse species including felines, canines, primates, squids, rodents, lagomorphs, and equines), G5 (originating from porcine and equine species), G6 and G8 (associated with bovine hosts), G9 (originating from porcine and ovine species), as well as G10 (originating from bovine hosts), have been conclusively isolated from the global human demographic [71].

As a result of these emerging strains, humans seem to be more susceptible to them than as a result of the common rotavirus strains [72], It may be because the emerging strains are less immune, or their genetic make-up confers greater virulence. The presence of animal viruses in humans has been demonstrated in a number of studies. Almost all of the gene segments of the rotavirus G3 strain (AU228) isolated from a child with a pet cat matched those found in the feline rotavirus strain (FRV-1. Humans may have been infected with strains similar to these [73]. A one-week-old Israeli baby infected by animal rotavirus G3 was living with a young dog (6 months old) [74]. Das et al. [75] reported that a rotavirus with VP7 and VP4 gene sequences identical to bovine rotaviruses circulated widely in India among newborn infants causing asymptomatic infection .

Certain strains of rotaviruses found in feline and canine species have been documented to traverse into human populations in the form of intact virions. Additionally, bovine rotaviruses have been implicated in a process of genetic reassortment with human rotaviruses, culminating in the emergence of atypical strains across diverse geographical regions. The phenomenon of concurrent infection with both human and animal-derived rotaviruses has been visibly noted in cases of recovery from G1P rotavirus infections [4] and G1P strains from an infant with severe diarrhea [7]. The G1P rotavirus exhibited genotypic resemblance to bovine strains [4]. Its isolation from the infant occurred in limited titers, potentially exerting a negligible influence on the child's ailment. Nonetheless, the plausible capacity for reassortment with the coexisting strain remains noteworthy [70].

4. Immunity and vaccination

4.1. Rotavirus interaction with intestinal epithelial cells

IECs are the first physical barriers against RV, because they are terminally differentiated tissues, particularly those of the ileum and jejunum [32]. IECs inhibit infections with enteric pathogens through innate immune mechanisms as well as physical barriers. In order to counteract RV infection, epithelial cells produce mucus, secrete cytokines and chemokines, and express and signal TLRs [76, 77]. In RV infection, SA, HBGA's, Hsc70's, and integrins are used as receptors and co-receptors in order to attach and enter the target cells [10, 78]. Rotavirus attaches to enterocytes when specific glycans are present, including mucin glycans and cell surface glycans (HBGAs and SAs) [79, 80]. There is no doubt that host glycan specificity is one of the key factors that regulate RV infectivity, but other factors may also influence the relative prevalence of different RV genotypes among different populations. RVs of different genotypes may recognize and bind glycans differently, exist or lack additional co-receptors or co-factors, have disparate immune responses, and other undefined host factors [81]. As RV species differ in tropism, zoonotic potential, adaptation, and epidemiological prevalence, so do their glycan recognition mechanisms. As RV species differ in tropism, zoonotic potential, adaptation, and epidemiological prevalence, so do their glycan recognition mechanisms. Changes in the HBGA phenotype of the host are unlikely to have an impact on the effectiveness of live attenuated RV vaccinations, as attenuation by cell culture adaptation reduces the genotype-specific HBGA selectivity of some RV strains [10].

4.2. Role of gut micro biome

The gut microbiome, RVs, and host epithelial cells interact threefold to maintain gut health. Multiple studies have shown that gut microbiota facilitate and prevent viral infection via a variety of methods [82]. Amongst the mechanisms which have been proposed are: (i) colonization of the intestinal epithelium that decreases the attachment of pathogens; (ii) bacterial binding to IEC receptors that prevents viral entry and attachment; and (iii) modulation of the intracellular transcription and translation processes that stimulate the host immune system [83]. In some studies, the gut microbiota has been hypothesized to influence RV infection by affecting the immunogenicity and protective efficacy of oral vaccines [65]. The role of the microbiome in regulating RV infection has not been fully explored. Intestinal mucus secretion or antiviral compound synthesis has been shown to be regulated by the enteric microbiota. Thus, commensal microbes may affect intestinal mucosal glycosylation patterns and status. In recent

years, lipopolysaccharides (LPS) have been observed to enhance the environmental stability of a variety of enteric viruses [84].

4.3. Host Responses and immune evasion strategies

In order to ensure successful replication and transmission, RVs use a number of strategies to evade the host immune system and gut microbiota. In addition to the mechanisms mentioned below, there are also several mechanisms identified and discussed here: (i) degrading IFN-regulating factors [85]; (ii) preventing the accumulation of STAT1 and STAT2 in the nucleus [86] as well as nuclear factor B [87, 88]; (iii) formation of vesicle-cloaked virus clusters [89, 90]. It is essential to understand mechanisms by which RVs evade host defense in order to develop RV genotype-specific or universal attenuated vaccines or anti-rotaviral drugs targeting RV proteins.

4.4. Degradation of IFN-regulatory factors

In addition to Developing new strategies to increase their chances of surviving and proliferation, rotaviruses have also acquired mechanisms to interrupt IFN-mediated responses [91]. As IFNs play a vital function in the elimination or reduction of RV antagonist action and the establishment of adaptive immunity that may result in an increased level of adaptive immune response post vaccination. Further, the expression of certain innate immune factors is also altered by HBGAs and other cell surface glycans, which in turn regulate RV infection [92].

In order to successfully replicate and avoid elimination, Rotavirus uses NSP1 protein to interfere with the host's IFN response. Combined degradation of IRF3 and IRF7 is demonstrated by Barro and Patton to disrupt IFN signaling via RV's NSP1 [93]. Dendritic cells and macrophages express IRF7, which facilitates RV's movement across the intestinal barrier. Apoptosis is also regulated by NSP1 along with IRF3 and IRF7 during viral infection by triggering the degradation of IRF5. As a result, NSP1 is a broad-spectrum antagonist of IRF activity. Interestingly, NSP1s from animal RVs degrade IRF3, IRF5, and IRF7, while NSP1s from human RVs primarily degrade IRF5 and IRF7, thus inhibiting IFN responses less effectively than NSP1s from animal RVs [94]. NSP1 may degrade IRF by downregulating the transcription of genes that produce proinflammatory cytokines that stimulate apoptosis by inhibiting the expression of IRF. The NSP1 may inhibit the expression of IRF by downregulating genes that produce proinflammatory cytokines that stimulate apoptosis. Thus, RV can persist in infected cells for longer periods of time because NSP1 inhibits apoptosis. NSP1 is therefore a key factor determining RV virulence, based on its effects on innate immunity and virus spread [93, 95].

NF-κB is required for the secretion of antiviral chemokines and IFNs [87]. NF-κB is also involved in inhibiting apoptosis and mediating proliferation of epithelial cells, which encourages viral replication since apoptosis is an essential host defense strategy for eradicating infected cells [96, 97]. A key viral immune evasion strategy of RVs is activating NF-B so that they can prevent cells from undergoing apoptosis. In order to prevent viral clearance, RVs temporarily inhibit NF-B activation in the initial stages of infection with the intention of delay the initiate of the innate immune response [86]. A Multi-subunit ubiquitination complex essential for NSP1 degradation had been demonstrated in earlier studies [98]. A further study is needed to determine exactly how NSP1 subverts the host's IFN response by using this complex to prevent other cellular activities.

1.1. Current vaccination strategies

Vaccination strategies against Rota virus in claves are as follow: Vaccines known as "Modified Live" (MLVs): These shots include rotavirus strains that have been attenuated. When given to calves, they multiply within the calf's body and activate a strong immune system. MLVs frequently offer quick and durable immunity [99].

Vaccines against killed viruses: These al shots include rotavirus inactivated versions. Although they are not able to multiply in the body like MLVs, they can nevertheless elicit an immunological response, but usually not to the same extent or duration. In circumstances when MLVs would not be appropriate, such as in pregnant cows, killed virus vaccinations are frequently utilized [100].

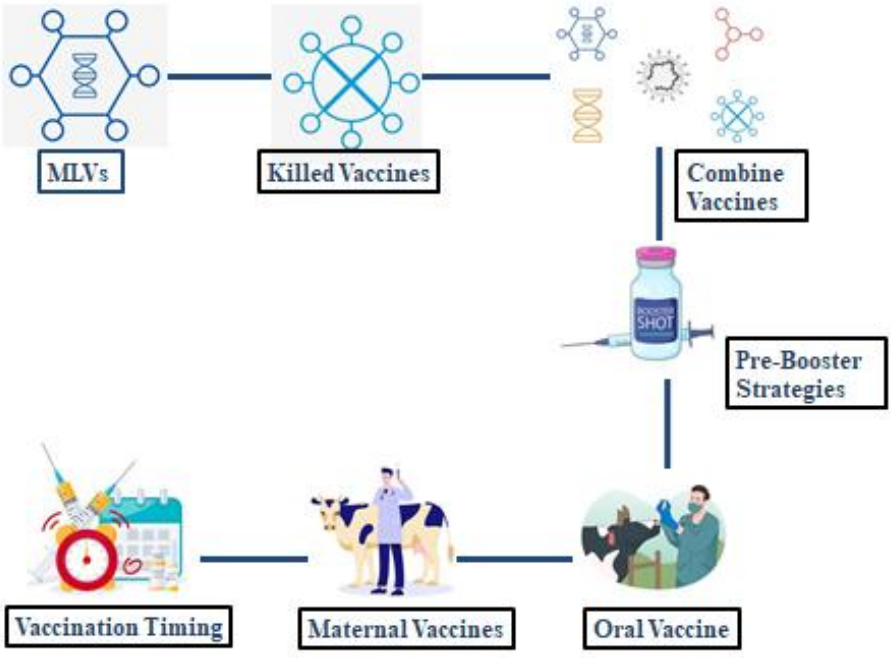

Figure 4. Strategies of Vaccination In Calves (1) Modified live Vaccines (MLVs) (2) Killed Vaccines (3) Combined Vaccines (4) Pre-Booster Dose (5) oral Vaccines (6) Maternal Vaccines (7) Vaccination timing.

Combination vaccinations: In order to offer broader protection against numerous illnesses in a single dose, certain vaccines contain antigens from various infections, including rotavirus. This can make immunization regimens simpler and require fewer shots overall.

Oral vaccinations: A few rotavirus vaccinations are given orally, either as a liquid or as freeze-dried pellets that have been lyophilized and then reconstituted with water. By imitating natural infection pathways, oral vaccinations may strengthen the immune response in the gastrointestinal tract.

Prime-Boost Strategies: To improve and extend immunity, calves may occasionally receive a first vaccination followed by one or more booster shots. This technique is known as the "prime-boost" approach.

Maternal vaccination: Immunization against rotavirus can be induced in pregnant cows. These antibodies are then delivered on to the calf over colostrum. This gives the calf passive immunity in the crucial first few weeks of life, when it is most vulnerable to illness.

Time of vaccination: A vaccine's efficacy is greatly influenced by when it is administered. Usually given at several weeks of age, calves receive their first vaccinations. Depending on the particular vaccine utilized and the frequency of the illness in the region, booster shots may be given as needed [101] (Figure 4).

4.5. Prevention and management

There is a high level of infectiousness and the rotavirus is comparatively resilient to being inactivated via chemical disinfectants as well as antiseptics. As a result of its widespread distribution, the tendency for the virus to persist in different climate conditions, and the high levels of shedding in infected animals' feces, Rotavirus infection can be difficult in Prevention and Control. Routine vaccination is the most effective method of reducing rotavirus infections. Vaccination protocols for rotavirus disease prevention differ from those for infants and children [26].

The prevention of NCD can be achieved by providing proper cow nutrition during pregnancy, managing dystocia, reducing environmental stresses and contamination, and transmitting passive immunity via colostrum [1]. When the calf is most

susceptible to NCD, ensure specific antibodies are present in the gut lumen and increase the calf's systemic uptake of antibodies to strengthen his or her immunity. Furthermore, vaccination of the cow affects the quality of the colostrum as well [102]. The main pathogens causing calf diarrhea can be vaccinated against with commercial vaccines that can be administered either to the dam or the calf. RVA diarrhea can be decreased by following a number of general recommendations. In addition to good hygiene and sanitation methods, these include pathogen-specific interventions, such as vaccination prophylaxis [45]. Antibodies against specific pathogens are increased in colostrum following vaccination of cows. Many reports state that pregnant cow vaccination programs are an effective strategy to prevent RVA diarrhea in cows

5. Conclusion

Rotavirus-induced diarrheal illness is a serious health concern for calves since it disrupts growth benefits through decreased weight gain and higher mortality, and having the potential to spread zoonotic infections. The significance of vaccination programs in lowering the frequency and severity of rotavirus infections in young calves is still being emphasized by research. Even if vaccines have proven successful against common strains, nonstop surveillance is essential to observe out for the appearance of novel variations and guarantee the sustained efficiency of vaccinations. Furthermore, improvements in diagnostic methods have made it easier to identify and describe the rotavirus strains that are circulating in calf herds, which help with focused control efforts. With advancements, issues like vaccination delivery and the possible influence of environmental variables on the spread of rotavirus still need to be looked at. Overall, controlling rotavirus infections in calves and reducing their negative effects on the health and economy of livestock production need a multimodal strategy that includes vaccination, surveillance, and research initiatives.

Data availability statement

The data supporting the results of this study can be obtained from the corresponding author upon request.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Ethical approval

Not applicable (N/A)

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Authors Contribution

Conceptualization, A.F, O.N and F.S.; methodology, A.F and A.S.; software, S.T and O.N.; formal analysis, U.I, A.F and S.K.; writing—original draft preparation, T.R. and U.Z.; writing—review and editing, A.F and A.S. All authors have read and agreed to the published version of the manuscript

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