Combatting infectious diarrhea: innovations in treatment and vaccination strategies

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REVIEW

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Combatting infectious diarrhea: innovations in treatment and vaccination strategies

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ABSTRACT

Introduction: The escalating prevalence of infectious diseases is an important cause of concern in society. Particularly in several developing countries, infectious diarrhea poses a major problem, with a high fatality rate, especially among young children. The condition is divided into four classes, namely, acute diarrhea, invasive diarrhea, acute bloody diarrhea, and chronic diarrhea. Various pathogenic agents, such as bacteria, viruses, protozoans, and helminths, contribute to the onset of this condition.
Areas covered: The review discusses the scenario of infectious diarrhea, the prevalent types, as well as approaches to management including preventive, therapeutic, and vaccination strategies. The vaccination techniques are extensively discussed including the available vaccines, their advantages as well as limitations.
Expert opinion: There are several approaches available to develop new-improved vaccines. In addition, route of immunization is important and aerosols/nasal sprays, oral route, skin patches, powders, and liquid jets to minimize needles can be used. Plant-based vaccines, such as rice, might save packing and refrigeration costs by being long-lasting, non-refrigerable, and immunogenic. Future research should utilize predetermined PCR testing intervals and symptom monitoring to identify persistent pathogens after therapy and symptom remission.

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Infectious diarrhea; invasive; vaccination; vaccine; therapeutic approaches; enteric pathogens; cholera toxin

1. Introduction

Infectious diarrhea is characterized by three or more episodes of loose or watery stools in a 24-hour period. Diarrhea is caused by enteric infections, which are a major cause of mortality and morbidity worldwide, particularly among young children [1]. Diarrhoeal sickness accounts for 1–1.5% of all emergency department visits in the United States, leading to 1.8 million hospitalizations and 3,100 fatalities per year [2]. Most affected individuals reside in underdeveloped and developing countries. Fatalities from infectious diarrhea surpass those from gastrointestinal malignancies, peptic ulcers, or inflammatory bowel disease [3]. Approximately 1.8 billion instances of severe diarrhea occur globally every year among children, which are caused by pathogenic agents [4]. Most pathogens causing diarrhea primarily spread through the fecal-oral route. However, each pathogen has a distinct method of infection and varied ways of inducing clinical manifestations of diarrhea [5].

Infectious diarrhea exhibits signs and symptoms such as fever, bloody, mucous or watery stools, sepsis manifestations or dehydration [6,7], vomiting, abdominal discomfort, and other disorders. These signs and clinical symptoms are considered to be the primary indicator, which can lead to diarrhea and, if not treated promptly, it can lead to hypoglycemia, convulsions, and death [8]. The etiology of infectious diarrhea differs markedly between countries with varying economic and hygienic statuses [9]. Infectious diarrhea has been associated with a broad range of distinct pathogens [10]. The rotavirus, *Salmonella* sp., Shiga toxin-producing *E. coli*, enterotoxigenic *E. coli*, *V. cholerae* 01, enteroaggregative *E. coli* [9], *V. cholerae* 0139, *Shigella, Listeria monocytogenes, Vibrio parahaemolyticus*, and other non-cholera vibrio are important pathogens responsible for infectious diarrhea in children in underdeveloped nations [11]. In patients with compromised immune systems, infectious diarrhea is caused by enteropathogenic *E. coli, Campylobacter jejuni*, enteroroadherent *E. coli*, and *Cryptosporidium* species. *Entamoeba histolytica, Cryptosporidium parvum*, and *Giardia lamblia* are a few of the parasites that can also cause infectious diarrhea [10]. Herein, we outline the current understanding of the pathogenesis of infectious diarrhea-causing organisms. The clinical symptoms, diagnostic procedures, treatment, and management of these vital pathogens are all shaped by their fundamental pathogenic mechanisms.

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Article highlights

- Infectious diarrhea accounts for approximately 1.8 billion cases every year among children, which is caused by pathogenic, bacteria, viruses, protozoans, and helminths.
- There are four types of infectious diarrhea, acute diarrhea, acute bloody diarrhea, invasive diarrhea, and chronic diarrhea.
- Chronic diarrhea is identified as the most prevalent health concern.
- The pathogenesis mechanism varies with the pathogen's nature. Enteric pathogens disrupt tight junctions, affecting ion transport and barrier function. Inflammation, neuropeptides, or absorptive surface depletion may also contribute.
- Diarrhea management in hospitals lacks consistency. Key strategies involve rehydration, electrolyte replacement, probiotics, diarrhea management algorithms, anti-diarrheal medications and.
- Rotarix® and RotaTeq®, two approved rotavirus vaccines, have been in use since 2006 and have significantly decreased the rate of rotavirus infections.

2. Types of infectious diarrhoea and mechanism of pathogenesis

2.1. Types of infectious diarrhoea

Infectious diarrhea is categorized into acute diarrhea, acute bloody diarrhea, and chronic diarrhea (Figure 1).

2.1.1. Acute diarrhoea

The term 'acute diarrhoea' refers to the increase in water content, volume, or frequency in the stool that lasts shorter than 14 days. Acute diarrhea is frequently caused by contaminated food and water sources and contributes significantly to morbidity and mortality [12]. A stool with an increase in water content [13] and passing more than three loose or watery stools in 24 hours are signs of acute diarrhea in infants and children [14]. Moreover, microbial species such as *Aeromonas, Campylobacter sp., E. coli, Salmonella*, and *Non-typhoidal S. enteric* are the common cause of diarrhea with symptoms like fever, nausea, abdominal pain, bloody stool, and cramps [15]. Furthermore, azithromycin, ciprofloxacin, doxycycline, and metronidazole are the most prescribed drugs which can be used for treating acute diarrhea infections.

The ileocecal valve of colon receives 8 liters of fluid but absorbs 93% of fluid resulting in remaining 600 mL, which is further reduced to 100 mL that is excreted as fecal matter. The absorption of water is regulated by the coupled systems comprising of Na/H cationic exchanger and Cl/HCO_3 anionic exchanger. In case of acute infectious diarrhea, the mechanism of electrogenic sodium absorption becomes impaired. The co-transport of sodium takes place which involves absorption of sodium in synergy with absorption of peptides, amino acids and glucose. Therefore, acute diarrhea requires administration of oral rehydration [15]. The infection is categorized by the presence of polymorphonucleocytes (neutrophils, eosinophils, basophils, mast cells) in the feces. Polymorphonucleocytes modulate absorption of fluid via secretion of cytokines as well as precursor of adenosine that causes activation of Cystic Fibrosis Transmembrane conductance Regulator (CFTR) [16].

Rotavirus, norovirus, adenovirus, and astrovirus are the primary causes of severe diarrhea in infants and young children globally [17]. Rotavirus is the primary factor behind acute diarrhea and the need for hospitalization. It is a significant factor contributing to disease and death on a global scale in children under the age of 5. Rotavirus is the predominant strain responsible for > 90% of all human infections. In a study in patients with acute diarrhea 68.8% tested positive for rotavirus of which 61.1% were males. Among them, 27.6% were less than 12 months old, 41.2% were 12–24 months, 19.4% were 24–36 months old, and 5.9% were 36–48 months and 48–60 months old [18].

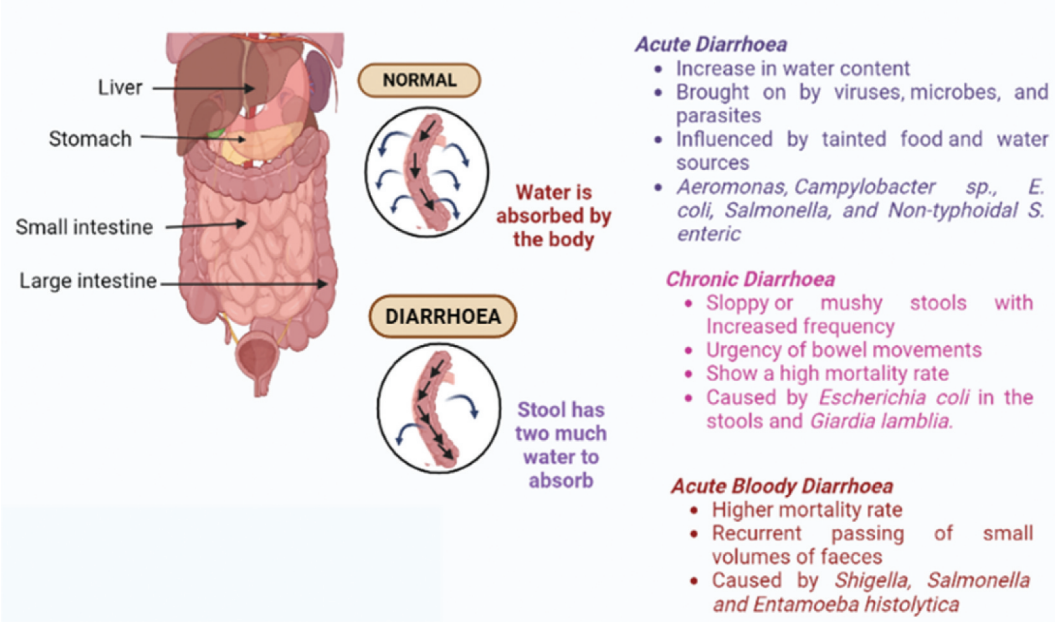

Figure 1. Types of infectious diarrhoea. The causative organisms of each type of infectious diarrhoea is described along with symptoms and complications. The categorization of the types of infectious diarrhoea is based on the pathogenesis, symptoms, and duration of the infection (Figure created by biorender.com).

2.1.2. Chronic diarrhoea

Chronic diarrhea is a prevalent health problem that affects a significant portion of the population. It is defined as the passing of sloppy or mushy stools with increased frequency, the urgency of bowel movements, or incontinence [19]. Abdominal pain, presence of bloody or bloodless diarrhea, and discharge of white blood cells in the feces are all signs and clinical symptoms of chronic diarrhea [15]. Chronic diarrhea typically leads to nutritional and metabolic consequences, such as stunted growth, and is more challenging to manage compared to acute diarrhea. Patients with chronic diarrhea exhibit high death rates. As such, it is imperative for physicians to adhere to the criteria pertaining to the management of sepsis, dehydration, fever, hypoglycemia, and malnutrition when treating patients. This entails consuming a nutritious and well-balanced diet that is devoid of allergenic proteins, as well as supplementing with additional minerals and vitamins. In addition, chronic diarrhea has been linked to the presence of aggregative, enterotoxigenic *E. coli* and *Giardia lamblia* in stools, although the precise underlying factors remain unidentified [20].

The coupled transporters in the colon, that are responsible for the absorption of fluid, are also known as solute carrier 9 (SLC9) belonging to sodium-hydrogen exchanger family and anion exchanger belonging to the family of SLC26. It is suggestive that a single nucleotide polymorphism in the gene SLC9A3 downregulates the activity of the intestinal transporters resulting in increased susceptibility to chronic diarrhea. Studies have reported that downregulation of Epithelial Sodium Channel in the case of microscopic colitis can lead to chronic watery diarrhea [21].

2.1.3. Acute bloody diarrhoea

Acute bloody diarrhea is a medical emergency as it can be life-threatening and requires immediate attention in the community in order to control epidemics. It usually lasts longer, has a higher mortality rate, and is more likely to have an adverse effect on the growth of children. The most typical sign of bloody diarrhea is the recurrent passing of small volumes of feces. Children aged 4 to 6 years are frequently infected with *Shigella* and *Salmonella* [22]. Further, *Entamoeba histolytica* was the main contributing factor for causing acute bloody diarrhea, especially in the age group of 1–3 years old. However, many substantial risk factors, including a contaminated environment, unclean living circumstances, incorrect handling of human waste, poor personal hygiene, lousy food preservation, and using non-filtered water for home use, contribute to the occurrence of bloody diarrhea [23]. Therefore, it is critical to rule out infection in all individuals who are presented with bloody diarrhea. The method by which enteric infections are detected have improved over the last few years, in light of advancements in the field of molecular diagnostics and the accessibility of commercial assays based on Nucleic Acid Amplification Techniques [24]. Unfortunately, advanced techniques are not available in developing nations. Still, macroscopic blood is the most important identifying factor in the diagnosis of bloody diarrhea. As a result, the WHO has not emphasized investigations into bloody diarrhea, particularly in children. In addition, pathogens such as *enteroinvasive E. coli, Campylobacter species, enterohemorrhagic E. coli, Shigella species, Salmonella species*, and *Entamoeba histolytica* can cause invasive diarrhea [11] and results from a pathogen's propensity to infect the distal small intestine and colon mucosa. The causative *Shigella species* produce the cytotoxin Shiga which causes hemolytic uremic syndrome. It can also result in sepsis, intestinal perforation, rectal prolapse, electrolyte imbalance, toxic megacolon, arthralgia, leukaemoid reactions and seizures. On entry into the host body, the bacteria multiply and invade colonic epithelium secreting pro-inflammatory cytokines. Consequently, this causes inflammatory reactions by accumulating polymorphonucleocytes cells, damaging the epithelial cells lining the gut mucosa [25].

2.2. Mechanism of pathogenesis

Diarrhea is merely a changed osmotic gradient-driven movement of ions and water. Normally, the intestine is exposed to 8–9 liters of fluids in a day out of which 100–200 mL is excreted. However, infection by enteric pathogens leads to diarrhea by increasing the volume of the secreted fluid. This affects the transporters involved in the movement of water such as the sodium-dependent glucose transporter, sodium-hydrogen exchanger isoform 3, and chloride-bicarbonate exchanger [16].

The mechanism of pathogenesis is dependent on the type of the causative organism (Figure 2). The enteric pathogens are capable of regulating the transportation of ions across the intestinal epithelium in addition to barrier function by disrupting tight junctions [16,26]. Additionally, the pathogenesis can also be facilitated by inflammation, neuropeptides or depletion of absorptive surfaces [16]. Studies reveal that cytotoxin-producing organisms cause the infection by anchoring on the mucosal layer leading to the activation of cytokine synthesis that further stimulates the mucosal layer of the intestine to secrete inflammatory mediators. In the case of invasive organisms, the synthesis of cytokine and inflammatory mediators is induced by the invasion of the intestinal mucosal layer [27]. Bacterial enteropathogens contribute to the majority of incidences of infectious diarrhea. In fact, pathogenesis of *C. difficile* related diarrhea is modulated by neuropeptides and inflammatory mediators. Whereas enteropathogenic *E. coli* pathogenesis is caused by the loss of microvilli which leads to a decrease in nutrient absorption. On the other hand, *V. cholerae* results in secretory diarrhea [16] and bacterial pathogens like *Salmonella spp.*, *Shigella spp.*, and *Campylobacter jejuni* lead to invasive and inflammatory diarrhea [16,27].

In the case of *V. cholerae*, the most prominent toxin produced is the cholera toxin which comprises two subunits-A and B, where A is a GTPase attached to B which facilitates its entry into the cell. The cholera toxin influences the cAMP-mediated activation of a chloride channel called the cystic fibrosis transmembrane conductance regulator. The toxin can follow another route of pathogenesis by activation of the calcium-activated chloride channel by altering the concentration of calcium ions. Furthermore, in the event of direct

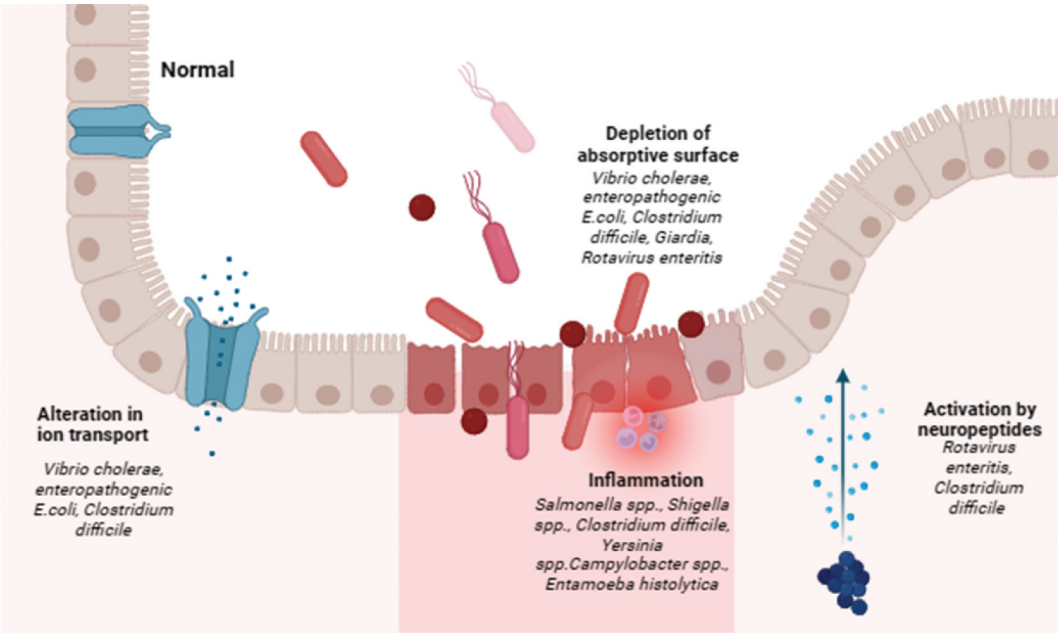

Figure 2. Mode of the pathogenesis of infectious diarrhoea and the corresponding enteropathogens (created using Biorender.com).

transportation of ions and molecules, the cholera toxin affects the activity of aquaporins, consecutively resulting in lower rates of fluid absorption. In the case of infections by *C. difficile* and rotavirus, in addition to the cytokine release and enteric nerve activation by neuropeptides, the subsequent regulation of ion transport likewise plays an essential part. On the other hand, Giardia causes the infection by depleting the brush border absorptive surface and reduction in the size of the villi [16].

The enteric pathogen, *Entamoeba histolytica* also causes invasive infectious diarrhea. It releases motile trophozoites which consecutively form cysts. The trophozoites anchor on the epithelium of the large intestine and results in its lysis. The target of galactose and N-acetyl-D-galactosamine on mucins mediates the anchorage of the pathogen to the colon [28].

Rotavirus is the primary cause of gastroenteritis in infants and is accountable for almost 20% of deaths related to diarrhea in children under the age of 5. The mechanism of Ca^{2+}-dependent endocytosis is the most favorable mode of entrance. It is characterized by the infectious rotavirus being taken up into the cytoplasm when the concentration of Ca^{2+} is very low. This causes a flow of Ca^{2+} from the vesicles into the cytoplasm. Other research has suggested that rotavirus specifically targets and infects the fully developed enterocytes in the small intestine's middle and upper regions of the villi. This infection ultimately results in the occurrence of diarrhea [29].

3. Diagnostic approaches

Despite the advancements that have been achieved in the diagnosis of infectious diarrhea, in low- and middle-income countries traditional macroscopic inspection of stool samples is still used [30]. This dependence on conventional techniques results from a number of interlinked reinforcing factors that define the healthcare environment in low- and middle-income countries. The primary reasons for this are infrastructure challenges, limited access to advanced diagnostic tools in urban areas, financial constraints, and the upkeep of sophisticated equipment. Recognising these challenges underscores the importance of tailored approaches that find a balance between the practical limitations faced by healthcare facilities in low- and middle-income countries and advancements in technology. Hence, early detection is crucial for its treatment. Methods for diagnosis include culture, microscopy, and antigen-based tests. It is challenging to culture enteropathogens, especially with antibiotics. Microscopy of parasites is inexpensive but insensitive and requires time, equipment, and training.

The predominant diagnostic method for infectious diarrhea currently revolves around the widely employed microscopic analysis of stool samples. While this technique is valuable, it may not adequately address availability issues. In many healthcare settings, especially those in remote or resource-constrained areas, advanced diagnostic tools such as PCR and molecular diagnostics may not always be readily accessible [31]. As such, the variety of diagnostic methods are limited, making prompt and precise diagnosis increasingly challenging. Diarrhoeal diagnoses have been improved by antigen-based testing; however, their properties vary and commercial assays are not available for all significant infections [32]. It is important that user-friendly, affordable, and widely accessible diagnostic technologies be developed in order to identify infectious diarrhea in any healthcare setting [33]. Table 1 summarizes some of the diagnostic approaches used.

4. Treatment approaches

Despite improvements in public health and economic wealth in the developed world, the incidence of intestinal infection remains high and remains a significant clinical problem [49]. Diarrhea management is still inconsistent in hospitals and in

Table 1. Diagnostic approaches for infectious diarrhoea.

Diagnostic Technique	Advantages	Disadvantages	Comments	Ref
Antigen-Based Diagnostics	• No special knowledge is necessary. • Simple to execute. • Fast.	• Not accessible for all enteropathogens. • Low sensitivity at times. • Compared to PCR gold standard this method is not very sensitive	• Improves the condition of patients suffering from viral and protozoal diseases. • In rotavirus vaccine clinical research, case determination was usually done using enzyme immunoassay (EIA)-based detection.	[32,34–37]
Serological Diagnostics and Biomarkers	• Conveniently accessible in laboratories. • High agreement is shown by statistics from the literature.	• Limited diagnostic sensitivity (only 50% of cases are positive).	• Assays for agglutination of *Vibrio cholerae*, *Salmonella* spp., *Campylobacter* spp., *Shigella* spp., and *Clostridium difficile*	[32,38]
Culture-Based Diagnostics	• Inexpensive and simple to execute. • Bacterial isolation and identification. • Evaluate susceptibility of isolated pathogens.	• Reaction time (1 to 2 days) • Limited sensitivity (esp. if the sample was collected after the antibiotic therapy began) • It might be difficult to distinguish between colonization and infection.	• Taking the example of *Campylobacter* spp. which is difficult to isolate when there is a normal stool flora present, hence selective approaches are often used.	[32,37]
Mass Spectrometry-Based Diagnostics	• Rapid • Precise • Affordable compared to molecular and immunological-based detection techniques. • No need for trained laboratory workers.	• The MALDI-TOF equipment's high upfront costs.	Falls under two categories: 1. Direct matrix-assisted laser desorption ionization time-of-flight mass spectrometry-Enables quick pathogen detection straight from colonies. 2. PCR-electrospray ionization mass spectrometry-Determines the nucleic acid content of several PCR-amplified, widely conserved sections of bacterial, viral, or fungal genomes.	[39,40]
Molecular Diagnostics	• The sample need not be cultured. • Specific, quick, and precise. • Contamination risk is reduced with a closed-tube system. • Can identify several diseases.	• Require very accurate thermal cycler. • Requires qualified laboratory workers.	• FDA authorized the first PCR-based multiplex panel for gastroenteritis aetiologies, which can identify *Campylobacter*, C. *difficile*, *E. coli* 0157, enterotoxigenic *E. coli*, *Salmonella*, *Shigella*, STEC, norovirus, rotavirus, *Cryptosporidium*, and *Giardia*.	[39]
Multiplex and Arrayed Singleplex PCR	• Rapid turnaround (1–6 hours). • Very sensitive and specific. • Some platforms provide quantification, which is crucial for separating infection from colonization and for follow-up. • Enables early, low-bacterial-load illness detection. • Pre-treatment with antibiotics has less of an impact than traditional culture. • Discovery of a few resistance indicators.	• The primary current issue is cost. • Some microbes that may not be clinically significant may be excreted in feces for many weeks. • Finding asymptomatic carriers. • They often do not provide epidemiological information or antimicrobial susceptibility data. • Not discriminate between microorganisms in viability and those that are not.	• By avoiding competition for the restricted nucleic acid substrate, arrayed single plex PCR may give better sensitivity and quantitation and is not limited by the range of fluorescent dyes employed in a multiplex method for differential detection. • Discrimination requires target-specific probes, gel analysis to assess DNA amplicon size or make-up, or amplicon melting characteristics.	[32,37,41–43]
Quantitative PCR	• Provides better sensitivity and a larger dynamic range. • During PCR's exponential phase, gene (or transcript) counts are quantified. • Accustomed workflow. • In most laboratories, capital equipment is already in place.	• Each target needs priming. • If there is a shortage of RNA, it is wasteful as well. • Recognizes only known sequences. • Almost no discovery ability. • Limited scalability.	• Molecular techniques may identify low levels of enteropathogens of unknown clinical importance, especially in impoverished nations where *Giardia, E. coli, Campylobacter*, and numerous viruses are common. • Real-time PCR uses fluorescence probes to measure nucleic acid synthesis. Mechanistic models that minimize baseline adjustment errors, changing reaction efficiencies, and low beginning template concentrations may enhance quantitation are recently being developed.	[32,44]

(*Continued*)

Table 1. (Continued).

Diagnostic Technique	Advantages	Disadvantages	Comments	Ref
Next-Generation Sequencing	• Increased capacity to spot unique variations (discovery power). • Greater sensitivity to quantify uncommon transcripts and variations. • Increased sample output. • Cheaper than qPCR.	• Low goal numbers make sequencing less economical (1–20 targets). • Sequencing a few targets takes a lot of time (1–20 targets). • Data analysis requires the use of sophisticated software and computers.	• Although substantial archives of clinical feces from multisite studies of diarrhoea now exist, providing a good chance to further investigate this, these results have yet to be verified in properly phenotyped diarrhoeal patients and controls. • Specific diarrhoeal infections may alter normal flora's makeup and diversity. Changing Bacteroides species makeup may identify rotavirus-infected people from healthy controls.	[32,45]
DNA Hybridization Assays	• Determining the cause of an outbreak of infectious diarrhoea quickly.	• Pairwise cross-hybridizations are tedious. • The prerequisite for using isotopes. • The difficulty of creating a centralized database.	• Hybridization assays contain labelled nucleic acid probes to identify DNA and RNA molecules. • The presence of: *Campylobacter* spp., *Salmonella* spp., Producing toxins, Parasitic plasmid (*Shigella* spp.). • Inherent characteristic (*Escherichia coli*)	[38,46]
Faecal Leukocyte Examination (FLT)	• Detecting rotavirus. • Examine bacteria. • Identifying invasive (*Salmonella* or *Shigella*) versus toxin-producing bacteria (*Escherichia coli* or *Vibrio cholera*).	• Faecal leukocyte/lactoferrin assay predicts *C. difficile* toxin positive poorly. • Long-term hospital patients shouldn't have this test. Faecal leukocyte/lactoferrin testing in this patient group yields false results, according to many studies. • Breast milk is rich in lactoferrin, and breastfed neonates have positive faecal lactoferrin. If a breastfed infant develops intestinal irritation, inspect feces for leukocytes.	• Faecal leukocytes test often useful to screen infectious diarrhoea. • Fecal leukocytes are present in diarrhoea patients with widespread colonic inflammation but absent in non-inflammatory instance • They are common in bacterial diarrhoea. • Fresh faeces (ideally mucus) are combined with dilute Loeffler's methylene blue and inspected microscopically.	[38,47]
Metagenomic assay	• Random pathogen detection. • Reduces turnaround. • Gives thorough details regarding pathogens.	• Time-consuming data collecting and analysis. • Required lab staff.	• Metagenomic procedures, including sample storage, DNA extraction, library preparation, and shotgun sequencing, affect data output. Extracting the full metagenome with little bias is a problem. • Faecal samples include several assay inhibitors and commensals. Several research has revealed protocols for sample preservation, such as freezing, affect the bacterial makeup of extracted DNA and how DNA extraction tools vary in DNA yield and bacterial community composition.	[39,48]

intensive care units. Rehydration, electrolyte replacement, probiotics, diarrhea management algorithms, and anti-diarrheal medications are all used to treat diarrhea. However, early detection of dehydration is the most important aspect of diarrhea management. Oral rehydration therapy, which restores water and electrolytes, is also an important part of diarrhea management. Rehydration fluids containing sodium chloride, potassium chloride, trisodium citrate, glucose, and water can be administered. In pediatrics, combining zinc with oral rehydration solution reduces the severity of acute diarrhea episodes, decreases diarrhea recurrence and fluid secretion in the intestine, strengthens immune responses, and aids in the regeneration of intestinal epithelial cells. Food items like bananas, toast, and rice benefit the patients. Furthermore, because anti-diarrheal drugs absorb water, cause swelling, increase consistency, and decrease the frequency of stools, they are useful in the short-term treatment of secretory diarrhea. Anti-microbial therapy and anti-motility drugs (opioid drugs, such as loperamide, provide symptomatic relief for diarrhea) can also be used. Racecadotril, crofelemer, and zaldaride are antisecretory agents that are available in several countries and may play a role in disease management.

With the introduction of new medications and streamlined treatment protocols, the function of antimicrobial agents in the treatment of infectious diarrhea is becoming more streamlined. Popular in patients with diarrhea, probiotics containing *Lactobacillus* species, *Bifidobacterium*, and *Streptococcus* faecalis in adequate amounts have been shown to restore healthy gut flora and prevent the colonization of pathogenic bacteria; however, they are not accepted as components of standard diarrheal therapy because they can cause systemic infections, acidosis, and excessive immune stimulation in immunocompromised patients. In addition, WHO collaborates with other partners to promote national policies and investments that support case management of diarrhea and its complications, as well as increasing access to safe potable water and sanitation in developing nations. Additionally, it conducts research to develop and evaluate new diarrhea prevention and control strategies in this region and builds capacity for implementing preventive interventions such as source water improvements, household water treatment, and safe sanitation [50]. The approaches prevalent for different types of infectious diarrhea are summarized in Table 2. In the last few decades, strategies to prevent diarrhea have relied on several potentially strong therapies that have been applied concurrently [53]. The four primary methods for treating infectious diarrhea are as follows:

- Replenishment of electrolytes and fluids during supportive treatment.
- Symptomatic anti-diarrheal therapy- to minimize stool recurrence as well as other sensations such as abdominal discomfort. Some important nonspecific anti-diarrheal agents (Figure 3).
- Anti-secretory medication treatment – intended to reduce fecal losses.
- To limit the length and severity of the sickness, specialized treatment such as antibiotic therapy has been used.

4.1. Probiotic therapy

The effectiveness of probiotics in treating acute infectious diarrhea has been evaluated in several randomized clinical trials. The administration of probiotics was not attributed to any adverse repercussions. In almost all clinical trial studies, subjects who received probiotics therapy had shorter occurrences of diarrhea and lower stool frequency. Generally, the administration of probiotics decreased the likelihood that diarrhea would persist for four or more days by 59%, the period lasted by 25 hours, and the number of diarrheal stools passed on day 2 following the intervention by around one [54]. In a meta-analysis study however, a few elevated odds of negative consequences were shown, such as, abdominal pain or discomfort, nausea, lack of appetite, headaches, and flu-like signs [55].

4.2. Oral rehydration by supplementing with oral rehydration solutions

The fundamental step in treating diarrhea is to adequately manage dehydration, which is the leading cause of mortality in patients with severe diarrhea. An oral rehydration solution with glucose and electrolytes, developed in the 1960s and 1970s has been shown to be a simple, affordable alternative solution, to prevent and manage dehydration caused by diarrhea [56]. By replenishing the body's electrolytes and lost fluid, oral rehydration therapy helps to treat diarrhea by retaining fluid in the body and providing energy [8]. Oral rehydration solutions that are hypotonic are highly advised for the treatment of mild to severe dehydration. With a blend of an alkali-containing dextrose sodium solution, intravenous rehydration is provided to those with extreme dehydration. For young children suffering from extreme dehydration who are unable to receive oral rehydration solution intravenously, nasogastric feeding tubes are utilized as rehydration methods [57].

Table 2. Treatment strategies for different types of infectious diarrhea.

Infectious Diarrhoea	Treatment approaches	References
Acute diarrhea	• Rehydration therapy • Antibiotic regime (fluoroquinolones, azithromycin, ciprofloxacin) • Symptomatic treatment	[15]
Chronic diarrhea	• Rehydration therapy • Administration of loperamide, cholestyramine, clonidine or tricyclic antidepressants	[51]
Acute bloody diarrhea	• Rehydration therapy • Antibiotic regime of ciprofloxacin, co-trimoxazole, ampicillin, azithromycin, pivmecillinam or ceftriaxone • Administration of metronidazole for amoeboid infection	[52]

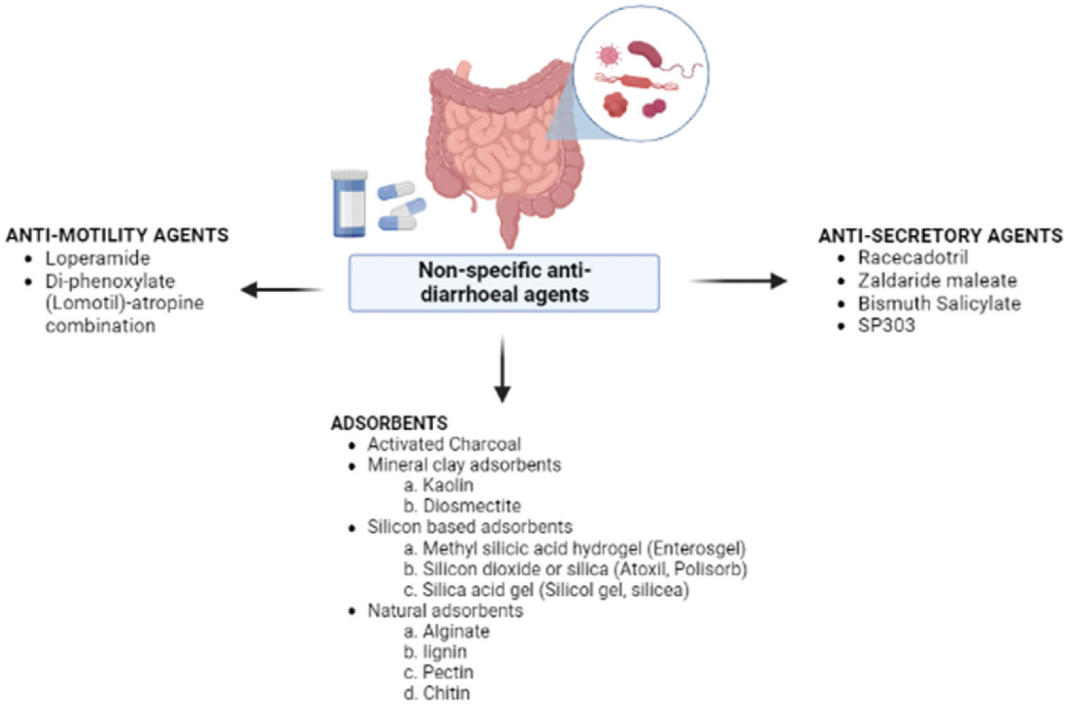

Figure 3. Non-specific anti-diarrhoeal agents (*Figure created by BioRender.com*).

For treating cholera in adults and children, rice-based oral rehydration salt solution is superior to regular oral rehydration solutions, and can be used anywhere it is practical to prepare [53].

- Young children with recurrent diarrhea are recommended to take daily supplements of multivitamins and minerals, including magnesium.
- Probiotics are considered safe and efficient, according to several meta-analyses of controlled clinical trials [53]. Studies on gastroenteritis caused by viruses provide more persuasive data than those on infections caused by bacteria or parasites. There is evidence for the efficacy of several lactobacilli strains, such as *Lactobacillus casei* GG and *Lactobacillus reuteri* ATCC 55,730, as well as *Saccharomyces boulardii*. Additionally, crucial is the administration's timing.
- Clear evidence supports the efficacy of *S. boulardii* or *L. rhamnosus* GG in treating antibiotic-associated diarrhea in adults or children following antibiotic therapy. In fact, *L. casei* DN-114 001 was found to reduce antibiotic-associated diarrhea and *C. difficile* diarrhea in admitted elderly patients [53].

4.3. Supplementation of zinc

Zinc deficiency is prevalent in low- and middle-income countries, particularly among infants. It impedes development and increases the morbidity and mortality caused by diarrhea, pneumonia, and malaria. Infants with diarrhea have a limited zinc intake at baseline, resulting in increased net zinc losses throughout the illness. Since 2004, the WHO and UNICEF have recommended zinc as a treatment for diarrhea. By administering zinc (20 mg per day until diarrhea ceases), the incidence, severity, and need for hospitalizations associated with diarrhea in children from developing nations can be reduced [56].

4.4. Antibiotic therapy

Early antibiotic therapy effectively manages the acute symptoms of diarrheal disease, reducing its duration to approximately 1.5 days [58]. Clinical trials assessed the efficacy of antibiotics like bicozamycin, norfloxacin, ciprofloxacin, and fleroxacin, showing a significantly higher rate of clinical cure within 72 hours in the antibiotics group (Table 3).

- Azithromycin has emerged as the drug of choice for the treatment of *Helicobacter pylori* infectious diarrhea as a result of the rise in enteropathogen resistance to first-line antibiotics such as fluoroquinolones and trimethoprim-sulfamethoxazole.
- An analogous range of effectiveness to ciprofloxacin is shared by another fluoroquinolone antibiotic called levofloxacin. Levofloxacin is widely utilized in treating diarrhea, just like ciprofloxacin, since it has the same potential to shorten the period to a therapeutic cure. Levofloxacin often only needs one dose to be successful; but, with some enteric pathogens, a three-day protocol may be recommended (e.g. *Campylobacter spp.*).

5. Preventive approaches

The administration of suitable oral solutions, i.e. oral rehydration treatment, is used to prevent or treat diarrheal

Table 3. Therapies for infectious diarrhea.

Therapy	Therapeutic Agents	Concentration	Comments	References
Supportive therapy	Oral Rehydration Solutions (ORS)	• ORS can be administered over the course of three to four hours in little periodic doses via oral syringe, spoon, bottle, or cup. • Concentration of 75 mEq/l sodium, 75 mmol/l glucose with osmolarity 245 mOsm/l can be administrated.	• Recommended by the WHO to prevent dehydration in patients with severe dehydrating diarrhea. • Rice-based oral rehydrating solutions, reduce the rate of stool output between treatments.	[7,53,59]
Anti-diarrhea therapy	Anti-motility agents- loperamide and a diphenoxylate-atropine	• A fixed-dose composition of diphenoxylate-atropine 2.5 mg/ 0.025 mg can be administrated. • The suggested dosage of loperamide is 4 mg initially followed by 2 mg after each bout of diarrhea.	• Recommended by the FDA • Anti-motility agents decrease bowel movement, so fecal transition time increases to retain fluids and electrolytes. • Loperamide is effective against severe diarrhea. • It is usually used as an adjunct to antibiotic therapy and not used as monotherapy.	[60]
Anti-secretory drugs	Racecadotril-enkephalinase inhibitor	• For adults, the dosage is 100 mg three times per day, and for children, it is 1.5 mg/kg three times per day.	• Racecadotril effective by reducing volume and frequency of stool output. • Well tolerated and provides symptomatic relief; also used as adjuvant therapy during acute attack of gastroenteritis. • Effective against *Vibrio cholerae*.	[61,62]
Anti-bacterial/ microbial therapy	Azithromycin	• 500 mg of a single oral dose of 3-day regimen.	• Recommended by the WHO • First line antibiotic defence treatment for acute watery diarrhoea. • Oral use; 37% bioavailability with a peak serum concentration of 0.4 mg/l. • It is more effective against *Campylobacter spp.*, *Salmonella spp.* and *Shigella spp.*, and preferred in regions where resistance to fluoroquinolones.	[58,63]
	Levofloxacin	• Levofloxacin 500 mg (single dosage) 500 mg once a day for up to 3 days in cases of dysentery or febrile diarrhea. After a single dosage, reevaluate 12 to 24 hours later. If the diarrhea persists, continue for up to 3 days.	• Recommended by the WHO. • Prescribed for acute watery diarrhoea. • Levofloxacin has similar spectrum of activity to ciprofloxacin. Oral bioavailability is approx 99% with high tissue concentration. • The half-life is 6–9 hours. • It is effective against *E. coli, Campylobacter jejuni* and *Shigella spp*.	
	Ciprofloxacin	• 750 mg of a single dose) and 500 mg twice a day for up to 3 days.	• Recommended by the WHO. • Ciprofloxacin is a wide spectrum antibiotic, oral administration results in rapid absorption through the gastrointestinal tract with 70–80% bioavailability. • The drug is effective against *E. coli, Campylobacter jejuni*, and *Shigella spp*.	
	Rifaximin	• Supplementation of 200 mg, 3 times for 3 days. • Recommended by the WHO. • Rifaximin have a broad spectrum of activity against aerobic and anaerobic bacteria. And show high effective against many enteropathogenes. • Oral administration results in poor absorption, having < 0.4% bioavailability and 97% being excreted in feces unchanged form. • Rifaximin is yet to receive approval • Effective against *E. coli, Campylobacter jejuni*, *Salmonella spp.*, and *Shigella spp*.		

(*Continued*)

Table 3. (Continued).

Therapy	Therapeutic Agents	Concentration	Comments	References
Zinc Supplement	Supplementation of zinc or zinc with oral rehydrating solution can be administrated	• Zinc dosage of 10 mg to 20 mg per day for 10 to 14 days.	• Recommended by the WHO and FDA • Zinc supplement with oral rehydrating solution, water soluble active ZnTe nano-composites have been used to treat zinc deficiency in diarrhea. • Zinc supplement may be useful, but the effectiveness and optimal mode of delivery is not yet clear.	[64,65]
Last line therapy- Probiotic Therapy	*Lactobacillus GG, Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium spp, Streptococcus spp*, and the *yeast Saccharomyces boulardii*	• 20 mg per day • Recommended by the WHO and UNICEF. • Specific probiotics strains normalize the increased intestinal permeability and improve intestinal barrier function, that can be helpful to prevent diarrhea. • Among all bacteria species, bifidobacterial and lactobacilli mainly used as dietary supplements for treatment of infantile diarrhea.	• In cases of acute infectious diarrhea, probiotics may provide an appropriate treatment to lessen the persistence of illness and aggravation.	[54]

dehydration. In both affluent and developing nations, oral rehydration treatment minimizes the need for hospitalization whilst being a cost-effective technique for treating acute gastroenteritis. Hand washing and sanitization also play an important role in the prevention of neglected diseases [66]. Global oral rehydration solutions coverage rates are still below 50%, and improvements are recommended. Specific quantities of significant salts lost in diarrheal stool are included in oral rehydration salts, which are utilized in oral rehydration treatment. Compared to regular oral rehydration solutions, the new lower-osmolarity of oral rehydration salts (recommended by WHO and UNICEF) with lower salt and glucose concentrations has less side effects, and a lower requirement for intravenous infusions. Regardless of age or the kind of diarrhea, including cholera, this formulation is advised [67].

The WHO advocates a comprehensive approach to prevent and alleviate diarrhea, especially in resource-limited environments with a high prevalence of diarrheal diseases. The solutions are intricate and encompass a spectrum of efforts focused on improving access to clean water, immunization, sanitation, and hygiene. The WHO supports various essential preventive measures. Rehydration can be achieved through the use of oral rehydration salt solution, an economical blend of clean water, salt, and sugar, typically available at a minimal cost per treatment. This solution is absorbed in the small intestine, replenishing the water and electrolytes lost in the feces [68].

In instances of severe dehydration or shock, the recommended approach for rehydration involves the use of intravenous fluids [69]. To disrupt the cycle of malnutrition and diarrhea, it is imperative to offer nutrient-rich foods, including breast milk, during episodes. Equally vital is providing children with a nutritious diet, specifically emphasizing exclusive breastfeeding for the initial six months of life, during times of good health. Further, the use of zinc supplements has demonstrated a 25% reduction in the duration of diarrhea episodes and a correlated 30% decrease in stool volume. It is imperative to consult with a healthcare professional, especially in instances of prolonged diarrhea, the presence of blood in the stool, or signs of dehydration [70]. The rehydration solutions prevent dehydration by facilitating the healing of the intestinal mucosa substituting the electrolytes and water lost (refeeding) [71]. Vaccination also provides a suitable and effective preventive strategy for infectious diarrhea. There are various vaccines approved or in the stage of clinical trials against various pathogens that cause infectious diarrhea.

6. Vaccination

An alternative approach to overcome infectious diarrhea is via vaccination, as a preventative measure, which will ultimately lower the number of cases, hospitalizations and mortality. In the field of public health, vaccination's accessibility, use, and efficacy in reducing diarrhea are essential elements. The worldwide impact of vaccinations is largely dependent on their accessibility, which includes their manufacture, distribution, and prices [72]. The use element entails the execution of vaccination programs, which include outreach initiatives, immunization campaigns, and the incorporation of vaccinations into standard healthcare procedures. In addition, the efficacy of these vaccinations is assessed based on their capacity to provide protection against particular diseases, lower the frequency of diarrhea, and lessen its intensity [73]. Preventing infectious diarrhea necessitates a comprehensive strategy that includes vaccination against targeted pathogens, advocating for proper hygiene practices [74], ensuring access to safe water and sanitation, and educating communities on appropriate food handling practices [30]. Additionally, maintaining sufficient nutrition, incorporating probiotics for gut health, and implementing surveillance for early detection all play crucial roles in preventing the occurrence of infectious diarrhea [75]. Effectively preventing diarrhea through vaccines necessitates a comprehensive strategy that considers not just their accessibility and usage but also their proven effectiveness across diverse populations.

In fact, a monovalent rotavirus vaccine in phase III human clinical trials in Malawi and South Africa was 77% effective against serious rotavirus infections [76]. Rotarix® and RotaTeq®, two approved rotavirus vaccines, have been in use since 2006 and have significantly decreased the rate of rotavirus infections throughout the world [5]. Generally, infants receive the vaccination via oral administration. The first dose is administered within 6 to 12 weeks after birth followed by a second dose at 24 to 32 weeks. However, bloody stools, excruciating stomach pain, and bilious emesis have been reported as adverse effects of the Rotarix and RotaTeq vaccines. The range of vaccines designed to combat diarrheal diseases goes beyond the Rotavirus vaccine, involving diverse strategies against pathogens such as cholera, *Shigella*, enterotoxigenic *E. coli* (ETEC), norovirus, and *Campylobacter jejuni*. Oral cholera vaccines, exemplified by Dukoral and Shanchol, have proven effective in reducing cholera incidence. Similarly, in several countries, studies have demonstrated the effectiveness of both the killed oral cholera vaccine (WC) and the inactivated or killed whole cell plus recombinant cholera toxin B subunit vaccine (rBS-WC) [76].

Vaccines targeting *Shigella* and ETEC are in development stages, with ongoing clinical trials assessing their efficacy. A norovirus vaccine, in preliminary studies is being evaluated, vaccines against *Campylobacter jejuni*, a prevalent bacterial cause of diarrhea, is also being evaluated [77]. Highlighting an all-encompassing strategy for vaccine development, with continuous evaluations of efficacy against different diarrheal infections, supporting the worldwide prevention and management of diarrheal illnesses. Currently, traditional (killed, live attenuated, toxoid or conjugate vaccines) and reverse vaccinology (DNA/mRNA, vector, recombinant subunit, plant vaccines) vaccines are in development or are already available. Adjuvants, delivery systems, and other vaccine components are also required for an adequate immune response. The classification of vaccines is presented in Figure 4.

Despite the well-established burden of infectious diarrheal diseases worldwide, there are currently only licensed vaccines for rotavirus, cholera, and typhoid fever based on *Salmonella typhi*. Additionally, current findings on the GI.1 and GII.4 genotype vaccines has shown a strong immune response against several infectious diarrheal illnesses in human clinical studies

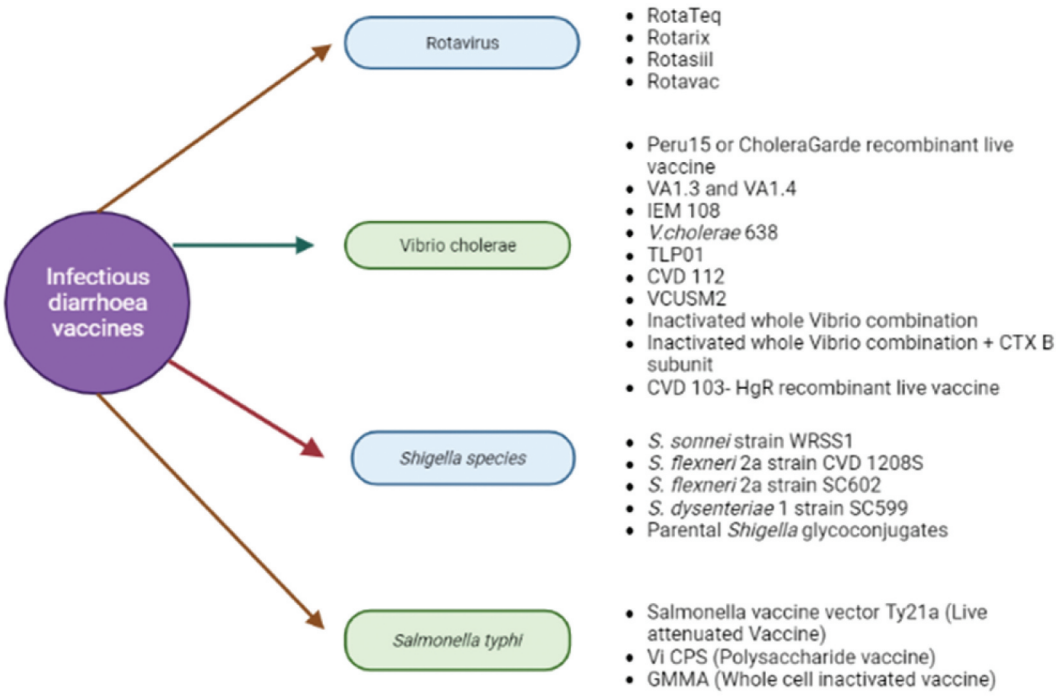

Figure 4. Classification of vaccines.

[78]. After a single dose, these vaccines strongly induce antibody responses. However, vaccines are also essential against contagious diarrheal diseases and, particular combinations must take into account the target population and severity of disease. The significant advancement of combination vaccines will contribute to the total eradication of various diarrheal pathogens, including ETEC, *Shigella, Salmonella, Campylobacter* and *Norovirus* [72,79].

6.1. Classification of vaccines

6.1.1. mRNA vaccines

In the case of infectious diarrhea, the mRNA vaccine would be designed to target specific pathogens that cause the illness [80]. An advantage of using mRNA-based vaccines is that they do not use live viruses, and as such, the risk of side effects is minimized. However, identifying the optimal viral antigens is a challenge and multiple vaccines would need to be developed incorporating multiple proteins antigens. Nevertheless, mRNA-based vaccines hold promise for next generation vaccines against infectious diarrhea.

6.1.2. Live vaccines

Live vaccines have been used for decades to prevent infectious diarrhea caused by bacteria and viruses. Live vaccines use weakened or attenuated forms of the pathogen to stimulate an immune response and protect against disease.

One prominent example of a live attenuated vaccine is the Rotavirus vaccine, which is intended to prevent watery diarrheal illness brought on by Rotavirus infections, which are an important root cause of serious intestinal infections in young children and newborns [81].

Rotavirus is extremely infectious and one of the leading global causes of acute gastroenteritis, which can have serious consequences for both morbidity and death, particularly in areas with scant resources. The WHO)has given initial endorsement to the following rotavirus vaccines: Rotarix (manufactured by GlaxoSmithKline), RotaTeq (developed by Merck), and, more recently, Rotasiil (produced by Serum Institute of India Ltd.) and Rotavac (created by Bharat Biotech Ltd.) [82]. These vaccines are generally very effective, but there are many adverse events reported with their use, especially in the very young or the immune compromised [82]. A disadvantage of live vaccines is that they are required be stored and transported at specific temperatures and can be difficult to maintain. In addition, live vaccines can be more expensive to produce than other types of vaccines, which can be a barrier to their widespread use.

6.1.3. Attenuated vaccines

Attenuated vaccines have been used successfully to prevent diseases such as measles, mumps, and rubella, as well as infectious diarrheal diseases such as rotavirus and cholera. Attenuated vaccines have the ability to provide long-lasting humoral and cellular immunity [5,83], however, as attenuated vaccines contain a live, weakened form of the pathogen, there is a risk that it could mutate back to its virulent form and cause disease. The risk is generally low, but it can be of concern in individuals with weakened immune systems or in populations with high rates of malnutrition.

In countries with low rotavirus mortality, it was found that the effectiveness of rotavirus vaccine was 86%, whereas in countries with medium rotavirus mortality, it showed 77% effectiveness, and in countries with elevated rotavirus mortality, it was 63%. Moreover, in low-mortality countries, the Rotarix vaccine showed 86% effectiveness, compared to 54% in medium-mortality countries and 58% in high-mortality countries. Furthermore, the

effectiveness of the RotaTeq vaccine among infants younger than 12 months and among children aged 12–23 months was 86% and 84%. Additionally, in countries that had high mortality rate the effectiveness of vaccines comes to be 66% [84]. Moreover, it was found that rotasiil significantly reduced the risk brought on by the rotavirus serotypes present in the vaccine with the vaccine efficacy 60.7%, 95% CI 44.1% to 72.3% [85]. RotaTeq is a pentavalent inactivated vaccine with five human-bovine reassortants that have 85% to 98% efficiency. In contrast, Rotarix is an attenuated monovalent vaccine with excellent tolerability and no difference in side effects when compared to placebo controls, especially intussusceptions. It has broad cross-reactivity against the most widely known serotypes and an efficacy of 85%-98% [86]. In the Kanungo study, a total of 1979 eligible infants were allocated randomly to either a single vaccine regimen or a mixed vaccine regimen (Rotavac- protein based vaccine). The results demonstrated that both Rotavac and Rotasiil showed similar efficacy with 53.6% and 36–67% [87,88] and protection [89]. Additionally, rotavirus-based vaccines promote the development of antibodies that are neutralizing to heterotypic human rotaviruses and shield kids from rotavirus infectious diarrhea [90]. The WHO has prequalified RotaTeq (Merck), Rotarix (GlaxoSmithKline), and, more recently, Rotasiil (Serum Institute of India Ltd.) and Rotavac (Bharat Biotech Ltd.) rotavirus vaccines [91].

Further, ETVAX, an oral, inactivated vaccine against toxin-producing *E. coli* bacteria that expressed high levels of proteins, elicited strong immune responses. The subunit protein, LCTBA, induced immune responses in 80–100% of children aged (2–5 years) and 50–80% in infants aged (6-11 months). The ETVAX vaccine also resulted in significant induction of mucosal immune responses against the wide array of target antigens identified in the study population (like colonization factors, heat-labile toxin B subunit, and O78 Lipopolysaccharides) and the effectiveness of the responses can be enhanced using dmLT adjuvants. The vaccine also exhibited efficacy in development of immunological memory effective against colonizing factors and heat-labile toxin B subunit that continued for around 1–2 years [92]. The dmLT adjuvant boosts the IgA antibodies by increasing the generation of IL-17A from mature T-cells, resulting in enhanced mucosal immune response [93]. Additionally, the vaccines also induces systemic immune responses targeting the O-78 lipopolysaccharides [92]. The IgA antibodies are secreted by lymphocytes and significantly target all five vaccine antigens (CS3, CS5, CS6, LTB and CFA/I)T. The secreted IgA is detected in the plasma. The IgA and IgG are reported to target LTB eliciting immune responses [94].

6.1.4. Recombinant vaccines

In the context of infectious diarrhea, recombinant vaccines have been developed for several pathogens, including rotavirus, enterotoxigenic *Escherichia coli*, and *Shigella*. Recombinant rotavirus vaccines, typically administered orally, are highly effective in preventing severe diarrhea and is included in routine childhood immunization programs in many countries [95]. Around the world, rotavirus is the main factor in severe acute gastroenteritis in children under the age of five, and it accounts for 128,500 to 215,000 vaccine-preventable fatalities each year. It has been found that rotavirus hospitalizations and diarrhea-related deaths have decreased by 36% and 59%, respectively, in countries that have introduced rotavirus vaccines into their national immunization programs [96]. Moreover, to enhance the immune response the recombinant VP8* subunit proteins with common strains of rotavirus infecting humans such as (DS-1 (P [4]), 1076 (P [6]), and Wa (P [8])) were combined with an aluminum adjuvant and the P2 epitope of tetanus toxoid. Its formulations involved choosing aluminum hydroxide as an appropriate adjuvant as it is the best buffer to preserve antigen stability and improve antigen binding to the adjuvant. Further, it was found that the neutralization titer against a homologous antigen was increased 20-fold by the adjuvant, and the P2-fusion also improved the serum neutralizing antibody responses [97].

Shigellosis is an infectious diarrheal disease that has been linked to multiple epidemics of shigella, which results in thousands of fatalities each year. Thus, as candidates for cross-protective vaccines, conserved subunit vaccines utilizing recombinant invasion plasmid antigens (Ipa) have been investigated [98].

Generally recombinant vaccines are safer with less side effects compared to live or attenuated-based vaccines. Recombinant vaccines have the added advantage of being produced in large quantities in a relatively short period of time [99]. This is particularly important in the context of infectious diarrhea, where outbreaks can occur rapidly and vaccines may need to be produced and distributed quickly to prevent the spread of disease. An exemplar of a recombinant vaccine is the inactivated Cholera vaccine with its recombinant toxin B subunit; correspondingly, *Shigella* vaccine strategies rely on recombinant protein synthesis. During the past 30 years, killed whole-cell oral cholera (rBS-WC, Dukoral) vaccine designed using recombinant cholera toxin B subunit provides protection and safety against cholera. This vaccine is primarily used by travelers to endemic regions where cholera management historically relies on access to clean water, good sanitation, and health education [100].

The exact methods by which mucosal vaccinations induce protective immune responses are still unclear. Dukoral is an oral vaccination intended to prevent both cholera, which is caused by *Vibrio cholerae*, as well as traveler's diarrhea, which is caused by ETEC [101]. *V. cholerae* and the recombinant cholera toxin B-subunit protein (CTB) are both included in the Dukoral vaccine. The heat-inactivated *V. cholerae* 01 Inaba classic strain and Ogawa classic strain, and formalin-inactivated *V. cholerae* 01 El Tor strain and Ogawa classic strain are used in vaccine preparation. To control and preserve the purity of vaccine antigens, a bicarbonate buffer is provided with the vaccine, in order to neutralize any remaining stomach acid [102].

National Institute of Child Health and Development (NICHD) researchers have created parenteral conjugate vaccines based on this idea. These vaccines are composed of O polysaccharides generated from the LPS of relevant Shigella serotypes covalently bonded to a carrier protein (PsA or CRM9-mutant diphtheria toxin) [103]. Live attenuated Shigella and lipopolysaccharide (LPS) conjugates have shown success in clinical studies among the many vaccination platforms examined [104]. Dukoral is a recombinant vaccine manufactured by Valneva, which is originally sold in many nations, including Canada, Australia, New Zealand, and Europe, which shows long term efficacy against infectious diarrhea [105]. Additionally, it has also demonstrated 77% vaccine efficiency against serious rotaviral infection.

6.1.5. VLP-based vaccines

In the last decade virus-like particles (VLP) have shown to be effective in stimulating protective antibody responses, especially against human papilloma virus which resulted in the commercialization of Gardasil, cervical cancer vaccine [106]. In this regard, the current preclinical studies of norovirus vaccines for infectious diarrheal diseases have focused on the application of VLPs, which mimic the structure of the virus and stimulate an immune response. For the optimum balance of immunogenicity and tolerability of the formulation, 50 g of GII.4 (Genogroup II.4) VLPs and 15 g of GI.1 (Genogroup I.1) VLPs are acceptable. Moreover, the safety and immunogenicity of several bivalent HuNoV VLP vaccine candidate formulations were evaluated in healthy 18- to 64-year-old people, demonstrating the safety of all candidate HuNoV formulations. Overall, with no discernible effect of monophosphoryl Lipid A, the formulation of 15 g GI.1 (Genogroup I.1) VLPs/50 g GII.4 (Genogroup II.4) VLPs evoked the greatest balance of immunogenicity, indicating its potential for advancement in clinical development [107].

The oligomeric RV-VP6 and the HuNoV GII.4–1999 and GI.3 VLPs were combined to create a trivalent vaccine. RV-VP6 increased activation and maturation of antigen-presenting cells (APCs), as well as the absorption of HuNoV VLPs by APCs, according to in vitro experiments [108]. According to in vivo research, the trivalent vaccination produced type-specific IgGs and antibodies that blocked the HuNoV VLPs' ability to attach to Human Norovirus Histo-Blood Group Antigen (HBGA) receptors [109]. A newborn gnotobiotic pig was utilized as a model in one investigation to assess the effectiveness of HuNoV P particles and VLPs as protective agents. Several VLP-based norovirus vaccine have shown broad spectrum humoral and cellular immune responses [110]. In phase I and II human clinical trials VLP vaccines are safe, well-tolerated and without any adverse effects. However, challenges remain in the development of a norovirus vaccine, including the need for a vaccine that is effective against the diverse array of norovirus strains and the development of a vaccine that provides long-term protection [111]. A list of vaccines for infectious diarrhea are presented in Table 4.

7. Conclusion

Diarrheal diseases continue to be a prominent global cause of mortality and morbidity. This category encompasses various infections such as typhoid, paratyphoid fever, cholera, bacterial and amoebic dysentery, emphasizing the necessity to extend attention beyond bacterial origins and acknowledge the substantial impact of viral diarrhea, especially in children. While bacterial infections have traditionally been the primary focus, recognizing the significance of viral diarrhea, predominantly affecting children, is crucial for global public health. Viruses like rotavirus and norovirus significantly contribute to childhood infectious diarrhea. Understanding the prevalence and severity of viral diarrhea, particularly in children, enables tailored public health initiatives addressing a broader range of infectious agents. This approach enhances the overall effectiveness of strategies aimed at reducing the occurrence and impact of diarrheal diseases among vulnerable populations. In many cases, the causative agent of diarrhea remains unidentified due to the involvement of several yet-to-be-identified pathogens.

Significant efforts have been made in managing and treating infectious diarrhea, with advancements in diagnostic approaches, therapeutic measures, and vaccination strategies targeting various pathogen classes. Preventive measures include consuming clean, contamination-free, hygienically prepared food or water, along with maintaining a nutrient-rich diet to prevent infectious diarrhea development. Rehydration solutions play a crucial role in prevention and treatment by keeping patients hydrated. Treatment often involves antibiotic therapy and/or other medications tailored to the causative organism, necessitating accurate diagnosis through microbiological or molecular screening. Diverse vaccine formulations, including killed, toxoid, conjugate, live attenuated, DNA/mRNA, subunit, vector-based, recombinant, or plant-based vaccines, offer a myriad of methods to develop improved vaccines. The integration of these multifaceted approaches in preventing, diagnosing, and treating infectious diarrhea is poised to enhance outcomes, reduce hospitalizations, and decrease mortality rates in the coming years

8. Expert opinion: new directions

Infectious diarrhea is a major problem in developing countries, leading to high fatality rates, mainly among young children. As such, early detection and identification of the etiologic agents are essential to diagnose, control and treat infections. Several therapeutic approaches were presented herein each with the aim to treat the disease and contain the transmission. Some management modalities include gut therapy using probiotics, oral rehydration, zinc supplementation, antibiotic therapies and vaccines. Rehydration therapy and other medical approaches are frequently employed in conjunction with probiotic therapy, which is regarded as a type of supportive care, for alleviating diarrhea [54]. It's crucial to remember that probiotic strains and formulations might differ, and their efficacy can vary depending on the root cause and symptoms of the diarrhea.

Extensive research has been conducted to develop safer, more efficient vaccines for infectious diarrhea, targeting various enteric pathogens with the goal of minimizing hospitalizations and fatalities. Progress in diagnosing infectious diarrhea has been achieved through the utilization of PCR testing for disease-causing pathogens, including, *C. difficile*. Serological testing is another method through which diarrhea-related infections can be identified. This testing is dependent on multiple factors, such as antibody titer for a particular antigen within the serum, or the capture antigen's specificity. In addition, through vaccination against microorganisms such as *Shigella* or *E. coli*. infectious diarrhea can be reduced. Recent efforts have made use of gold nanoparticles for DNA-based vaccines with preclinical animal testing showing promise in animal models, preventing bacteria such as *E. coli* from forming colonies in the digestive tract and causing symptoms such as diarrhea [136].

Newer interdisciplinary techniques such as machine learning and deep learning are proving extremely useful in predicting when new waves of infectious diarrhea approach. In the context of shifting weather patterns, machine learning offers a potentially useful method for forecasting patterns of infectious diarrhea. One such case study could be observed in South Africa, in

Table 4. Vaccines for infectious diarrhea.

Vaccine Details (Target Pathogen)	Product name, Clinical phase and efficacy	Advantages and Disadvantages	Refs
RotaTeq Live attenuated oral pentavalent vaccine (*Rotavirus*)	Merck Sharp & Dohme Corp Prequalified and licensed internationally by World Health Organization.	FDA approved Prevents rotavirus gastroenteritis caused by (types G1, G2, G3, G4, G9) Used in infants, 6–32 weeks old	[91,112]
Rotarix Live attenuated oral vaccine (*Rotavirus*)	GlaxoSmithKline Biologics Rotarix has received prequalification from the World Health Organization	FDA approved Prevents rotavirus gastroenteritis caused (by G1, non-G1 types) Used for infants, 6–24 weeks old	[91,113]
Rotasiil Live attenuated oral vaccine Freeze-dried (*Rotavirus*)	Serum Institute of India Ltd Rotasiil has qualified in phase-IV and has shown efficacy	Active immunization of healthy infants (age of 6 weeks) Prevents gastroenteritis caused by rotavirus infection	[82,114]
Rotavac Live attenuated oral vaccine (*Rotavirus*)	Bharat Biotech Ltd 56% efficacy in phase III clinical trials.	Prevents gastroenteritis caused by rotavirus infection Safe and effective	[82]
Peru15 or CholeraGarde recombinant live vaccine Live attenuated oral vaccine It involves the Core deletion of CT and Modification of recA (*Vibrio cholerae*)	Avant Immuno-therapeutics Peru15 or CholeraGarde recombinant live vaccine in phase II and III trials, showed it to be safe and effective.	Effect of booster dose Easy to manipulate Elicits mucosal immunity Disadvantage: it can undergo reverse mutations	[115]
VA1.3 and VA1.4 Live attenuated oral vaccine Non-toxigenic V. cholerae and insertion of the ctxB, VA1.3 and AmpR (*Vibrio cholerae*)	Different laboratories are involved	High side effects Advantages - safe and immunogenic	[116]
IEM 108 Live attenuated oral vaccine Introduction of ctxB gene and rstR gene Insertion of the *Clostridium thermocellum endoglucanase* A, thereby Inactivation of hemagglutinin activity. (*Vibrio cholerae*)	China CDC IEM 108 in preclinical studies is effective in killing bacteria and other toxoids.	It is cultivable Single dose could cause active colonization Elicits high-titre serum vibriocidal antibodies (neutralizes the toxin). Stimulates mucosal immunity Provides high protection	[117]
V. cholerae 638 Live attenuated oral vaccine Deletion of CTXφ (*Vibrio cholerae*)	Finlay Institute, Cuba A single dose of live-attenuated oral vaccine against *Vibrio cholerae* 638 is both safe and effective.	Provides complete protection against cholera toxin Protection against faecal shedding of the challenge agent	[118,119]
TLP01 Live attenuated oral vaccine Deletion of CRC266 0139 strain with CTXφ, mshA (*Vibrio cholerae*)	Finlay Institute, Cuba In terms of attenuation and immunogenicity, preclinical studies in animal models have shown that the live attenuated vaccine strain TLP01 performs satisfactorily.	Good colonizing capacity Reduces the possibility of stable virulence reversion in the human gut. Vaccine strain is unable to produce biofilms, which may have implications for vaccine biosafety.	[120]
CVD 112 Live attenuated oral vaccine Deletion of VC 0139 with ctxA, zot, ace, and, cep (*Vibrio cholerae*)	University of Maryland, U.S.A. CVD 112 in initial pre-clinical studies shows short term protective efficacy of 84%.	Safe and effective Provides protection against O1 and O139 *V. cholera* species	[121]
VCUSM2 Live attenuated oral vaccine Deletion causes an ALA auxotrophy (*Vibrio cholerae*)	University of Sains Malaysia VCUSM2, a recently developed vaccine is immunogenic and generates mild adverse effects in animal models.	Safe and effective Provides protection against O139 *V. cholera*	[122]
S.sonnei strain WRSS1 Live attenuated oral vaccine Involves the deletion of the plasmid-encoded virG (icsA) protein Loss of motility (actin mediate) (*Shigella sonnei*)	Walter Reed Army Institute of Research The WRSS1 oral vaccine in phase I clinical trial was found to be immunogenic in both adults and children at doses up to 10^6 CFU.	Not suitable for immuno-compromised people Well tolerated and immunogenic in phase I human clinical trials	[123]
S.sonnei strain WRSs2, WRSs3 Live attenuated oral vaccine Deletion of the plasmid-encoded virG (icsA), senA, senB, msbB2 (*Shigella sonnei*)	In volunteer trials and animal model studies, these candidates were shown to be innocuous and immunogenic, as well as effective against *shigellosis*.	Refrigeration required Against shigellosis it is efficacious, safe and immunogenic	[124]
S.flexneri 2a strain CVD 1208S Live attenuated oral vaccine Deletion of guaBA, setAB, and senA (*Shigella sonnei*)	Center for vaccine development During phase I and II clinical trials, the *S. flexneri* 2a strain CVD 1208S showed promising outcomes.	41% coverage against *Shigella* strains Safe and effective	[125]

(*Continued*)

Table 4. (Continued).

Vaccine Details (Target Pathogen)	Product name, Clinical phase and efficacy	Advantages and Disadvantages	Refs
S.flexneri 2a strain SC602 Live attenuated oral vaccine Deletion of the plasmid-encoded virG (icsA) protein (*Shigella flexneri*)	Pasteur Institute A relatively straightforward vaccine concept, Sf2aWC vaccine was shown to be both safe and immunogenic in phase I clinical trial.	Safe, effective, immunogenic	[126]
S.dysenteriae 1 strain SC599 Live attenuated oral vaccine Loss of invasion IcsA, and Shiga toxin A subunit (stxA) (*Shigella dysenteriae*)	Pasteur Institute *S.dysenteriae* 1 strain was found to provide protection in animal studies	Safeguard against the toxicity of other Shiga toxins Pathogens that express gene 1. Effective	[127]
Inactivated whole Vibrio combination Oral vaccine Killed whole cells only (O1 classical and El Tor biotypes O139) (*Vibrio cholerae*)	Shanchol or mOrcVAX Since it's in preclinical trial and animal model study it was initially treated with inactivated whole vibrio and elicits immune responses	Increases the bioavailability of vaccine Therapeutic efficacy is improved Safe and immunogenic	[128]
Inactivated whole Vibrio combination + CTX B subunit Oral vaccine (*Vibrio cholerae*)	Dukoral Inactivated whole vibrio combination in phase-III study produced the "gold standard" efficacy study outcomes.	Safe, effective, immunogenic, protection for up to 2 years	[129]
CVD 103-HgR recombinant live vaccine Oral vaccine Deletion of 94% of the gene encoding the CT A, Hg2, and resistance gene (*Vibrio cholerae*)	Orochol, Mutachol, Berna Biotech CVD 103-HgR has passed the phase-I clinical trial and efficacy of the vaccine was considered to be 90%.	U.S. FDA approved Well-tolerated Provides protection against *V. cholerae* O1 for up to 6 months 90% efficacy in a single dose	[130]
Parenteral *Shigella* glycoconjugates O-polysaccharide is covalently linked with the carrier protein (*Shigella flexneri*)	NICHD Parenteral *Shigella* glycol-conjugate vaccine have reached phase I and II human clinical trials with immunogenic outcomes.	Phases I and II human clinical trials completed Cost-effective, safe, and, immunogenic. Intra-muscular injection	[131]
Inactivated *S. sonnei* Formalin inactivated Oral vaccine (*Shigella sonnei and Vibrio cholerae*)	Emergent Biosolutions In animal studies, inactivated *S. sonnei* was immunogenic and protective, and in a Phase I trial, it was well tolerated and immunogenic.	Phase I trial completed Shows tolerability and immunogenicity	[132]
Shigella invasion complex (Invaplex) Inactivated nasal vaccine Production by purification of LPS and recombinant IpaB, IpaC Inactivated (*Shigella flexneri*)	Walter Reed Army Institute of Research *Shigella* invasion complex (Invaplex) has passed phase-I and II trials shown antigenicity and protection during the preclinical trials in humans.	Excellent safety and immunogenicity profiles in preliminary clinical studies, and it is currently being evaluated in specific populations (children and travellers to endemic countries)	[133]
Proteosomes to which S. sonnei or S.flexneri 2a LPS is adsorbed Nasal vaccine Outer membrane protein vesicles of Group B meningitides (*Shigella flexneri and Shigella sonnei*)	ID BiomedicalA This vaccine has qualified the phase 2a trials and shown a greater efficacy and highly immunogenic during clinical trials.	Shows tolerability and immunogenic responses Multivalent vaccine approach	[134]
Salmonella vaccine vector Ty21a Oral vaccine Live *Salmonella typhi* vaccine vector expressing *S.sonnei* or *S.dysenteriae* antigens (*Salmonella Typhi*)	Aridis *Salmonella* Ty21a vector vaccine is an attenuated licensed vaccine Ty21a which elicits antigenicity and humoral immune response.	Highly stable, easy to manipulate DNA-based vaccine Effective delivery system Safe and immunogenic	[135]

a dataset located across nine provinces, the machine learning technique Support Vector Machines, as well as deep learning techniques such as Long Short-Term Memory Networks, were used for prediction via climate change. Forecasting patterns of infectious diarrhea amidst changing weather necessitates a thorough strategy that combines epidemiological and environmental data utilizing advanced analytics, notably machine learning [137]. The initial stages encompass the compilation of historical data concerning infections and weather factors, succeeded by preprocessing to manage anomalies and identify correlations. Public health practitioners can utilize real-time technologies as part of the implementation, and updates based on new data and changing trends guarantee continued relevance and accuracy through continuous monitoring. In response to shifting patterns of infectious diarrhea brought on by fluctuations in the weather, this meticulous methodology allows for early planning in public health and focused treatments [138].

These methods are also employed for other diseases such as Hepatitis, Typhoid, and Scarlet fever. The methodology employed in these studies involved the use of loperamide purchases as substitute data for diarrhea cases in the region (readings were taken over 10 years from November 2008 to March 2018), as well

as eight other environmental factors – wind velocity, maximum and minimum temperature, specific humidity, air temperature, precipitation rate, surface pressure, and potential evaporation rate. From the data, it was observed that the parameters which were most effective with regard to increasing diarrhea occurrence were evaporation, humidity, precipitation, and temperature, which were in line with evidence from other studies that indicated correlations between temperature, evaporation, and diarrhea [137,139]. A similar test was also conducted in China using artificial neural networks – specifically, the back-propagation neural network. The study was based on prior studies with data indicating that morbidity related to diarrhea was highest on days with extreme temperature or rainfall levels. Data from January 2005-January 2009 were collected, with all of the cases of infectious diarrhea within the dataset being confirmed (either by clinics or laboratories). Nine parameters were employed including, weekly average minimum and maximum temperatures, overall average temperatures, average humidity, and wind speed [139]. Further, the method used for prediction was regression modeling – for which three models were used i.e. back-propagation neural network, with an additional model (multiple linear regression), was used to predict the next week's number of infectious diarrhea cases. The results revealed that of all the prediction models used, the back-propagation neural network demonstrated the best performance prediction-wise, with the meteorological factors that had the most correlation with infectious diarrhea identified as being temperature-related – minimum, maximum, and average temperature [139].

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Declaration of interest

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•• **This paper dicusses the use of artificial intelligence like artificial neural network in the prediction of infectious diarrhea.**