

Afflictions of enteric diseases in human population with reference to diarrhoea – A Review

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ABSTRACT

Diarrhoea is a worldwide profound problem for the people of all age groups including new born, young children, adults as well as old age people. About 88% of diarrhoea associated mortality is mainly attributed to poor sanitization and lack of awareness. Despite the global decline in diarrhoea associated mortality by 50% between 2000 and 2013, the disease still carries a high burden of morbidity. Commonly used treatment regimen includes the measures for preventing dehydration and use of antibiotics. Exclusive breastfeeding, vitamin A and Zn supplementation have been recommended as preventive strategies. Recently, two live oral rotavirus vaccines have been licensed in more than 100 countries, including India, which are very effective in lowering the incidence of diarrhoea and frequency of death. Treatment options for diarrhoea are ORT such as glucose-based ORS, intravenous infusions, normal saline, Zn supplementation, antibiotics, and anti-motility drugs such as loperamide hydrochloride. Efficacy of the traditional phyto-medicines is evident from long history of use of several plants to treat diarrhoea. Approximately 80% of world population relies on traditional medicines using plant extracts or their active constituents. Pre-clinical evaluations of anti-diarrhoeal activity of several medicinal plants have been extensively carried out which supports their traditional uses. However, lack of clinical data is a major limiting factor towards development of phyto-drugs against diarrhoea. Phytochemicals identification from these plants and their clinical studies are an excellent area to explore towards development of safe phyto-pharmaceuticals for management of diarrhoea and associated enteric disorders. Probiotics are also one of the safe alternative options which need to be given attention in future researches. Thorough review of different research databases was carried out and compiled to depict overview of the disease, its pathophysiology, intervention strategies, drawbacks of current treatment methods and safe alternate treatment options available against diarrhoea.

KEY WORDS: ENTERIC DISORDERS, DIARRHOEA, TRADITIONAL MEDICINE, PATHOGENS

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INTRODUCTION

Despite substantial progress in the understanding of pathogenesis and management, diarrhoeal diseases are the second leading cause of death (after pneumonia) in infants and young children, and are responsible for around 18% of all deaths, more than 5000 every day. The World Health Organization (WHO) and UNICEF have estimated that worldwide about two billion cases of diarrhoea occur annually, mostly in developing countries (Fig 1). Diarrhoea has created a massive economic burden on health services, and accounts for more than 578,000 deaths per year in paediatric patients younger than 5 years in low and middle income countries (Leung *et al.*, 2016).

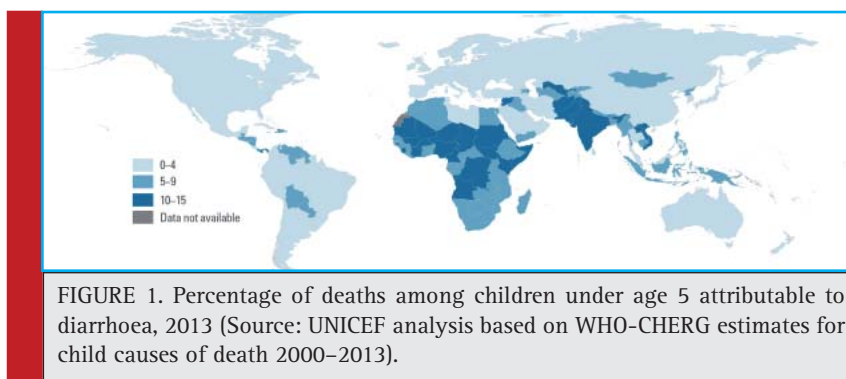
During last 15 years, various preventive and curative solutions were developed and systematically implemented worldwide to combat diarrhoeal diseases. From 2000 to 2013, significant reduction of more than 50% (from 1.2 million to 0.6 million approximately) in total annual number of deaths due to diarrhoea was observed. Oral rehydration and zinc supplementation are the key therapies which have been recommended by WHO and UNICEF for treating diarrhoea. Despite the cost effectiveness, affordability and easy implementation, oral rehydration therapy (ORT) covers only about 40 per cent of the children under 5 years of age. From 2009 - 2013, in sub-Saharan Africa and South Asian countries with most death of children attributed to diarrhoea, the percentage of children receiving ORT encompasses 36% and 38% respectively. Surveys and studies conducted during 2009-2013 shows that the countries with highest number of child deaths due to diarrhoea are having lowest number of coverage by ORT (Fig 2).

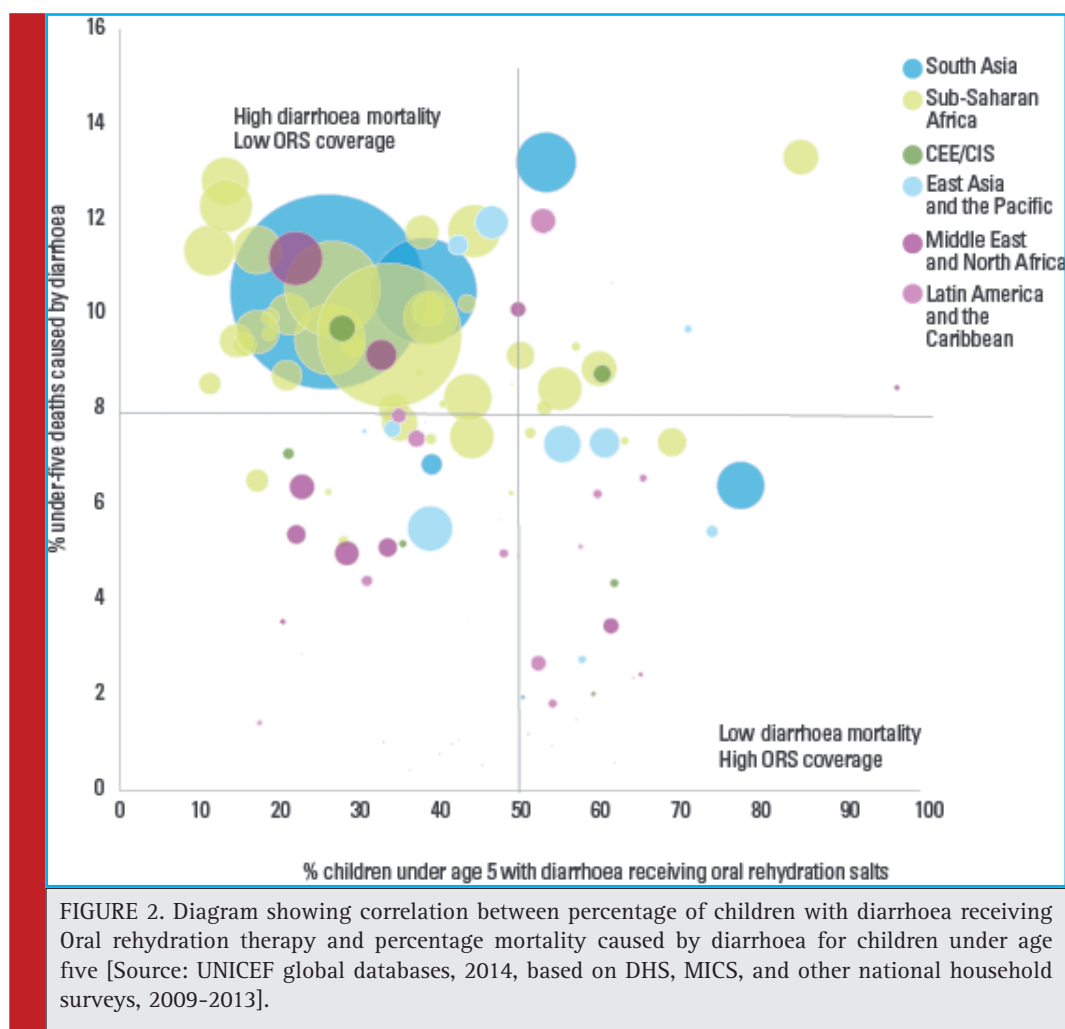
It is evident from the literature that about 78% of child deaths due to diarrhoea occur in the African and South-East Asian countries. Among 15 highest burden countries, India is grouped in top three countries with the maximum child deaths due to pneumonia and diarrhoea. Compared to developing countries, lesser number

of deaths are recorded in the less developed countries. In African, South-East Asian and least developed countries, generally children from high income family groups are more likely to receive ORT than the children from low income families. Children in low and middle-income countries have high risk of getting frequent diarrhoea epidemics (Julian, 2016).

In 2013, the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) was developed and released by the WHO and UNICEF, with an objective to eradicate the preventable pneumonia and diarrhoeal mortality in the children by 2025. WHO and UNICEF have adopted this cohesive approach because of interdependency of many of the solutions desired to combat diarrhoea and pneumonia. As per Pneumonia and Diarrhoea progress report (2014), published by International Vaccine Research Center (IVAC), India and Nigeria are the two countries with highest burden of child deaths. The slow implementation and poor accessibility of children under five to vaccination programs are key reasons for continued child deaths. About 20% of the Asian countries have introduced rotavirus vaccination programs, compared to 47% of the countries in the Africa. Various factors suggested for delayed introduction of rotavirus vaccine in these regions are poor acceptance by end users, logistic challenges and supply issues. Diarrhoeal treatment rates are far below the GAPPD target (90%) in all the 15 highest-burden countries in which coverage of Zn supplements are extremely lower than the ORS. Inclusive GAPPD intervention scores in the 15 countries having highest burden of child mortality due to diarrhoea and pneumonia, ranges from 23 to 63 per cent which is far below the set target (Fig 3).

Zinc supplementation coverage in India has increased substantially from 2005-06 to 2012-13. Goa was among the top performing states in terms of zinc and ORS coverage with GAPPD score of about 66%. According to IVAC report, 2014, overall GAPPD score in India across all the states ranged from 38 to 66% (Fig 4).





CLINICAL MANIFESTATIONS

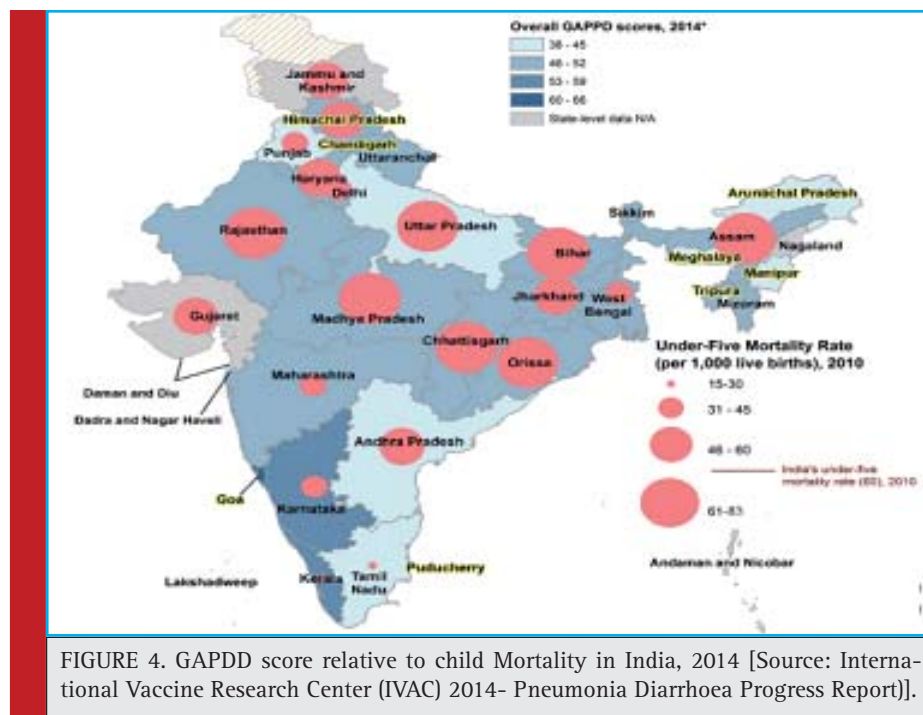
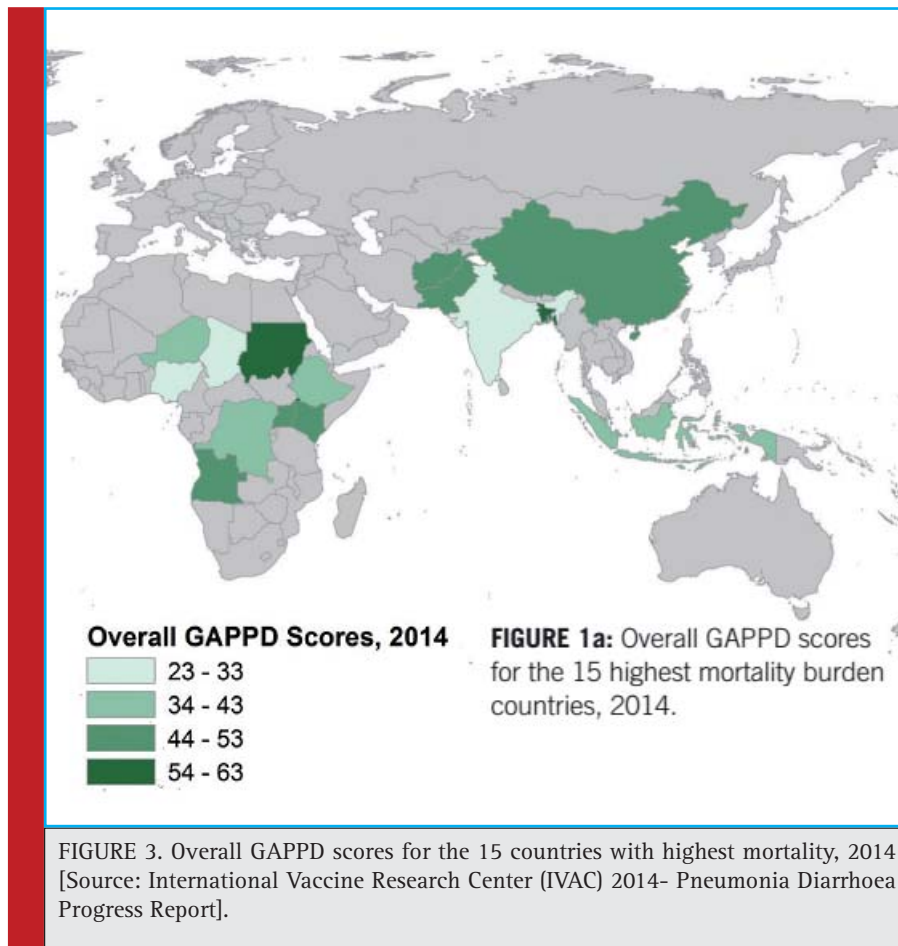
Gastroenteritis is a generic medical term for various pathological conditions of the gastrointestinal tract. The primary indication of gastroenteritis is diarrhoea; which may be generally accompanied by mild abdominal pain, nausea and vomiting. Diarrhoea gets more complicated due to occurrence of other gastrointestinal tract syndromes such as emesis, abdominal pain and distension (China, 2005). Diarrhoea, as defined by WHO, is having three or more stools per day, or having more stools than is normal (Ahs et al., 2010). There are several causes for diarrhoea which includes overeating or eating unhealthy food, inadequate personal hygiene, food putrefaction in intestine, nervous irritability, microbial fermentation due to inadequate digestion of carbohydrate, intestinal infection, overuse of antibiotics, drug reaction, food intolerance and excess ingestion of purgatives. (Tarricone et al., 2016, McQuade et al., 2016).

Rotavirus is the leading cause of severe diarrhoea in children across the globe (Bahl et al., 2005, Kumar et al.,

2016). A wide variety of protozoans inhabits human intestinal tract, but majority of them are non-pathogenic or cause very mild diseased condition. Virulent strains including *Entamoeba histolytica*, *Giardia*, *Cryptosporidium parvum*, *Cyclospora* species and microsporidia (Hashmey et al., 1997) contributes to very less percentage (0-12%) of acute traveler's diarrhea. However, prevalence of such infection is as high upto 30% in people with HIV or immune-compromised individuals (Ericsson et al., 2001). The microbial species causing intestinal diseases include *Shigella*, *Bacillus*, *Vibrio*, *Salmonella*, *Listeria*, *Escherichia*, *Clostridium* (Hosokawa et al., 2016, DeMeo, 2016).

PATHOPHYSIOLOGY OF DIARRHOEA

Absorption and secretion of ions and solutes is the fundamental process taking place throughout the length of intestine, starting from duodenum to distal part of colon. Secretion process takes place through a cyclic AMP-dependent chloride channel, also known as cystic fibrosis trans-membrane conductance regulator (CFTR),



present in the apical or luminal membrane of crypt epithelial cells. The channel regulates secretion of Cl^- into the lumen which leads to movement of Na^+ through creation of electric potential. The osmotic gradient created by net movement of NaCl results in the secretion of water by crypt epithelial cells (Frizzell and Hanrahan, 2012, Camilleri et al., 2016).

Pathophysiology of enteric diseases involves several mechanisms by which infectious agents interact with intestinal mucosal cells. Infection with enterotoxin producing bacteria can lead to diarrhoea through toxigenic effects or inflammation. Cholera, an infection of small intestine is caused by some strains of bacterium, *Vibrio cholera*. The disease is characterized by severe diarrhoea leading to dehydration and electrolyte imbalance. The diarrhoea symptoms are due to the secretion of toxin, known as cholera toxin (CT) by *V. cholera*. CT is an 84-kDa protein consisting of a dimeric A subunit and five identical B subunits. CT irreversibly activates adenyl cyclase resulting in increased mucosal concentration of cAMP. Increased cAMP results in the increased secretion of Cl^- into the lumen, leading to loss of water through creation of osmotic pressure (Fig 5). The toxin also mediates its effect through inhibition of NaCl absorption by decreasing the activity of NHE and Cl^- bicarbonate antiporter which leads to electrolyte imbalance. However, CT mediated toxigenic mechanism does not have any effect on glucose-stimulated Na^+ absorption, which is inhibited in case of infection with *Shigella* spp. or *Salmonella* spp. (Anand et al., 2016, Barrett, 2016).

Diarrhoeal diseases in case of enterotoxigenic strains of *E. coli* is caused by two enterotoxins, a heat-labile toxin (LT) and a heat-stable toxin (ST). Action of LT is similar to CT, which mediates its action through activation of adenylate cyclase. However, ST activates guanylate cyclase, resulting in increased mucosal cyclic GMP. cGMP has similar effects on ion transport as cAMP leading to water secretion and impaired absorption. Enterotoxin

released by rotavirus has been identified to be nonstructural protein (NSP4), which mediates its effect through impairment of lactase enzymatic activity in brush border of human enterocyte-like Caco-2 cells (Beau et al., 2007). An intact intestinal mucosa was detected in the histological analysis of proximal intestinal biopsy samples from infected individuals. Mild inflammatory infiltration into the lamina propria was also observed in infected individuals (Troeger et al., 2009).

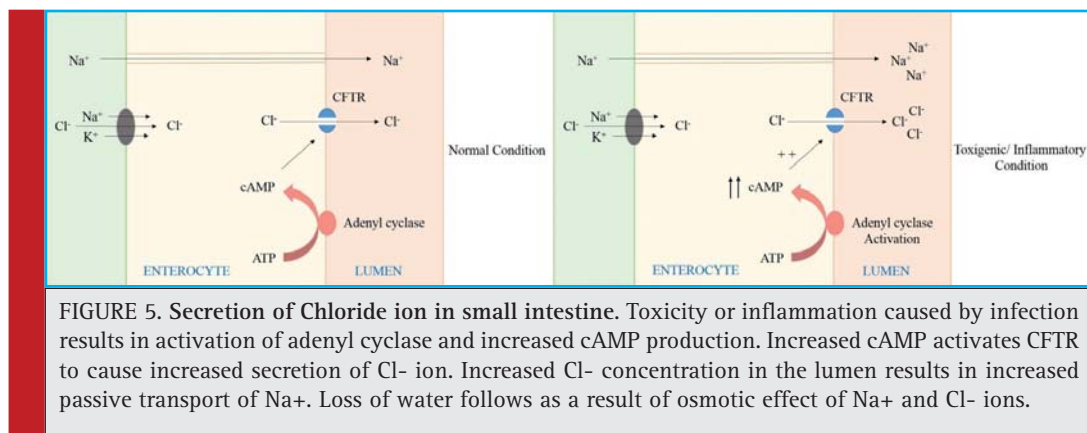
TYPES OF DIARRHOEA

Osmotic diarrhoea

Osmotic diarrhoea occurs when too much water is drawn into the lumen and happens after ingestion of large amount of poorly absorbable osmotically active solutes such as lactulose, sorbitol etc. The condition may also result when a person with a particular absorption defect ingests such nutrients. Examples include lactose intolerance in lactase deficient individuals, mal-digestion in case of pancreatic insufficiency and hydrolysis of unabsorbed carbohydrates into short chain fatty acids, which exceed beyond the absorptive capacity of the colon.

Secretory diarrhoea

Secretory diarrhoea results due to overstimulation of intestinal tract's secretory capacity or due to inhibition of absorption. Bacterial toxins, luminal secretagogues (such as bile acids or laxatives), reduced absorptive surface area caused by disease or resection, circulating secretagogues (such as various hormones, drugs, and poisons), and medical problems that compromise regulation of intestinal function (Schiller, 1999) are the key factors for secretory diarrhoea. The most common example is cholera toxin that stimulates the secretion of anions, especially Cl^- ions and subsequently results in movement of Na along with water to maintain a charge balance (Thiagarajah et al., 2015).



Inflammatory and infectious diarrhoea

Gastroenteritis or infectious diarrhoea, is an inflammation of the gastrointestinal tract that comprises the stomach and small intestine. Epithelium destruction causes exudation of serum and blood into the lumen and also associated with the destruction of absorption function. In such cases, absorption of water occurs very inefficiently resulting in diarrhoea. Pathogens frequently associated with infectious diarrhea include bacteria (*Salmonella*, *E. coli*, *Campylobacter*), viruses (rotaviruses, coronaviruses, parvoviruses, norovirus) and protozoa (*Coccidia* sp., *Cryptosporium*, *Giardia*).

Diarrhoea associated with deranged motility

Disorders in motility may lead to poor absorption resulting in diarrhoea. Both increase and decrease in gut motility can lead to diarrhoea. Examples of the former are dysthyroidism (Daher et al., 2009). Decreases in effective motility in the small intestine due to large diverticula, smooth muscle damage (scleroderma, dermatomyositis, amyloidosis, muscular dystrophy, or radiation injury), or autonomic neuropathy (diabetic, idiopathic) can result in bacterial overgrowth which may lead to diarrhoea.

Genetic factors implicated in susceptibility to enteric disease

A number of studies have implicated association of genes with the susceptibility of an individual to infections with enteric disease causing pathogens. Genes associated with the susceptibility to enteric diseases have been summarized in Table 1.

Preventive interventions

Several preventive measures have been recommended by WHO on the basis of a systematic review. Exclusive breastfeeding to infants has been recommended as one of the preventive strategy for diarrhoeal disease (Shah et al., 2012). Breast milk contains several antimicrobial factors and exclusive breastfeeding excludes the consumption of contaminated food and water. It has been reported that breastfed children below age 6 months are 6 times less likely to die due to diarrhoea than other infants (Victoria, 2000). Fewer than 4 in 10 children worldwide are exclusively breastfed during their first six months of life (Unicef, 2015).

Data from 2005- 2013 for 15 highest burden countries shows that the exclusive breastfeeding percentage of infants ranges from <3% to 64%. In India, this percentage is 46% and less than GAPPD target of 50%. WHO has also recommended vitamin A supplementation for all HIV-infected and exposed infants and children aged 6 months to 5 years, in doses given every 6 months (100 000 IU for those aged 6–12 months and 200 000 IU for those aged > 12 months). Though no effect of vitamin A supplementation was observed on occurrence of diarrhoea in infants and children less than 6 months (Shah et al., 2012, Organization, 2010). Zinc supplementation (10 mg elemental Zn for 14 days for children aged 2–6 months and 20 mg/day for older children) is an important preventive measure to lower the incidence rate, mortality and morbidity associated with diarrhoea (Shah et al., 2012).

Changes in public health policy also results in significant reduction in overall prevalence of diarrhoea (Emina

Table 1: Genes implicated in susceptibility to enteric diseases

Pathogens	Genes implicated in susceptibility
Bacteria	
EAEC	IL-8 (Jiang et al., 2003)
<i>Clostridium difficile</i>	IL-8 (Jiang et al., 2006)
<i>Salmonella</i> spp.	HLA-DRB1 (Dunstan et al., 2014), TNFA, IL-12B, IL-12RB1, IFNGR1, HLA-DQB18*0201-3 allele (Dunstan et al., 2001)
<i>V. cholera</i>	O blood group (Glass et al., 1985)
Virus	
Norwalk Virus	FUT2 (Lindesmith et al., 2003)
Protozoans	
<i>Cryptosporidium parvum/ hominis</i>	DQB1*301 allele, DQB1*301/DRB1*1101, HLA class 1B*15 (Kirkpatrick et al., 2008)
<i>Entamoeba histolytica</i>	DQB1*0601/DRB1*1501(Duggal et al., 2004)

and Kandala, 2012). A median reduction of 55% (range 20–82%) in child mortality was observed with improved access to sanitation facilities. Effective immunization with the vaccines can have major impact on diarrhoea mortality in developing countries. Since 2009, the WHO has recommended inclusion of rotavirus vaccine in all the national immunization programmes. The diarrhoeal disease caused by the rotavirus kills about 500,000 children annually; of which more than 85 per cent deaths are from developing nations. (Verma *et al.*, 2012).

Recently, two live oral rotavirus vaccines (one derived from attenuated human strain of rotavirus and second contains five bovine-human reassortant strains) have been licensed in more than 100 countries, including India, which are very effective in lowering the incidence of diarrhoea and frequency of death (Morris *et al.*, 2012, Glass *et al.*, 2006). Eighty one countries have introduced Rotarix or RotaTaq rotavirus vaccines into their national immunization program (Burnett *et al.*, 2016, Kuate Defo and Lee, 2016).

There is, however, a significant debate on the introduction of such vaccines in India, mainly because of their high costs. Killed whole cell vaccines are being used for vaccination for cholera. Both oral and injected vaccines are safe to use and effective for up to two years after single dose and three to four years after annual booster dose (Sinclair *et al.*, 2011, Graves *et al.*, 2010). Killed whole cell oral cholera vaccine (Dukoral®) is recommended to combat the infections due to Enterotoxigenic *Escherichia coli* (ETEC) bacteria, common cause of travelers' diarrhoea in the adults and children in developing countries. It contains a recombinant B subunit of cholera toxin and is similar to heat labile toxin of ETEC. However, an assessment of twenty four randomized controlled trials (RCTs) was carried out which indicated lack of sufficient evidences for use of Dukoral® for protecting travelers' against ETEC diarrhoea (Ahmed *et al.*, 2013). Several whole cell oral cholera vaccines have been tested and found to be effective against diarrhoea (Desai *et al.*, 2015, Baik *et al.*, 2015, Desai *et al.*, 2016a, Desai *et al.*, 2016b).

Treatment methods

WHO has recommended following strategies for the treatment of diarrhoea:

Oral and Intravenous Rehydration therapy

The introduction of ORT has played a crucial part in reducing the mortality rate due to diarrhoea. For more than 35 years, WHO and UNICEF have recommended a single formulation of glucose-based ORS to prevent or treat dehydration, irrespective of the cause or age group. Administration of appropriate solutions by mouth, is now routine therapy for managing diarrhoea. Modified

ORS such as polymer-based ORS is found to be better than the standard one, due to its cost effectiveness in managing acute gastroenteritis and also reduces hospitalization requirements in both developed and developing countries (Suh *et al.*, 2010). Apart from oral rehydration therapy, a number of solutions for intravenous infusions are also available including Ringer's Lactate Solution (also called Hartmann's Solution for Injection) and Ringer's lactate solution with 5% dextrose. Normal saline (isotonic or physiological saline) is also an acceptable solution, however it does not contain a base to correct acidosis and does not replace potassium losses.

Zinc Supplementation

Use of Zinc has been recommended by WHO for the treatment of children with diarrhoea. Zinc supplementation is recommended for a period of 10–14 days, with increased fluids and continued feeding, for all HIV-infected and -exposed children with diarrhoea (10 mg per day for infants under 6 months of age, 20 mg per day for infants and children over 6 months) .

Antibiotic treatment

Antibiotics aim at treating dehydration, shortening the length of illness and reducing the infection period (Allen *et al.*, 2003). Formerly used antibiotics such as ampicillin, doxycycline, and trimethoprim-sulfamethoxazole for the treatment of traveler's diarrhoea have become less effective because of increasing microbial resistance. Loperamide is the agent of choice for antimotility in the adults but not in children below 2 years of age. Ciprofloxacin and azithromycin are indicated drugs for moderate to severe disease to reduce the duration of illness. In recent times, rifaximin, a semi-synthetic, poorly absorbed, broad-spectrum antibiotic with minimal effects on gut flora, has been added for the treatment of noninvasive forms of traveler's diarrhoea (Ouyang-Latimer *et al.*, 2011).

Although antibiotics are beneficial in certain types of acute diarrhoea, these are customarily not used except in specific conditions. This is because drug resistance to human pathogenic bacteria has been frequently reported in recent years. In addition, antibiotics are sometimes associated with adverse effects on host, including hypersensitivity, depletion of beneficial gut and mucosal micro-organism, immuno-suppression and allergic reactions. Besides, antibiotics may disturb the natural balance of human intestinal tract as well as colonization resistance of the gut flora. This may lead to overgrowth of certain enteropathogens such as *C. difficile*, leading to antibiotic-associated diarrhoea (Johnston *et al.*, 2011, Hempel *et al.*, 2012).

Antimicrobials that are ineffective for treatment of Shigellosis include metronidazole, streptomycin, tetra-

cyclines, chloramphenicol, sulfonamides, amoxicillin, nitrofurans (e.g. nitrofurantoin, furazolidone), aminoglycosides (e.g. gentamicin, kanamycin), first and second generation cephalosporins (e.g. cephalexin, cefamandole). Antidiarrhoeal treatments also include adsorbents such as; kaolin, attapulgit, smectite, activated charcoal, cholestyramine, antimotility drugs such as; loperamide hydrochloride, diphenoxylate with atropine, tincture of opium, camphorated tincture of opium, paregoric, codeine and Bismuth subsalicylate. These antidiarrhoeal drugs are however not recommended for treatment due to lack of practical benefit. Resistant strains of a number of microbes including *V. cholerae*, *Shigella dysenteriae* type I, *Salmonella enterica* subsp. *Typhi*, Enteropathogenic *E. coli*, have been reported over the past few decades (Cooke and Wain, 2004, Mwansa et al., 2007).

In developing countries, the major problem with antimicrobials is the way these antibiotic therapies are used. Most of such medicines are taken without prescription and without monitoring the usage by the patients, not completing the prescribed drug regimen resulting in multidrug resistance. Another major factor contributing to increased resistance is the substandard drugs available in the market, containing doses lower than required, further predisposing the population towards increased drug resistant.

Traditional plant based medicines

Owing to the enormous clinical problems associated with diarrhoea, there is a need to develop alternative anti-microbial drugs for its treatment. Since ancient times, traditional medicines have been in use to cure several diseases (Rawat et al., 2016, Farag et al., 2016, Patel et al., 2014). In developing countries, healthcare management by the people living in rural areas depends upon use of traditional plant based medicines (Gaikwad et al., 2015, Pandit et al., 2015, Kumar, 2016).

As per WHO, approximately eighty percent of world population relies on traditional medicines using plant extracts or their active constituents (Umamaheswari et al., 2008). The biological activity of extracts, combination of extracts, fractions and compounds of several plants has been investigated against diarrhoea. These plants are reported to have anti-spasmodic effects, gut motility suppression activity, intestinal transit delay, water adsorption stimulation or reduction in electrolyte secretion. Numerous phyto-chemicals such as tannins, alkaloids, flavonoids and terpenes identified in these medicinal plants have been stated to be responsible for anti-diarrhoeal activity. Anti-microbial properties of medicinal plants are also being reported from different parts of the world (Namita and Mukesh, 2012).

Several RCTs have been conducted to evaluate the anti-diarrhoeal potential of herbal medicines. In one

of the study, compared with the patients in placebo group, patients in the group treated with Chinese herbal formulations showed significant improvement in the symptoms (Bensoussan et al., 1998). Pre-clinical safety and efficacy studies of SP-300, a standardized botanical extract formulated from the latex of *Croton lechleri* was conducted. Efficacy studies in cholera mouse model demonstrated significant inhibitory effect on fluid secretion into the intestinal lumen. The effect was found to be mediated through inhibition of cAMP mediated Cl⁻ ion secretion. Clinical studies of SP-303 was also conducted in travelers' diarrhoea. Significant reduction in diarrhoea and improvement in the subjective symptoms such as; relief from cramping and urgency was observed compared to placebo controlled group. Crofelemer, a purified proanthocyanidin oligomer from bark latex of the plant has been investigated against secretory diarrhoea. It was found that the oligomer inhibits the Cl⁻ channel with maximum inhibition of ~60% and an IC₅₀ ~7µM (Tradtrantip et al., 2010). Indigenous anti-diarrhoeal plants such as; *Acacia burkei*, *Brachylaena transvaalensis*, *Cissampelos hirta*, *Sarcostemma viminalis*, *Psidium guajava*, *Catharanthus roseus*, *Melia azedarac*, *Sclerocarya birrea* and *Strychnos madagascariensis* etc. are reported from KwaZulu-Natal Province, South Africa (de Wet et al., 2010, Offiah et al., 2011).

Holarrhena antidysenterica, *Curcuma amada*, *Ficus glomerata* and *Butea monosperma* are reportedly used for treating diarrhoeal condition by tribals from Madhya Pradesh, India (Singh and Sharma, 2011). Pharmacological activity against diarrhoea was investigated for *Acacia nilotica*, *Acanthospermum hispidum*, *Gmelina arborea*, *Parkia biglobosa* and *Vitex doniana*, the plants used for diarrhoea treatment in Kaduna State, Nigeria (Agunu et al., 2005). Randomized controlled trials for the herbs; *Curcuma longa*, *Cynara scolymus*, *Hypericum perforatum*, *Iberis amara*, *Maranta arundinacea*, *Mentha piperita*, *Paeonia lactiflora* and *Plantago psyllium* revealed that herbs are effective in management of IBS associated symptoms. However, no relief was observed in case of herbal preparations made up of *Aloe vera*, *Curcuma xanthorrhiza* and *Fumaria officinalis*. Apart from single herbs, several polyherbal preparations such as; Carmint, Padma Lax, STW 5, Tong-xie-ning and Tong-Xie-Yao-Fang (traditional Chinese herbal preparation) and DA-IBS have also been found effective in management of symptoms. STW-5 is most efficacious among these preparation, with different mechanisms of action such as anti-inflammatory activity, prosecretory activity, and effect on gastrointestinal motility (Rahimi and Abdollahi, 2012).

Antidiarrhoeal activity of *Psidium guajava* Linn. (Myrtaceae) is well studied (Salgado et al., 2006, Gakunga et al., 2013). The plant is reported to show anti-

diarrhoeal activity through several mechanisms such as; anti-microbial activity (Lutterodt et al., 1999), reduction in gastrointestinal motility (Ezekwesili et al., 2010), inhibition of adherence and invasion by pathogen (Birdi et al., 2010). Broad spectrum antibacterial properties was observed in case of *Terminalia chebula* and *Syzygium cumini*. The study revealed inhibition of multidrug resistant strain of *V. cholerae* non-O1, non-O139 (strains PC4 and PC65), *Klebsiella pneumoniae* strain PC36, *A. hydrophila* strain PC16, *Escherichia coli* strain PC80 (ETEC), *E. coli* strain VT3 (Enterohaemorrhagic *E. coli*, EHEC), *Pseudomonas aeruginosa* ATCC 15442 and *Bacillus subtilis* ATCC 6623, with MBC ranging from 0.25 to 4 mg/ml (Acharyya et al., 2009). Medicinal Plants, *Caesalpinia bonducella*, *Gardenia gummifera* and *Acacia arabica* from Melghat Forest in India, showed antibacterial potential against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Salmonella typhi*, *Shigella flexneri*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, and *Enterobacter aerogenes* (Tambekar et al., 2009).

Apart from these, several plant preparations mentioned in Ayurveda such as; Pashanbhed churna, Arjuna churna, Bilba churna, Amla churna, Gokharu churna, Panchasakar churna, Trikatu churna, Avipattikar churna, Chandanadi churna and Pushyanug churna used for treatment of various infectious diseases have been shown to possess antibacterial activity (Tambekar et al., 2010). The natural compounds have proven to be a rich source of biologically active materials. This has resulted in the development of several new lead chemicals for pharmaceuticals. The plant extracts and their phyto-constituents can therefore be utilized as an alternative to antibiotics and other medicines for treatment of enteric infections and diseases caused by microbes. The plant based medicines though considered to be safe for human consumption also presents with the problem of drug resistance, known as herbal antimicrobial drug resistance (HADR), with cases of resistance observed in case of a number of clinical and non-clinical isolates (Kavanaugh and Ribbeck, 2012, Pattiyathane et al., 2009, Vadhana, 2015).

Probiotics

Probiotics, are live organisms which when consumed in adequate amount confer a health effect on host (Hotel, 2001). There is mounting evidence that several defined strains of non-pathogens such as; *Lactobacilli* and *Bifidobacterium* are safe for human consumption and beneficial for prevention and treatment of acute infectious diarrhoea (Allen et al., 2010, Johnston and Thorlund, 2009) as well as antibiotic associated and travelers' diarrhea by restoring the natural balance in the intestinal tract. Culturelle, one of the probiotics, reduced the inci-

dence of diarrhoea by 41% in one of the study. The daily dose for Culturelle is one pill containing 10 billion CFU.

There are no reports suggesting its significant side-effects except for the rare cases of people having compromised immune systems. In one of the metaanalysis study of sixty-three randomized and quasi-randomized controlled trials, effect of probiotic agent was studied and it was concluded that the probiotics provide beneficial effects in shortening of the duration and reduction in the stool frequency in case of acute infectious diarrhoea (Allen et al., 2010). Similar results were observed in another meta-analysis study evaluating the use of probiotics for prevention and treatment of antibiotic associated diarrhoea (AAD). A total of 82 RCTs of probiotics (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus*) were analyzed. Significant association of probiotic administration with reduction in AAD was observed (Hempel et al., 2012).

SUMMARY

Child mortality due to diarrhoea in developing countries can primarily be attributed to infections caused by pathogenic microorganisms. Significant reduction in mortality has been achieved over the past 15 years by adopting simple prevention initiatives such as; better sanitization practices, encouraging longer breast feeding of infants and vaccination. Complete eradication of the diarrhoea related mortality is possible by timely management and prevention of severe dehydration associated with the disease. Oral rehydration therapy is simple and cost effective to achieve the targets. Herbal medicines and phyto-ingredients based therapeutics is well proven through scientific studies and long history of their traditional use. These potential therapeutics are economical to produce and easily accessible to the people who generally don't have easy access to antibiotics and other treatment methods. Phytochemicals therefore represent a potentially effective management strategy for diarrhoea in high risk populations.

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