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Treatment of Acute Diarrhoea: Past and Now

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Abstract

Context: Since ancient times diarrhoea has been a highly fatal disease and even today diarrhoea, the topic of this review, is a problem affecting millions of people around the world despite the efforts of governments and professionals from the medical area. Worldwide the most common cause of children's death is diarrhoea.

Evidence Acquisition: Diarrhoea disorders generally appear with watery stools, sometimes mixed with blood, accompanied by abdominal pain, vomiting and fever. The symptoms depend on the content and distribution of body fluid, daily water requirements and physiological water loss in connection with age through sweating, urination and breathing, the degree of fluid and electrolyte loss in the liquid stool.

Results: Several effective interventions have been introduced as part of diarrhoea management in the last two decades such as oral rehydration solution, zinc supplementation, vitamin A supplementation and oral administration of antibiotics and vaccines. To reduce the mortality rate, control of safe drinking water, good sanitation and vaccination against typhoid and cholera are recommended, especially in high-risk populations. Probiotics have been proposed, after more than a half of century, as additional therapy in the treatment of acute diarrhoea. Several probiotic strains showed benefit in meta-analyses of randomised controlled trials.

Conclusions: Due to the high level of evidence available, the term "oral bacteriotherapy", used for decades in the prevention and therapy of gastroenteritis in the growing age and adults, has expanded, but probiotics are acquiring significant scientific value based on the results from human trials. The future of probiotics depends on further explanation/elucidation of basic mechanisms, allowing scientists and physicians to maximize their health benefits.

Keywords: Probiotics, Diarrhoea, Oral Rehydration, Alternative Therapy

1. Context

The present paper is a review on diarrhoea, including pathogens that cause several types of diarrhoea, mortality trend around the world and methods to detect the causative agents. The authors overviewed all the interventions to fight diarrhoea, such as oral rehydration therapy (ORS), zinc and vitamin supplementation, antibiotics, vaccine and probiotics in diarrhoea management.

1.1. Diarrhoea Definition

Diarrhoea is defined as stool emission with an excess weight of 200 grams per day and "pseudo diarrhoea" when faecal weight is < 200 g/24 hours (1, 2). Diarrhoea is an alteration of normal bowel movement, variation characterized by increased water content, volume and frequency of stools. Intestinal water balance results from a complex regulation involving inflammatory mediators, hormones, neuropeptides, intestinal wall integrity, enteric nervous and circulatory system efficiency (3).

1.2. Diarrhoea Epidemiology and Trends in Mortality in WHO Regions

Worldwide, diarrhoea is the second most frequent fatal childhood disease after pneumonia, estimated to cause 1.34 million of children deaths. Different causes of death in children younger than five years vary over the world and WHO regions, although pneumonia and diarrhoea, remain the same, significantly increase where the health systems are inefficient (4, 5) (Table 1, Figure 1).

Of all deaths from diarrhoea, 78% of children live in the African and South-East Asian regions, which are disproportionately loaded with infant and childhood HIV infec-

tions (7). Diarrhoeal disease occurs more frequently in HIV-infected children and their consequences are worse. Administration of antiretroviral therapy (ART) and restoring the immune system are critical for preventing and treating diarrhoea in children affected by HIV (8). Research on diarrhoea in children is a priority of WHO for achieving the United Nations' Millennium Development Goal of reducing childhood mortality.

1.3. Types of Diarrhoea

Diarrhoea, from a clinical point of view, needs to be classified according to certain characteristics such as trends over time (acute or chronic) and faeces characteristics (watery, fatty, inflammatory, etc.) (3, 9).

Generally, episodes of diarrhoea can be classified into three categories including acute diarrhoea with presence of three or more watery stools within 24-hours, dysentery with bloody diarrhoea and mucous presence, persistent diarrhoea when episodes of diarrhoea last more than 14 days, while chronic diarrhoea when the episode lasts for more than a month (10, 11). Diarrhoea reflects higher water content in the stool, number of stools that may reach 20 or more per day, with defecation every 20 - 30 minutes.

1.4. Main Pathogens Responsible for Acute Diarrhoea

Diarrhoea is caused by infections, often spread from person-to-person or contaminated sources, water contaminated with human or animal faeces and other causes including poor personal hygiene, food conservation in unhygienic conditions and malnutrition. Dysenteric cases often have no identifiable agent (12, 13).

1.4.1. Bacteria

Bacteria may be the causative pathogens (15 to 20%) including *Salmonella* spp., *Campylobacter* spp, and *Escherichia coli*. Bacteremia, sepsis, spreading to other organs represent systemic symptoms that complicate gastrointestinal infection, especially by *Campylobacter*, *E. coli*, *Salmonella*, *Shigella*, *Aeromonas* and *Yersinia* (Table 2). *Clostridium difficile* is a pathogen that causes uncomplicated antibiotic-associated diarrhoea and severe, possibly fatal, antibiotic-associated colitis (14). Prevention is possible through infection control measures both clinical and epidemiological (15). Many pathogenic serotypes of *E. coli* may cause different diarrhoea conditions. Some *E. coli* have evolved the ability to cause a wide spectrum of human diseases such as urinary tract infection, sepsis and/or meningitis and enteric/diarrhoeal disease. Also, *Helicobacter pylori* and *Vibrio cholerae* can be problematic, since they are pathogens that colonize the gastric mucosa and cause acute inflammation, damaging the gastric epithelium with serious consequences as superficial gastritis, chronic atrophic gastritis and gastric cancer.

1.4.2. Fungi

One of the major causes for morbidity and mortality in immunocompromised children are represented by the invasive fungal infections (IFIs), caused by *Candida* and *Aspergillus* species (16). *Candida*-induced diarrhoea is associated with prolonged secretory diarrhoea with abdominal pain and cramping, without blood, mucus, fever, nausea and vomiting (17).

1.4.3. Protozoan Parasites

Protozoan parasites, such as *Cryptosporidium parvum|hominis*, *Cyclospora cayetanensis*, *Giardia lamblia* and *Isospora belli* are infrequent causes of acute diarrhoea in healthy children (10 to 15%).

1.4.4. Parasites Helminths

Parasites Helminths affect adults and children worldwide caused by predominantly rural settings, low personal hygiene, unsafe drinking water, poor sanitation, non-usage of toilets and the immune status of the child (18, 19).

1.4.5. Viruses

Adenovirus, Human Bocavirus, Human Astrovirus, Norovirus, Sapovirus and Rotavirus are known as the most common causative pathogens of gastroenteritis (50 to 70%) and compared to bacterial enteritis, usually have a better prognosis with a lower mortality, but they show a high morbidity. Toxin production, intestinal cells and tissue invasion, with consequent alteration of their function, are usually mechanisms of viral infectious diarrhoea.

1.5. Diagnostic Methods

Many brief episodes of diarrhoea and gastroenteritis do not require any laboratory investigations and are managed without seeking professional advice. In particular circumstances, identification of the causative agent of infection is not possible only by history of disease, environmental risk factors, clinical signs and symptoms or characteristics of the faeces. Enteric infections diagnosed by analysis of bacterial cultures and microscopy detecting the bacterial enteric pathogen, ova and parasites has been the main method of diagnose for many years. Especially *Campylobacter*, *Salmonella*, *Shigella*, *Vibrio*, and *Yersinia* species are quite easily cultivated, isolated and finally identified. Isolation of cultured organisms is essential to determine sensitivity to antimicrobial agents for treatments and identify specific strains and their virulence factors (19). These traditional methods are time-consuming and since patients do not have a diagnosis for days, the risk of untreated infection and spreading of infection to other persons is high.

Polymerase chain reaction (PCR) is a shorter, but more expensive assay with clinical applications, more sensitive and accurate using just few colonies from a patient with early-infections. With newer techniques available, laboratories are able to identify up to 70% of pathogens that cause acute diarrhoea. While, multiplex PCR allows simultaneous amplification and identification of multiple organisms in a single reaction (20, 21). Moreover, molecular techniques, as sensitive ELISA and latex agglutination, are required and very important for their highly sensitivity and specificity on infection detection in very small samples and in cases of multiple infections (19).

2. Evidences Acquisition

The patient generally develops watery stools, according the pathogen type, sometimes mixed with blood, after an incubation period up to seven days, accompanied by vomiting and fever (Tables 3 and 4). Symptoms depend on the content and distribution of body fluid (BF) by age, daily water requirements in connection with age, physiological water loss in connection with age through sweating, urination and breathing, the degree of fluid and electrolyte loss (sodium, chloride, potassium and bicarbonate) in the liquid stool. Clinical estimation of the fluid deficit and dehydration, the most important symptom of acute gastroenteritis, occurs when all these losses are not replaced adequately altering plasmatic volume and composition of interstitial liquids and therefore homeostasis and metabolism of water.

Intra- and extracellular water, contained apparently completely in the lean mass, is the most important component of the organism mostly in the first months of life when it represents approximately 80% of the body weight to be reduced to approach the value of adult as 60% of the body weight, after the first year of life (2, 22). For this reason, daily water needs become more as child grows up. Dehydration is classified light if the loss of weight is below 3% in the first year of life and below 5% subsequently, moderate if it is 3%, (< 5%) -8% until 9% and serious if it is more than 9% with tachycardia, tubular necrosis to shock and coma.

However, vomiting and respiratory involvement are associated to a viral aetiology, in particular Norovirus and Rotavirus. When the infection affects children of a few months, diarrhoea tends to persist. High fever (> 40°C), presence of blood in faeces, abdominal pains, and central nervous system involvements are associated more frequently to one bacterial aetiology (Tables 3 and 4).

Serious dehydration (weight loss > 10%), neurological anomalies (lethargy, convulsions, etc.) intractable or biliary vomit, inadequate oral rehydration and/or familiar assistance to domicile, or suspicion of a surgical pathological picture, are necessary for hospitalization (1, 2).

3. Results

- Preventive and therapeutic aspects are as follows:

3.1. Vaccines

For years, there are vaccines against cholera, typhoid and lately, given the high frequency and severity of Rotavirus infection, particularly during the first year of life, two orally administered Rotavirus vaccines, Rotarix™, which is a single-strain attenuated human Rotavirus vaccine, while RotaTeq is a multistrain bovine-human vaccine. They are safe and effective to prevent these enteric diseases with a 90% to 100% efficacy rate against severe Rotavirus in Europe, Latin America and North America, (23-25). Rotavirus vaccines prevent deaths of approximately 225000 children/year in the poorest countries and in the next 20 years more than 2.5 million would be protected by the infection (Figure 2) (25-27). Omenaca and coworkers (28) showed that Rotarix™ was well-tolerated and immunogenic; however, in pre-term children in Europe, safety and reactogenicity were equal to that of full-term infant.

3.2. Probiotics

Elia Metchnikoff (1845 - 1916) was the first to introduce "oral bacteriotherapy" using "good" and efficient bacteria present in fermented milk that prevent putrefaction and aging. In his book "The prolongation of life. Optimistic studies", Metchnikoff confirms that not all microbes are harmful to human health and suggests that useful microorganisms may replace the harmful one, modifying the intestinal flora. According to the FAO/WHO (29), probiotics are defined as "Live microorganisms, which confer a health benefit on the host when administered in adequate amounts". They have been proposed in the prevention and as adjunctive therapy in the treatment of acute diarrhoea and other pathologic conditions. The probiotics effects on the intestinal microflora and antibacterial, immunostimulatory and anti-inflammatory properties have been investigated in acute diarrhoea, travellers' diarrhoea, antibiotic-associated diarrhoea (AAD), *Clostridium difficile* gastroenteritis, chemo- or radiotherapy-induced diarrhoea, inflammatory bowel diseases, small bowel bacterial overgrowth and irritable bowel syndrome (IBS) (30-35).

3.2.1. Probiotics as Preventive Therapy

Several studies reported the use of probiotics (such as *Lactobacillus* GG) to prevent and treat acute diarrhoea with a significant decrease in the rate of diarrhoea incidence (36). Invasive fungal infections are common and difficult to diagnose in infants; empirical treatment with antifungal therapy should be considered for those who fail to quickly respond to empirical antibacterial

preventive treatment. Risk factors to administer empirical antifungal therapy include extreme prematurity, exposure to third-generation cephalosporins and presence of central venous catheters. To prevent gastrointestinal colonization by *Candida* spp., the use of probiotics, *L. rhamnosus* and *L. reuteri*, appears to be effective with no associated adverse effects. They are effective in the protection from necrotizing enterocolitis (NEC), late-onset sepsis and reducing abnormal neurological outcomes in preterm neonates (37-39). *L. reuteri* probiotic strains have potential therapeutic value in the prevention of experimental NEC. *L. reuteri* improves mucosal barrier and anti-inflammatory properties, feeding tolerance, probably due to its changes in intestinal flora, bowel habits and gastric motility (39). Administration of *L. reuteri* is always safe and well tolerated (39, 40). *L. reuteri* (DSM 17938) may prevent diarrhoea, especially in children with lower nutritional status (41).

A randomized controlled clinical trial on infants treated with probiotics showed no significant effect on growth and neurodevelopmental outcomes, but confirmed reduction in the incidence and severity of NEC (42). Another similar trial in newborns weighing below 1500 grams showed potential benefits of probiotics for premature infants in reduction of NEC risk (43). Antibiotics, prescribed frequently in children, alter the microbial balance within the gastrointestinal tract and cause associated diarrhoea (AAD).

Other studies on children and teenager under 18 years old receiving antibiotics, treated with two probiotic strains, *Lactobacillus rhamnosus* and/or *Saccharomyces boulardii* showed a protective effect of probiotics (44). Probiotics can prevent AAD by several mechanisms mostly by maintaining a healthy microflora. Another in vivo study of a probiotic formula containing *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R (for prophylaxis of AAD and *Clostridium difficile*-associated diarrhoea) indicated a lower incidence of AAD and CDAD in patients treated with probiotic combination compared with the placebo group (45).

Also, recent randomized controlled trials (RCTs) of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus* and/or *Bacillus* probiotic strains indicated a statistically significant association of probiotic administration with reduction in AAD incidence.

3.2.2. Probiotics as Therapy

Acute diarrhoea is the most investigated field in the area of probiotic use, especially in children and many systematic reviews described the probiotics role. Probiotics demonstrated a good safety profile, significantly reduction of diarrhoea duration, reduction of stool frequency and reduction of hospitalization period (46). Using probiotics to treat diarrhoea is based on the modification of the intestinal microflora and it is well known that probiotics fight against enteric pathogens. Moreover, beneficial effects of probiotics in acute diarrhoea seem to be strain-specific, dose-dependent ($>10^{10}$ CFU), significantly efficient in viral gastroenteritis and more evident when probiotics treatment is initiated at the beginning of disease (46).

A recent meta-analysis designed to determine whether some probiotics (11 probiotics species and species mixtures) are beneficial, showed a positive effect in prevention and/or treatment of Infectious diarrhoea, Antibiotic Associated Diarrhoea, *Clostridium difficile* disease, *Helicobacter pylori* infection, Irritable Bowel Syndrome and Pouchitis, but did not show significant effects in Travellers' Diarrhoea and Necrotizing Enterocolitis.

Probiotic strains with demonstrated beneficial effects, decreasing the frequency of diarrhoeal infections and increasing production of Rotavirus-specific antibodies are *L. reuteri*, *L. rhamnosus* GG, *L. casei* Shirota, *L. acidophilus*, *Bifidobacterium animalis* ssp., *B. lactis* BB-12, *E. coli*, *Enterococcus faecium* SF68 and *Saccharomyces boulardii* (33). These probiotics showed a significantly reducing incidence of acute diarrhoea when the treatment dose reaches the concentration of 2×10^8 CFU/die (35).

Other studies showed that both probiotic strains *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475 decreased concentrations of proinflammatory cytokines, enhanced intestinal microbiome richness, enterocyte proliferation, villus repopulation and virus-specific antibodies. All these facts contribute to a better nutritional status and reduce diarrhoea duration (47).

All these studies and trials may provide understandings into the clinical application of probiotics, but it is important to elucidate the mechanisms of probiotics to maximize their health benefits (48).

3.3. Oral Rehydration Therapy (ORT)

Rehydration therapy, either intravenous or oral, is a choice treatment for fluid and electrolyte losses caused by diarrhoea, decreasing the number of deaths to less than 1% from 25 - 50% (49). Oral rehydration therapy (ORT) and in particular oral rehydration solution (ORS) are the standard therapies for an efficient and cost-effective management of acute gastroenteritis. ORS has several advantages, such as reduced need of intravenous infusions, less stool output and less vomiting. New formulations with a better taste and/or efficacy of oral rehydration solution (ORS) are available (Table 5) (50).

Among all oral solutions, the ideal one has a low osmolarity (210 - 250 mOsm/L) and a sodium content of 50 – 60 mmol/L to avoid high levels of serum sodium. The low osmolarity oral rehydration solution with reduced concentrations of sodium and glucose, (≤ 270 mOsm/L) and zinc supplementation is associated with fewer unscheduled intravenous fluid infusions, lower stool volume and less acetone vomiting than the standard ORS and is recommended in treating adults and children

(1, 51). The solution should be administered frequently and in small amounts to prevent vomiting, 50 – 100 mL/Kg in the first four hours (11, 52).

3.4. Inhibitors of Intestinal Secretions

Several measures have been investigated as adjunct therapy to ORS including a variety of non-specific anti-diarrhoeal agents, anti-motility agents and anti-secretory agents such as racecadotril (or acetorphan). The American Academy of Paediatrics and Centres for Disease Control and Prevention published practice parameters for management of acute gastroenteritis, but studies have shown ORS underuse globally (53).

In patients with various forms of acute diarrhoea, after oral administration, racecadotril is rapidly converted into thiorphan, acting on the enkephalins, which inhibits pathologic (but not basal) secretion of water and electrolyte from the gut, without modifying the gastrointestinal transit time and motility. In general, racecadotril has been reported to have a good safety profile as side effects were similar with placebo and no serious events were observed in all trials in adults and children (53, 54).

Several guidelines on children with acute diarrhoea recommend a treatment with oral rehydration enriched/supplemented with racecadotril. The cost utility of racecadotril with oral rehydration solution (ORS) for the treatment of acute watery diarrhoea (AWD) was studied on children younger than five years showing that racecadotril is more effective as adjuvant therapy and less costly compared to ORS (54, 55).

3.5. Antibiotic Treatment

3.5.1. Bacterial Infection

Since most of diarrhoea causes are not able to be identified, empiric antibiotic treatment gives a harmful eradication of normal flora, which increases the risks of diarrhoea and other fatal infections and emergence of multidrug resistant microorganisms (3, 13). Antibiotic therapy is not indicated but is helpful for children with bloody diarrhoea (most likely shigellosis), severe dehydration (like suspected cholera cases) and non-intestinal associated infections (like pneumonia).

Aeromonas spp.: pathogenicity can be influenced by the immune status of infected child, various virulence factors and production of β-lactamases, which induces resistance to penicillin and first-generation cephalosporins (cefotaxime) (56-58).

Campylobacter infections may be treated with ampicillin and azithromycin when patient has severe symptoms (59). *Clostridium difficile* (CDI) can be recovered from newborns as early as the first week of life and 71% of children below 12 months of age are colonized without traditional risk factors as antibiotic use and health-care exposure. Recent studies suggest discontinuous treatments of the offending antibiotic, such as metronidazole, linezolid and vancomycin.

Diarrhoeagenic *Escherichia coli* (DEC) usually heals itself contrary to common *E. coli* gastroenteritis within a couple of days, especially preventing dehydration. It is therefore appropriate to drink in small sips, to prevent vomiting, water and/or sports drinks in proportion to the amount of liquid stools within 24 hours, eat small meals throughout the day instead of three large meals, with some salty foods and potassium-rich foods such as bananas and potatoes. Antibiotics are contraindicated and should be prescribed only on specific clinical and laboratory indications.

Early empirical therapy of Enterotoxigenic *E. coli* (ETEC) with probiotics, antibacterial drugs (rifaximin, fluoroquinolone, azithromycin) decreases the disease duration.

Helicobacter pylori causes diarrhoea, but also gastritis, peptic ulcer and gastric cancer. Eradication of the pathogen includes a therapy for 7 - 14 days with lansoprazole, omeprazole, pantoprazole, rabeprazole, dexlansoprazole or esomeprazole to decrease the stomach production of acid (60).

In cases of *Salmonella* spp. infection, several trials suggest that a treatment with antibiotics, such as ampicillin, amoxicillin, cefixime, azithromycin or cotrimoxazole could be appropriate (59).

Shigella spp. cause an invasive gastroenteritis and are relatively common in children. Symptoms are mild and self-limiting. In more severe cases, diverse antibiotics (ciprofloxacin, ampicillin, cotrimoxazole, nalidixic acid, ceftriaxone and azithromycin) are recommended as the pathogens have regional differences in sensitivity.

Without treatment, severe infection of *Vibrio cholerae* has a mortality rate of 30 - 50%, but by an effective therapy mortality can decrease reaching 0.2%. The therapy includes ampicillin, ceftriaxone, ciprofloxacin, tetracycline and trimethoprim.

Infections by *Yersinia enterocolitica* resolves spontaneously within two weeks. *Y. enterocolitica* is sensitive to meropenem, ceftriaxone, ciprofloxacin, ceftazidime and amikacin, while is resistant to ampicillin (61).

The high antibiotic resistance registered worldwide elevates a wide discussion on randomly and inappropriate use of antibiotics and surveillance of preponderance of the main pathogens and their resistance.

3.5.2. Fungal Infection

Recently three new antifungals drugs, anidulafungin, caspofungin and micafungin, have been introduced, with advantages on fluconazole and amphotericin B, which might better fit with the needs of paediatric patient, neonate and preterm with invasive candidiasis and/or diarrhoea.

Micafungin has fungicidal activity against *Candida*

species, invasive candidiasis, diarrhoea, necrotizing enterocolitis and lateonset sepsis; the recommended dosage in children is 2 mg/kg/day (100 mg/day if > 40 kg body weight) (62). Caspofungin (1 mg/kg of body weight/day), as micafungin, has similar activities against natively *Candida* strains resistant to fluconazole, invasive candidiasis and diarrhoea and are well tolerated also in neonates (63).

3.5.3. Parasitic-Protozoan

The most common treatments for *Cryptosporidium parvum|hominis* infections are paromomycin, azithromycin and nitazoxanide (NTZ) (64). The therapy for *Cyclospora cayetanensis* infections is constituted by TMP-SMX (5 - 25 mg/kg of body weight/day) or ciprofloxacin as an alternative therapy (65). *Giardia lamblia*, a diarrheagenic protozoan pathogen, is commonly treated with metronidazole (MTZ), tinidazole, albendazole, auranofin or NTZ, reducing the duration of diarrhoea (Table 6) (66, 67). Diarrhoea caused by *Entamoeba histolytica* can be treated with metronidazole and other nitroimidazoles, supplemented with luminal amebicides (paramomycin). A more recent therapeutic advance is nitazoxanide decreasing diarrhoeal illness period.

The World Health Organization classified auranofin as an antirheumatic agent, identified as 10 times more potent than metronidazole, in culture and a mouse model, on *Entamoeba histolytica*. Auranofin could represent a promising therapy for amebiasis (64).

3.5.4. Parasitic-Helmints Nematodes

Parasitic-helmints nematodes do not exert significantly negative effects on the growth and education of children. *Strongyloides stercoralis*, which causes several diseases, may be eradicated by Ivermectin therapy (68).

While to treat *Trichuris trichiura*, mebendazole demonstrates a good efficacy, since albendazole shows a low effect (69, 70).

Table 1. Distribution of Deaths From Diarrhoea in Children (Aged Less Than 5 Years) by Region (Modified Rudan et al. 2008 (6))

Regions	Deaths	
	Millions	Percentage
Africa	4.396	16
America	0.439	12
Eastern-Mediterranean	1.409	17
Europe	0.263	13
Southeast Asia	3.070	18
Western Pacific	1.020	17

3.6. Alternative Therapies

3.6.1. Zinc

Zinc represents a new intervention for treating diarrhoea, which activates transcription factor NF-κB and modulates host defence and since its deficiency is associated with high inflammation and bad outcomes in fighting bacterial infections (71). Several studies showed that 10 – 20 mg zinc per day for 10 - 14 days significantly reduces the gravity and duration of diarrhoea in small children (72, 73).

Some studies found that supplementation of ORS with zinc and probiotics limits diarrhoea duration. The explanations for this differential effect of zinc benefits only in children from developing countries might be due to the fact that zinc deficiency (secondary to malnutrition, causing decreased absorption of zinc, diarrhoeal disease itself causing excess zinc loss in stool, dietary factors causing low intake due to poor socio-economic status, etc.) is associated with impaired water and electrolyte absorption, in children from developed countries (74).

3.6.2. Vitamin A

It is well known that the relative risk of death from diarrhoea increases twice in children with vitamin A deficiency. It has been demonstrated that a daily dose of vitamin A (400 μg) for newborns is effective in reduction of mortality (75).

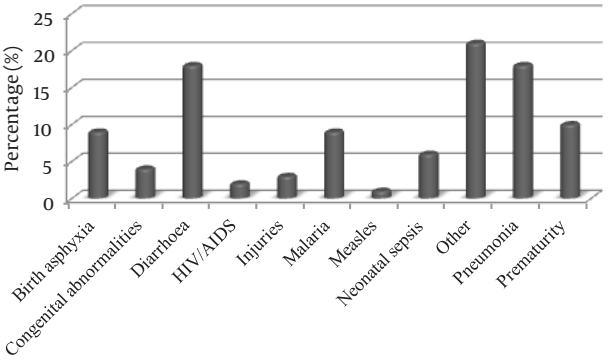

Figure 1. Causes of Child Deaths in Low-Income Countries

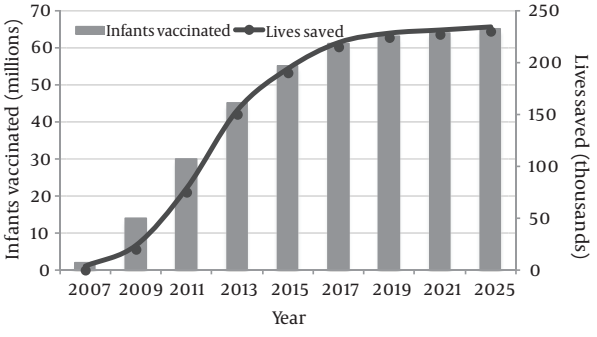

Figure 2. Potential Lives Saved by Rotavirus Vaccination (Modified Path et al. 2009 (80))

Table 2. Main Pathogens Responsible for Acute Diarrhoea[a]

	Responsible for 20% of All Types of Diarrhoea
Bacteria	
Aeromonas hydrophila	Aerobic bacillus Gram-negative. which is likely but not universally, accepted causes of acute diarrhoea.
Campylobacter jejuni	Persist a long-time in the intestine, cause recurrent diarrhoea and often the traveller's diarrhoea with *Salmonella* is the principal cause of diarrhoea.
Clostridium difficile	Saprophyte that give virulence as a result of antibiotic or immunosuppressive therapy.
Escherichia coli	EAEC (enteroaggregative, 0104: H4 serogroup, gained foreign genetic material including Shiga toxin and aggregative-adherence fimbriae), EHEC (enterohaemorrhagic, 0157: H7 serogroup, in 10% of young people, leads to hemolytic-uremic syndrome CHUS) by Shiga-like-2 toxin), EIEC (enteroinvasive), EPEC (enteropathogenic), ETEC (enterotoxigenic).
Salmonella species	*S. choleraesuis*, *S. enteritidis* (with more than 1000 strains responsible for minor Salmonella diseases).
Shigella species	*S. dysenteriae*, *S. sonnei*, *S. flexneri*, *S. bovdii* release Shiga toxin, which is cytotoxic and neurotoxic that causes watery diarrhoea may progress to bloody diarrhoe.
Vibrio cholerae	Often fatal for the rapid and severe depletion of volume. Today much less frequent, but is a potential for epidemic spread.
Yersinia enterocolitica	Can cause chronic forms with abdominal pain, like appendicitis, with or without blood.
Fungi	Responsible for 1% of all diarrhoea.
Candidia spp.	Often after antibiotic or immunosuppressive therapy or in preterm infants or in neonate.
Parasites-Protozoa	Responsible for 9% of all diarrhoea.
Cryptosporidium parvum/ hominis	Encrypt sporidiosi. Frequently asymptomatic. Affects small intestines causing mucosal damage and malabsorption.
Cyclospora	Frequent watery stools, which can be accompanied by fever and a relapsing course. Gastrointestinal tract symptoms are followed by muscle inflammation and periorbital edema.
Entamoeba histolytica	Amoebiasis. It invades the large intestine and causes bloody diarrhoea.
Giardia intestinalis	Giardiasis. It affects the small bowel and leads to acute or persistent diarrhoea with malabsorption and bloating.
Parasites-helmints	
Strongyloides stercoralis	Chronic or watery diarrhoea, abdominal cramping, failure to thrive, cachexia; fatal hyperinfection if immunity is suppressed.
Trichuris trichiura	Inflammatory damage to mucosa, diarrhoea and bloody diarrhoea, iron-deficiency anemia.
Viruses	Responsible for 70% of all diarrhoea.
Adenoviridae (DNA virus)	Adenovirus serotypes 40 and 41, III viral pathogen.
Astroviridae (DNA virus)	Human Astrovirus, frequent severe vomit ++++
Parvoviridae (DNA virus)	Bocavirus involved in many clinical manifestations, including gastroenteritis Dependovirus.
Calicivirides (RNA virus)	Noroviruses, the II pathogen after Rotavirus (4 - 19%) vomit +++ and diarrhoea Human Sapovirus, sporadic cases mainly in young children aged 5 years; transmission by the faecal-oral route.
Reoviridae (RNA virus)	Orthoreovirus, sporadic cases; respiratory infections Rotavirus A, B, C, responsible for 30 - 60% of all viral diarrhoea and diarrhoea hospitalizations. It also propagates by air. Vomit +++

[a]Intensity of vomit presented as +, slight; ++, mild; +++, moderate; ++++, severe.

Table 3. Clinical Features of Infection With Selected Diarrhoeal Pathogens (Modified WGO 2008 (11))[a]

Pathogens	Clinical Features					
	Abdominal Pain	Bloody Stool	Faecal Evidence of Inflammation	Fever	Heme-Positive Stool	Vomiting and/or Nausea
Campylobacter		O			V	O
Clostridium difficile	O	O		O	O	
Shiga toxin-producing *E. coli*			N	A		O
Salmonella		O			V	O
Shigella		O			V	
Vibrio	V	N	V	V	V	V
Yersinia		O	O		O	O
Candida	O		N			V
Cryptosporidium	V		O	V		O
Cyclospora	V			V		O
Entamoeba histolytica	O	V	V	O		V
Giardia	O			N		V
Norovirus	V			V		O

[a]Common: O-occurs, V-variable. Not common: A-atypical, N-often not.

Table 4. Microorganisms and Frequency of Symptoms

Microorganisms	Incubation	Duration	Vomiting	Fever	Abdominal Pain
Bacteria					
Aeromonas species	None	0 - 2 [a]	+/-	+/-	No
Bacillus species	1 - 16 [b]	1 - 2 [c]	Yes	No	Yes
Campylobacter species	2 - 4 [c]	5 - 7 [c]	No	Yes	Yes
Clostridium difficile	Variable	Variable	No	Few	Few
C. perfringens	0 - 1 [c]	1 [c]	Mild	No	Yes
Enterohemorrhagic *E. coli*	1 - 8 [c]	3 – 6 [c]	No	+/-	Yes
Enterotoxigenic *E. coli*	1 – 3 [c]	3 – 5 [c]	Yes	Low	Yes
Listeria species	20 [b]	2 [c]	Few	Yes	+/-
Plesiomonas species	None	0 - 2 [a]	+/-	+/-	+/-
Salmonella species	0 - 3 [c]	2 - 7 [c]	Yes	Yes	Yes
Shigella species	0 - 2 [c]	2 - 7 [c]	No	High	Yes
Staphilococcus aureus	2 - 6 [b]	1 [c]	Yes	No	Yes
Vibrio species	0 - 1 [c]	5 - 7 [c]	Yes	No	Yes
Yersinia enterocolitica	0 - 6 [c]	1 - 46 [c]	Yes	Yes	Yes
Fungi					
Candida	0 - 1 [c]	1 [c]	No	No	Few
Parasites					
Cyclospora	1 [a]	Up to 2 [d]	+/-	Yes	Yes
Giardia	10 [c]	10 - 14 [c]	No	No	Yes
Viruses					
Norovirus	12 - 48 [b]	2 - 5 [c]	Yes	Yes	Yes
Rotavirus	2 - 4 [c]	Variable	Yes	Yes	Yes

[a]Values unit is week.
[b]Values unit is hour.
[c]Values unit is day.
[d]Values unit is month.

Table 5. Rehydration Compounds on the Worldwide Market (Modified Caramia et al. 2009 (9))[a]

	Glucose mmol/L	Na mEq/L	K mEq/L	Cl mEq/L	HCO_3 o Citrate mEq/L	mOsm/L	Kcal/L	Aroma	Probiotics
ESPGHAN (1989/97)	74 - 111	60	20	> 25	20	200 - 250	52 - 80	No	No
WHO (1984/2002)	110/75	90/75	20	80	30/C.8 - 12	311/245	80	No	No
AMESOL	111	90	20	60	9	245	80	Lemon	No
DICODRAL	111	30	20	40	10	211	80	No	No
DICODRAL 60	90	60	20	37	14 citrate	211	80	Banana	No
DICODRAL FORTE	111	90	20	80	30	331	80	No	No
FLORIDRAL	83	60	20	37	14 citrate	214	80	Banana	LGG CFU = 5×10^9
GES 60	108	60	20	50	14 citrate	270	80	No	No
IDRATON 245	75	75	20	65	10 citrate	245	79.1	Orange	No
IDRAVITA	120	60	20	50	10 citrate	230	80	Banana	No
PREREID®	77	50	20	40	10	200	79.35	Citrus	No
PREREID® LIQUID	1.91	50	20	57	66	230	80	Citrus	No
REIDRAX	75	60	20	60	10 citrate	225	60.8	No	No
REUTERIN BRICK	61	58.5	19.2	44.3		230	45	Apricot	*L. reuteri* DSM 17938 CFU = 10^8
REUTERIN IDRO	83	61	20	46	11	220	60	No	*L. reuteri* DSM 17938 CFU = 10^8
Home solution	Water 1 liter, Sugar 1 spoon (19 g), Salt 1 spoon (3 g), Bicarbonate one needle (0, 5 g).								

[a]CFU, colony forming units; C, chloride; ESPGHAN, European Society of Paediatric Gastroenterology, HCO, Hepatology and, Nutrition; HCO3, bicarbonate; K, potassium; L, liter; LGG, *Lactobacillus rhamnosus* GG; *L. reuteri*, *Lactobacillus reuteri*; Na, sodium; WHO, World Health Organization.

Table 6. Antibiotics Used to Treat Specific Causes of Diarrhoea

Pathogen	Antibiotic/s of Choice	Antibiotic/s Alternative
Aeromonas hydrophila	Ciprofloxacin	Meropenem
Campylobacter	Azithromycin	Erythromycin
Clostridium difficile	Metronidazole or Vancomycin	Linezolid or fidaxomicin
Cholera	Doxycycline or Tetracycline	Furazolidone or Erythromycin
***E. coli* EAEC; *E. coli* EHEC; *E. coli* EIEC; *E. coli* EPEC; *E. coli* ETEC**	Cephalosporin of III generation or Ciprofloxacin or Rifaximin	Colistin or Azithromycin or Meropenem
Salmonella	Ceftriaxone or Ampicillin	Amoxicillin or Cephalosporin of III generation or Fluoroquinolones
Shigella dysentery	Ampicillin or Ciprofloxacin	Nalidixic Acid or Fluoroquinolones
Candida	Fluconazole	Amphotericin B
Amoebiasis	Metronidazole or Tinidazole	Paromomycin
Cryptosporidium*, *Cyclospora cayetanensis	Nitazoxanide, Cotrimoxazole	Paromomycin and azithromycin
Giardiasis	Tinidazole or tazoxanide	Metronidazole
Isospora belli	Cotrimoxazole	Pirimetamina
Strongyloides stercoralis	Thiabendazole	Albendazole or Ivermectin

4. Conclusions

UNICEF and WHO published an exhaustive report on diarrhoea in 2009. This report includes a key package on diarrhoea prevention and treatments to reduce diarrhoea morbidity and mortality. The recommendations include improved access to safe water, promotion of sanitation, vitamin A and zinc supplementation, promotion of breastfeeding and treatment with ORS (76). A scale-up scenario using data from 2010 presumed a linear increase from the baseline coverage year (2010) through 2015, allowing to determinate total number and percentage of diarrhoeal deaths (Figure 3). The results of this modelling application demonstrate that diarrhoeal deaths might be decreased by at least 78% until 2015 with current available therapies.

Intensive promotion of ORS use, zinc and vitamin A supplementation and training health staff can be successful in reducing diarrhoeal deaths (76). On the other hand, fortifying and stimulating the community management of diarrhoea, superfluous and unnecessary antibiotic use can be significantly reduced.

It was shown that probiotics can be an effective supplement for diarrhoea management. It is very important and essential to prescribe strains documented to be effective, such as *L. reuteri*, *Lactobacillus* GG, *L. acidophilus*, *L. bulgaricus* and *Saccharomyces boulardii*. Moreover, the concentration has a significant relevance and it was demonstrated that a dose of 10^{10} CFU/day is effective, reducing diarrhoea duration and spreading (78, 79). Furthermore, probiotic strain alone or in combination (2 or more strains) provides significant protective effects against intestinal disorders (80).

Many studies showed that probiotics significantly reduce the risk of acute diarrhoea, antibiotic-associated diarrhoea and traveller's diarrhoea. Regarding different described approaches to control intestinal disorders, as diarrhoea, the effects exerted by different probiotics give promising alternatives, so clinicians should advise those probiotic strains proven to be efficacious in relevant patient groups and encourage further clinical research studies to define its proper place in the management of several gastrointestinal tract disorders.

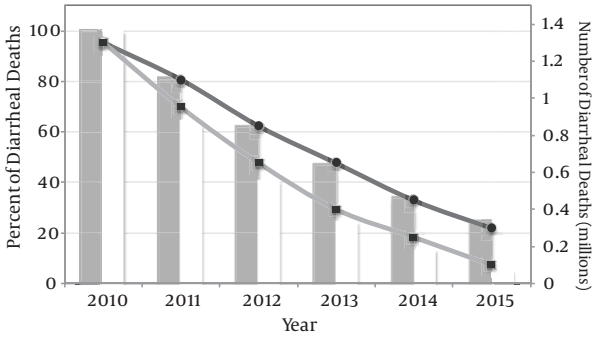

Figure 3. Trends in Percentage and Number of Diarrheal Deaths, Under Ambitious (●) and Universal (■) Scale-up Plans (Modified Fischer Walker et al. 2011 (77))

In conclusion, there are several tools to manage and reduce diarrhoea incidence such as adopting practices to decrease risk factors, using feeding guidelines (including breastfeeding) and probiotics.

Footnote

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