Review

Diarrhoea in children: an interface between developing and developed countries

Nikhil Thapar, Ian R Sanderson

Despite much progress in the understanding of pathogenesis and of management, diarrhoeal illnesses remain one of the most important causes of global childhood mortality and morbidity. Infections account for most illnesses, with pathogens employing ingenious mechanisms to establish disease. In the developed world, an upsurge in immune-mediated gut disorders might have resulted from a disruption of normal bacterial-epithelial cross-talk and impaired maturation of the gut's immune system. Oral rehydration therapies are the mainstay of management of gastroenteritis, and their composition continues to improve. Malnutrition remains the major adverse prognostic indicator for diarrhoea-related mortality, emphasising the importance of nutrition in early management. Drugs are of little use, except for specific indications although new agents that target mechanisms of secretory diarrhoea show promise, as do probiotics. However, preventive strategies on a global scale might ultimately hold the greatest potential to reduce the burden of diarrhoeal disease. These strategies include vaccines and, most importantly, policies to address persisting inequalities between the developed and developing worlds with respect to nutrition, sanitation, and access to safe drinking water.

In the early 1980s, diarrhoeal disorders were the biggest child killers, responsible for an estimated 4·6 million deaths worldwide every year. Despite widespread use of oral rehydration therapies (ORT) and an increased understanding of the pathogenesis of diarrhoea, 2·5 million children still die from these illnesses every year, almost all of them in developing countries. This review covers the current state of diarrhoeal illnesses throughout the world, focusing on recent advances in pathophysiology, treatment, and prevention. Detailed discussions of the many causes of diarrhoea have been well reviewed in other publications.[1,2]

Definitions: acute, and chronic or persistent diarrhoea

Definitions of diarrhoea include increases in volume or fluidity of stools, changes in consistency, and increased frequency of defecation. The measurement of stool fluid content is impractical and assessment of stool frequency is preferred for diagnostic purposes. WHO defines diarrhoea as the "passage of loose or watery stools at least three times in a 24 h period", but emphasises the importance of change in stool consistency rather than frequency, and the usefulness of parental insight in deciding whether children have diarrhoea or not.[3] Blood in stool could indicate an acute diarrhoeal illnesses or dysentery, irrespective of frequency.[4,5] Diarrhoeal disorders can further be divided into acute and chronic, allowing some categorisation of causes (panel 1) and associated management. Acute diarrhoeas, the most usual form of diarrhoeal illness, have an abrupt onset, resolve within 14 days, and are mostly caused by infections. Chronic diarrhoeas last for at least 14 days.[6] Persistent diarrhoeas usually arise secondary to

Lancet 2004; **363:** 641–53

Centre for Adult and Paediatric Gastroenterology, Institute of Cell and Molecular Science, Barts and the London, Queen Mary School of Medicine and Dentistry, University of London, London, UK
(N Thapar MRCPCH (UK), Prof I R Sanderson MD)

Correspondence to: Dr Nikhil Thapar, Digestive Disease Research Centre, Royal London Hospital, Turner Street, London E1 2AD, UK
(e-mail: thaparn@doctors.org.uk)

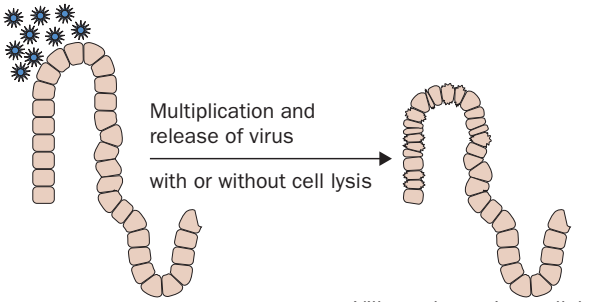
Panel 1: **Causes of acute, and chronic or persistent diarrhoeal disorders**

Acute diarrhoea
Infections
Drugs or poisons
Immediate onset hypersensitivity reactions

Chronic or persistent diarrhoea
Infections with parasites such as cryptosporidium and giardia
Other infections, usually in the presence of specific risk factors such as malnutrition, immune deficiency (including HIV, post measles), associated illnesses (pneumonia, urinary tract infections), or mucosal injury
Congenital disorders of digestion and absorption including:
Exocrine pancreatic insufficiency (eg, cystic fibrosis)
Enteropathies (coeliac disease, food allergies, autoimmune disorders)
Specific enzyme defects (sucrase-isomaltase deficiency)
Transport defects (glucose-galactose transporter)
Congenital intractable diarrhoea (microvillous inclusion disease, tufting enteropathy)
Short gut syndrome (bowel resection after necrotising enterocolitis)

Search strategy and selection criteria

We did a detailed search of MEDLINE and PubMed to identify studies about the epidemiology, pathogenesis, clinical aspects, and management of the various causes of diarrhoea in children. WHO publications and reference lists from highly regarded articles and book chapters were also searched for relevant articles. We focused on original reports published since 1998, and those associated with major breakthroughs in the pathogenesis and management of diarrhoea. Selection criteria included a judgement about novelty and importance of studies and relevance to medical doctors involved in the care of children in both developed and developing countries. In citing treatment studies, emphasis is given to those interventions with efficacy supported by at least one randomised, double blind, clinical trial. Keywords included "diarrhoea", "dysentery", and "oral rehydration therapy".



Possible mechanisms

- Absorptive capacity reduced by selective loss of mature absorptive enterocytes, cryptal secretion is increased
- Non-structural viral protein (NSP4) functioning as an enterotoxin[38]
- Stimulation of secretory and motility reflexes of the enteric nervous system via chemokine mediators
- Villous ischaemia secondary to derangement of intestinal microcirculation[34]

Figure 1: **Action of rotaviruses in diarrhoea**
Rotavirus thought to target mature enterocytes at the tips of villi in the small intestine by attachment to cell surface receptors and invasion through direct entry or Ca^{2+} dependent endocytosis.[32–35]

infections in the presence of complications such as malnutrition; whereas the remaining chronic diarrhoeas are mainly due to congenital defects of digestion and absorption. We will not separate persistent from other chronic diarrhoeas because the two often overlap.

Global burden

First estimates of the global burden of childhood mortality and morbidity became available in the early 1980s. Diarrhoeal illnesses accounted for about 4·6 million deaths from around 1 billion episodes of diarrhoea every year in children younger than 5 years.[7] As these data were emerging, WHO was coordinating the worldwide implementation of ORT.[8] A decade later, despite little change in incidence of diarrhoea, the number of deaths attributable to the disease fell to 3·3 million per year.[9] Most recent estimates suggest the number of deaths is closer to 2·5 million.[10] Diarrhoea, however, remains a prolific killer of children. Some data suggest that in children younger than 5 years it accounts for 15% of cause-specific proportional mortality and is exceeded only by perinatal causes (23%) and acute respiratory infections (18%).[11] The burden of diarrhoeal illness sits firmly in the developing world, both for morbidity (6–7 episodes per child per year compared with 1 or 2 in the developed world[12]) and mortality. Malnutrition and the wholly inadequate provision of safe water, sanitation, and hygiene highlight the stark inequalities that exist within our world. A quarter of children in developing countries are still malnourished, 1·1 billion people do not have access to safe drinking water, and 2·4 billion are without adequate sanitation.[13,14] In the developed world, deaths caused by diarrhoeal illness are rare, and the effect of these illnesses are often measured in financial terms. In US children younger than 5 years, there are about 25 million episodes of diarrhoeal illness and 200 000 hospital admissions every year,[12] accounting for 4% of all admissions (average cost US$2307) and 2% of outpatient visits at about $50 a time.[15]

Causes

So finely tuned is normal intestinal fluid and electrolyte balance that even simple changes in luminal contents can result in diarrhoea. In children, extraintestinal infections with clear foci such as otitis media and urinary-tract infections are also often associated. Possible causes are many[1,2] and we will discuss three main causes, chosen for their pathophysiological interest and their predominance in developing and developed countries.

Intestinal infections

In a multicentre European study,[16] pathogens were identified in 65% of stool samples from children with acute diarrhoea, a rate similar to that reported in developing countries.[17,18] Many viruses and bacteria

	Epidemiology		Main site of action	Primary mechanism	Clinical features and treatment
	Developed countries	Developing countries			
***E coli* type**					
Diffusely adherent (DAEC)	? Up to 10% of cases in the UK[39]	–	? Small intestine	–	Watery diarrhoea. Supportive treatment.
Enteroaggregative (EAggEC)	Rare–mostly sporadic cases	Common—persistent diarrhoea	Small intestine	Aggregating pattern of adherence to intestinal mucosa	Incubation 8–18 h. Watery mucoid diarrhoea. Bloody diarrhoea in approx 30%. Consider antibiotics for persistent cases
Enterohaemorrhagic (EHEC)	Rare epidemics in contaminated food	Rare	Colon	Elaboration of potent shiga-like cytotoxins I and II	Incubation 3–9 days. Abdominal pain, vomiting, bloody diarrhoea (90%). Haemolytic uraemic syndrome in 10%. Supportive treatment
Enteroinvasive (EIEC)	Rare—foodborne	Endemic	Distal ileum and colon	Tissue invasion and mucosal destruction	Watery diarrhoea. Occasional bloody diarrhoea requires treatment with antibiotics
Enteropathogenic (EPEC)	Very rare	Common cause of persistent diarrhoea	Proximal small intestine	Attachment/ effacement of enterocytes, alteration of intracellular calcium and cytoskeleton	Incubation 6–48 h self-limiting watery diarrhoea. Occasional fever and vomiting. Antibiotics for selected cases
Enterotoxigenic (ETEC)	Common	Very common	Small intestine	Elaboration of heat stable (ST) or labile (LT) toxins inducing secretory diarrhoea	Incubation 14–30 h. Watery diarrhoea with associated fever, abdominal cramps, vomiting. Treatment mostly supportive with antibiotics for selected cases

Table 1: **Classification of diarrhoeagenic *E coli*, epidemiology, main site of action, mode of pathogenicity, and clinical features**

pathogenic to the intestine have been identified, of which rotavirus and pathogenic *Escherichia coli* are the most common. Other important ones are *Campylobacter* spp, *Salmonella* spp, *Shigella* spp, and *Yersinia* spp. *Shigella* spp are the most important causes of acute bloody diarrhoea (dysentery) and account for about 15% of all deaths attributable to diarrhoea in children younger than 5 years.[5] *Vibrio cholerae* remains a major cause of epidemic diarrhoea, especially where sanitation is compromised after a disaster. Non-agglutinating or non-O1 strains of *V cholerae*, previously thought to be non-pathogenic, have been identified as responsible for outbreaks of diarrhoeal disease.[19]

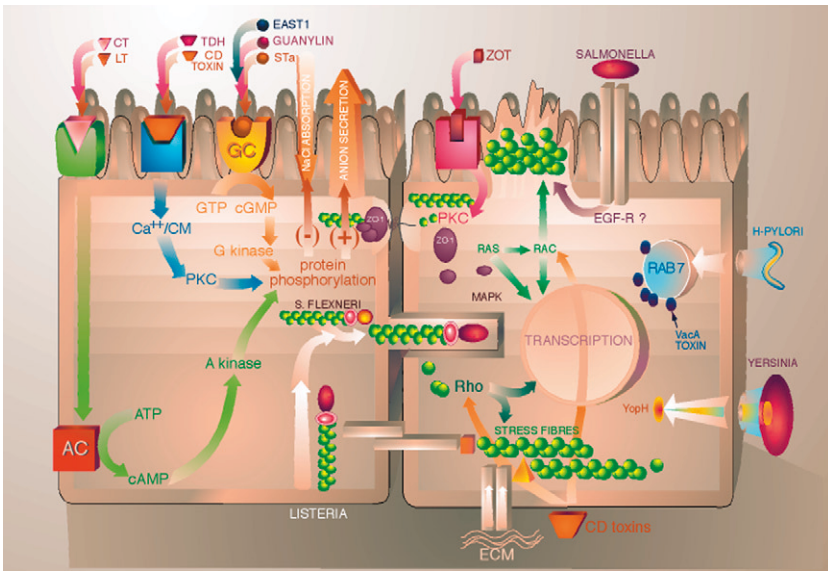


Figure 2: **Enterocyte intracellular signalling leading to intestinal secretion**
Four main pathways seem to be involved in the intestinal secretion of water and electrolytes: cAMP, cGMP, Ca, and cytoskeleton. These pathways are activated by several enteric pathogens, either directly or through the elaboration of enterotoxic products. CT=cholera toxin; LT=heat labile enterotoxin; TDH=thermostable direct haemolysin; CD=*Clostridium difficile*; EAST1= enteroaggregative *E coli* heat stable toxin 1; STa=heat stable toxin a; AC=adenylate cyclase; GC= guanylate cyclase; CM=calmodulin; PKC=protein kinase C; ZOT=Zonula occludens toxin; EGF-r=epidermal growth factor receptor; ECM=extracellular matrix. Reproduced with permission from Alessio Fasano.[42]

Rotavirus

Rotaviral infections account for up to 60% and 40% of all diarrhoeal episodes in developing and developed countries, respectively, and an estimated 870 000 deaths in children every year.[20,21] The genus Rotavirus, first identified in the duodenal mucosa of children with gastroenteritis by electron microscopy in 1973,[22] is divided into groups A–E and further into serotypes G and P.[23] Group A rotaviruses and specifically the G1, G2, G3, G4, and G9 serotypes are responsible for most infections.[24] Rotaviruses most commonly cause diarrhoea between the ages of 6–24 months, with severe infection occurring at a younger age in developing than in developed countries.[25–27] Neonatal infection is probably nosocomial and tends to be mild.[23] Children develop natural immunity after repeated exposure.[28–30] Rotavirus epidemics peak in the winter in temperate climates.[23,31] The role and action of rotavirus in diarrhoea is shown in figure 1.[32–38]

Clinically, rotavirus disease is usually mild, but severe dehydration and even death can ensue in the developing world, where malnutrition compounds the problem. The severity in certain cases underlines the potential of this virus to evoke significant watery diarrhoea very quickly.

E coli

E coli are the archetypal intestinal organisms capable of most known commensal and pathogenic interactions between intestinal microflora and host. Antigenic classification is based on somatic (O) and flagellar (H) antigens, and the diarrhoea-causing forms are categorised into six groups (table 1).[19,39] Estimates in symptomatic patients suggest a prevalence of 2–5% and 14–17% in developed and developing countries, respectively.[40]

Enterotoxigenic *E coli* (ETEC) is most commonly associated with diarrhoea[40] and it accounts for up to 70% of cases of traveller's diarrhoea.[41] Enterotoxins activate second messenger intracellular signal transduction pathways to cause secretory diarrhoea (figure 2).[42] Infection results in watery diarrhoea, which can be associated with fever, abdominal pain, and vomiting. Spontaneous recovery usually occurs within 7 days but infection can persist if nutrition is compromised.[43] Supportive treatment with rehydration is usually the only treatment required, although antibiotics such as co-trimoxazole or ciprofloxacin might be beneficial in refractory cases.[19] Use of probiotics, namely lactobacillus GG, is associated with a decreased risk of developing traveller's diarrhoea.[44,45]

Food allergies

A reproducible clinical reaction and evidence of a pathological immune reaction to ingestion of a particular food are needed before food allergies are confirmed, and they should be differentiated from food intolerances such as lactose intolerance caused by insufficient intestinal lactase. Food allergies exhibit a vastly discordant disease burden between developing and developed countries, with evidence of increasing prevalence in the latter.[46] Allergy to cow's milk seems to be the most frequent form during infancy, with a suggested prevalence of 2%;[47] peanut allergy is most common in older children.[48]

Why is food allergy so rare in developing countries? The gastrointestinal tract is continually involved in the uptake of food antigens;[49] usually there is physiological oral tolerance to non-harmful antigens and pathological sensitisation is rare. The gradual loss of oral tolerance is probably the result of disordered maturation of the gut-associated immune system that follows from a decline in microbial stimulation. Food antigens most likely to cause an allergic response include cow's milk, soya and egg proteins, and nuts. A family history of atopy and immunodeficiency is a risk factor. Food sensitive enteropathy sometimes follows an acute diarrhoeal illness.[50]

Most food allergic reactions are immediate onset (type I) or delayed onset (type IV), although type III IgG immune-complex mediated allergic reactions have been reported. Patients present with various responses from severe anaphylaxis and shock to mild manifestations of eczema or respiratory tract symptoms. Food allergies, most notably to cow's milk protein, can cause partial villous atrophy within the syndrome of food allergic enteropathy or an inflammatory colitis. Enteropathy can manifest as vomiting and diarrhoea with evidence of malabsorption and failure to thrive, and often coexists in

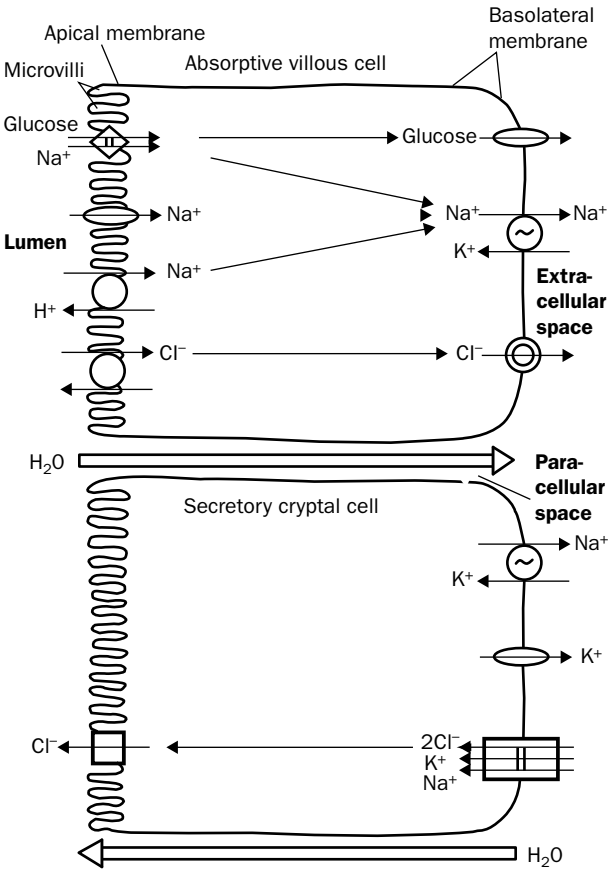


Figure 3: **Movement of water and electrolyte transport across cell membranes**
There are differences in transporters between absorptive villous cells and secretory cryptal cells.

children with colitis where bloody diarrhoea can be prominent. Recurrent abdominal pain, constipation often starting early in life, anaemia and gastro-oesophageal reflux might also be reported.

Diagnosis of allergic enteropathy relies on the presence of a reproducible history of reaction to particular foodstuffs with relapse on rechallenge after a period of elimination. Such rechallenge often requires a controlled and monitored clinical setting, but this process might not be necessary in instances of clear-cut or severe reactions. Laboratory tests (total serum IgE, specific food IgE antibodies), endoscopic appearances, and histology serve to aid diagnosis but skin prick tests do not always correlate with gut sensitivity.

Treatment is essentially by exclusion of the offending food and should be done under the supervision of a paediatric dietician. A child with more than one allergy or severe atopy might need to accept some gut symptoms to ensure adequate nutrition for normal growth. Breast milk should be continued, but mothers might need to exclude certain foods in severe allergy to prevent the transmission of food antigens. For children who are lactose intolerant or who cannot breastfeed, commercial formulae such as hydrolysates in which antigens such as cow's milk protein are modified, or elemental aminoacid feeds are available.

Drugs, beyond emergency kits for allergic reactions, have been used in difficult cases with variable success. Such treatment includes mast-cell inhibitors and antihistamine preparations. Potent immunomodulators such as steroids and immunosuppressive agents have been used in severe refractory cases.[51] Probiotics have also been shown to be useful in food allergy.[52,53] Food allergic enteropathies in children are usually transient with symptomatic improvement by the second year of life.

Toddler diarrhoea

Although the term toddler diarrhoea might not describe a very specific diarrhoeal condition, in the developed world it probably represents the most common cause of chronic diarrhoea in children aged 1–5 years.[54] The classic presentation is protracted diarrhoea in a healthy looking child who is not failing to thrive. The passage of watery offensive stool containing mucus and undigested vegetable material explains the reference to the disorder as "pea and carrot diarrhoea".

The mechanism for this illness is unclear. Parents often report a short time to the appearance of specified food materials from the latest meal. There is evidence for disordered small-intestinal motility[55] but the absence of nutritional compromise and the normal mouth-to-caecum time[56] points to disturbed large-intestinal transit.

Dietary factors implicated include carbohydrates in fruit juices and squashes. Osmotic effects directly from the ingested nutrients and fermentation by gut commensals is one possible mechanism. These drinks provide calories and often replace the recommended dietary content of fibre and fat. Parental education and dietary interventions to restore normal content and pattern of meals are often successful. Hoekstra[54] suggests adherance to the "4 Fs" (fat, fibre, fluid, fruit). Sensible restriction of fluid could help to increase appetite for a normal diet. Medication is not usually warranted.

Mechanisms of diarrhoea

In adults, the intestine handles 8–9 L of fluid every day, but normal stool fluid losses are only 150 mL,[57] underscoring the enormous absorptive capacity of the intestine. However, the intestinal lining undertakes both absorptive and secretory functions (figure 3) under the

Panel 2: Regulators of intestinal water and electrolyte transport

Stimulators of absorption
Somatostatin
Adrenaline
Noradrenaline
Neuropeptide Y
Mineralocorticoids

Stimulators of secretion
Vasoactive intestinal polypeptide (VIP)
Serotonin
Nitric oxide
Substance P
Prostaglandins
Calcitonin
Acetylcholine
Guanylin
Neurotensin

control of regulators (panel 2), and it is the balance between the two that dictates stool output. In normal circumstances, net absorption predominates. The cellular mechanisms that allow the coupled and uncoupled absorption of water with electrolytes and nutrients are shown in figure 3. This coupled mechanism requires adequate digestion of nutrients to allow the formation of molecules to which electrolyte and water absorption is coupled (eg, glucose, galactose, and aminoacids), and prevent the persistence of unabsorbable osmotically active substrates in the lumen.

Diarrhoea results when the normal balance in electrolyte and water transport is upset in favour of net secretion because of decreased absorption from the intestinal lumen or increased secretion or water loss into the lumen. Both mechanisms can coexist, exemplified in rotaviral diarrhoea where the virus targets mature absorptive enterocytes while in an effort at regeneration, immature cryptal secretory cells become prominent, driving increased secretion. Loss of brush border enzymes exacerbates malabsorption. The increased volume of luminal contents stimulates peristaltic activity, further contributing to fluid loss.

The pathophysiology of drug-associated diarrhoea is even more complex, and mechanisms include disruption of normal enteric flora by antimicrobial agents and overgrowth of pathogens, disturbance of intestinal carbohydrate and bile acid metabolism, allergic effects, toxic effects, and direct effects on motility.[58,59]

Decreased absorption of water and electrolytes

Loss of functional absorptive area

Causes of loss of functional absorptive area are shown in figure 4.[60–64] The small intestine is the most common site of disease caused by ingested pathogens and food constituents. Although idiopathic, damage like that caused by bacterial pathogens is seen in ulcerative colitis and Crohn's disease.

Decreased intraluminal digestion

Maldigestion of nutrient subtypes with secondary malabsorption is seen in exocrine pancreatic insufficiency (eg, cystic fibrosis, chronic pancreatitis) and congenital and acquired deficiencies of digestive enzymes. These enzymes are usually present in secretions into the intestinal lumen or within the brush border of intestinal epithelial cells. Abnormalities in synthesis, secretion, or deconjugation of bile salts can result in malabsorption of fats. Undigested substrates cannot take part in coupled absorption (figure 3); they remain in the intestinal lumen and give rise to osmotic diarrhoea.

Decreased enterocyte cellular absorptive function

Some substrates are absorbed via specific intestinal transporters. These substrates include glucose and galactose absorption (where one transporter is sodium glucose cotransporter, SGLT), aminoacids, triglycerides, sodium, chloride, and folate. Congenital defects in such transporters that result in osmotic diarrhoea and specific deficiency states are very rare.

Decreased intestinal transit

Some physiological states (eg, anxiety), drugs, and toxins have a direct effect on the enteric nervous system; thus, intestinal motility is increased, intestinal transit time is reduced, and there is poor absorption of water and substrates—all giving rise to diarrhoea. The responses designed to decrease intestinal transit are advantageous,

1. Decreased intestinal length. True short bowel signifies nutrient malabsorption secondary to significant loss of small intestine[60]

Necrotising enterocolitis (NEC) Volvulus Inflammatory bowel disease Tumours Radiation enteritis Hirschsprung's disease	Surgical resection of nonviable or dysfunctional bowel

2. Loss of instestinal villi and absorptive enterocytes

Rotavirus Enteric adenovirus Norwalk viruses	Lytic destruction of enterocytes often with little host inflammation
Malnutrition Zinc deficiency Vitamin A deficiency	Relative immunodeficiency and delayed intestinal repair. Substantial risk of persistent diarrhoea and mortality
Cytopathic bacterial pathogens (Enteropathogenic *E coli*, Giardia, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, Yersinia spp, enteroinvasive *E coli*).	Invasion and immune mediated destruction of enterocytes. More invasive pathogens associated with systemic manifestations[61]
Coeliac disease (gluten sensitive enteropathy)	Abnormalities in cell mediated and humoral immunity arising in genetically susceptible individuals
Autoimmune enteropathy	Associated with presence of gut auto-antibodies, usually anti-enterocyte, in the absence of an identifiable trigger[62]
Allergic (Cow's milk protein sensitive) enteropathy	Immune mediated damage resulting in partial villous atrophy
Congenital intractable diarrhoea (microvillus inclusion disease, tufting enteropathy)[64]	Likely mechanisms of enterocyte destruction are: Autophagocytosis of enterocyte apical membrane with engulfment of microvilli[63] Abnormal tufting and loss of enterocytes

3. Disruption of colonic mucosa

Salmonella spp, *Shigella* spp, *Campylobacter* ssp, enteroinvasive and enterohaemorrhagic *E coli*, *Clostridium difficile*, Yersinia and Amoeba	Invasion and destruction of host cells largely mediated by bacterial proteins. Induction of inflammatory response with mucosal ulceration and haemorrhage[19,61]

Figure 4: **Three main mechanisms for loss of functional intestinal absorptive area**

Panel 3: Four main mechanisms of epithelial disruption

Distortion of enterocyte cytoskeleton[41]
(eg, *C difficile* toxins[68] and *E coli* enterotoxins[69])

Formation of pores
(*C perfringens* enterotoxin, *Staphylococcus aureus* alpha 4 toxin)[41]

Effects on protein synthesis
S dysenteriae and EHEC toxins;[41] NF-kB Activation[70,71] and upregulation of interleukin 8[72] in *S flexneri* infection; and staphylococcal enterotoxin A and EAEC up-regulating synthesis of proinflammatory mediators

Inflammation
Usually via upregulation of proinflammatory cytokines and infiltration by host inflammatory cells, a response that eliminates pathogens and prevents bacteraemia at the expense of damage to the mucosa. In inflammatory bowel disease, benefit to the host is not obvious[73]

however, with respect to enteric pathogens where they act to expel the noxious agents.

Increased secretion or loss of water and electrolytes into the intestinal lumen

Net increase in secretory cells

To replace loss of villous absorptive cells, intestinal crypts undergo hyperplasia and the number of immature cryptal "secretory" cells (figure 3) will increase. This cause of increased secretory loss into the intestinal lumen is noted in illnesses where there is enterocyte destruction and villous atrophy, such as viral enteritis, coeliac disease, and food allergic enteropathy.

Stimulation of secretory pathways

Most bacterial pathogens elaborate enterotoxins and the rotavirus protein NSP4 acts as a viral enterotoxin.[38] Bacterial enterotoxins can selectively activate enterocyte intracellular signal transduction, the second-messenger pathways (figure 2). Toxins may also act through cytoskeletal rearrangements, which have also been shown to regulate water and electrolyte fluxes across enterocytes.[42] Upregulation of these pathways results in inhibition of NaCl-coupled transport and increased efflux of chloride resulting in net secretion and loss of water into the intestinal lumen. Coupled transport of sodium to glucose and aminoacids is largely unaffected.[65,66] Plasma nitrate concentration as a marker of endogenous nitric oxide production is significantly higher in infectious compared with non-infectious diarrhoea.[67]

Distorted or altered epithelium

Mucosa is normally an effective barrier but any disruption can lead to increased leakiness of the epithelium, and, if severe, results in mucosal ulceration and bleeding. There are four main mechanisms of epithelial disruption (panel 3).[41,68–73]

Osmotic shift and loss of fluid across the epithelium

Malabsorption or maldigestion can result in the presence of osmotically active molecules within the intestinal lumen. These molecules draw water into the lumen at a rate directly proportional to their concentration. This fluid loss is exacerbated in the colon where bacterial digestion and fermentation propagate osmotic diarrhoea and interfere with sodium absorption, thus lowering luminal pH. The increased volume in the lumen then stimulates peristalsis. Osmotic laxatives act via this mechanism.

Effects on the enteric nervous system

The enteric nervous system, part of the autonomic nervous system, can function independently to control intestinal motility and water and electrolyte fluxes, and there is evidence that it has a role in the pathogenesis of diarrhoea.[74,75] Lundgren[74] has reviewed this evidence, using cholera toxin as a key model. Cholera toxin evokes a net fluid secretion, even though it does not reach cryptal cells or affect villous absorption when administered into the intestinal lumen, and it seems that the effect of this toxin is mediated through the enteric nervous system. Lundgren proposes a model whereby cholera toxin activates afferent neurones of the enteric nervous system by releasing 5-hydroxytryptamine (5-HT) and other peptides from mucosal enterochromaffin cells. Then, the afferent limb of the neuronal reflex is stimulated through binding to 5-HT_3 receptors. Cholinergic interneurons seem to mediate the propagation of this activation down the small intestine and the stimulation of secretion by cryptal cells via vasoactive intestinal peptide (VIP). Such peptides could bind to receptors to activate second-messenger systems and induce secretion.

Management

Although not discussed here, the importance of careful clinical examination of the child, especially the assessment of dehydration, cannot be overstated. Clinical evaluation is systematically covered in publications by WHO and others.[76,77]

In view of the natural history of most acute diarrhoeas, management is supportive until the mucosa heals. This support almost always includes fluid therapy and nutrition with the objectives of preventing dehydration if there is no sign of it, rehydrating a dehydrated child, and preventing nutritional damage by feeding during and after diarrhoea.

Fluid therapy

In the developed world, most children with an acute episode of self-limiting diarrhoea will have only mild to moderate fluid loss. These cases often require little intervention except an emphasis on ordinary oral fluids and a simplification of diet. Attempts to switch fluids to standard oral rehydration formulations are usually met with refusal and upset, further increasing parents' anxiety. Some children have substantial fluid loss, especially with vomiting. As clinical deterioration ensues, children are less likely to voluntarily seek fluids and dehydration is exacerbated. In the developing world, malnutrition and coexisting diseases delay recovery and put children with persistent diarrhoea at highest risk.[78,79]

ORT was probably the greatest medical innovation of the 20th century, providing an example of the transfer of technology from developing to developed countries.[12,80] ORT solutions contain specific concentrations of sodium, glucose, potassium, chloride, and alkali (bicarbonate or citrate) in water. The rationale for this treatment stems from the observation that in most causes of acute infectious diarrhoea, including cholera, the coupled transport of sodium to glucose or other solutes (figure 3) is largely unaffected.[65,66] By the 1970s, studies that showed the value of ORT in children with acute diarrhoea of varying causes, led WHO to recommend its use for diarrhoea of any cause in all age-groups. Access to and use rates of ORT rose from almost zero in 1979 to 80% by 1995.[81] During this same period, although diarrhoea-

related morbidity had hardly changed, the number of deaths in children younger than 5 years fell by about 2 million.[7,82] Victora and colleagues[8] explored whether this change was attributable to ORT or merely reflected a global trend secondary to other concurrent interventions. On the basis of correlations between the start of national control of diarrhoeal disease programmes and the decline in diarrhoea-related deaths, they concluded that ORT had contributed substantially to the reduction in childhood death due to diarrhoea. Pierce[81] notes that the other interventions promoted by national diarrhoea programmes, such as continued feeding, breastfeeding, access to clean water, and use of antimicrobials in dysentery, could also have had an important effect on death rates, and that the individual contribution of these factors remains to be determined.

ORT composition

ORT concentrations were derived to promote optimum cotransport of sodium by presenting equimolar concentrations of sodium and glucose, and to ensure adequate replacement of potassium, chloride, and bicarbonate. The initial formulations, based on work with cholera patients, contained 90 mmol/L of sodium with an osmolarity of 310 mOsm/L. Concern that such formulations might be inappropriate for all forms of acute diarrhoea, especially in developed countries where water and electrolyte losses and malnutrition were unlikely to be of the same order as that seen in developing countries, prompted the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) to recommend a 60 mmol/L sodium, hypo-osmolar solution.[83] Hahn and colleagues'[84] meta-analysis of studies of reduced osmolarity ORT solutions showed that children who were admitted to hospital and received reduced osmolarity ORT had reduced stool output, less vomiting, and less need for intravenous infusions than did those who had the standard WHO solution, with no significant difference in the rate of hyponatraemia.

WHO now recommends a single oral rehydration solution of intermediate sodium content (75 mmol/L), but it has published ranges of safe and effective concentrations.[85] Hahn's analysis did not specifically address childhood cholera. Data in adults suggest that both formulations are equally effective but that hyponatraemia, albeit asymptomatic, arises more frequently in patients given the hypo-osmolar solution.[86] More information on the use of reduced osmolarity ORT in children with cholera is needed before the standard WHO recommended doses are abandoned.

Home-made fluids and cereal-based oral therapies have proved effective in diarrhoeal dehydration, more so in high output diarrhoeas, such as cholera, than in non-cholera diarrhoea.[87–91] Cereals include rice, maize and wheat, and ready-to-use powders in place of raw ingredients have simplified the preparation of these formulations. The hunt for the ideal ORT solution is still underway. Researchers in a study of non-absorbable amylase-resistant starches added to ORT solution noted that this preparation was associated with less faecal fluid loss and duration of diarrhoea in children and adults than were ORT alone or ORT in combination with rice or amylase degradable starch.[92] Non-absorbable starches are fermented in the colon to short-chain fatty acids able to enhance sodium and water absorption.

Poor uptake of ORT remains a major concern.[13,93] Studies from India and Bangladesh suggest use rates below 20%.[94,95] Even in developed countries, the use of inappropriate fluids or regimens for hydration is still widespread.[96,97]

Management of ORT

ORT by mouth or via nasogastric tube has been shown to be as effective as intravenous fluid in the treatment of even severe dehydration,[98] although the intravenous route is recommended in the presence of shock. Colloids such as modified fluid gelatin or albumen are traditionally used to correct intravascular hypovolaemia but crystalloids are very effective too, and even dextrose-containing intravenous fluids can be used in an emergency. Monitoring of serum electrolytes is essential when using intravenous fluids for resuscitation or fluid maintenance. In all other cases of acute diarrhoea, and after correction of hypovolaemia or shock, ORT should be instituted as early as possible. The aim is to rehydrate within 4 h of presentation, and then maintain hydration until recovery.[3,99] There are special considerations in rehydrating severely malnourished children.[76] Total parenteral nutrition is necessary where intestinal failure is present (eg, tufting enteropathy and short gut syndrome).

Nutrition

Malnutrition is an adverse prognostic indicator for diarrhoea.[78,100] In up to 40% of diarrhoea-related deaths malnutrition is associated with prolonged diarrhoeal episodes.[79] In developing countries, where recurrent diarrhoea is common, a vicious cycle of diarrhoea and undernutrition is set up, with dire consequences. Once it became clear that ORT had an important effect on outcome, the rationale for withholding food during diarrhoeal episodes became less clear. Cereal or food-based oral rehydration solutions provided some hope of addressing nutrition and rehydration at the same time, but they are more complicated to prepare than food in normal diets. Furthermore, they are of doubtful value if solid food can be tolerated.

Early refeeding and continued breastfeeding are both desirable[3,101] and feasible, because some absorptive and digestive capacity is retained during diarrhoea.[101] Early refeeding after initial rehydration is safe, well tolerated, and clinically beneficial.[102–105] An ESPGAN study suggested that resumption of the normal premorbid diet, including lactose, after early rehydration improved recovery weight gain and was not associated with worsening of symptoms or prolongation of diarrhoea.[106] Postenteritis syndrome with acquired intolerance to cow's milk protein does exist but seems to have become less important, possibly because of the shift of emphasis towards a refeeding diet rather than milk feeds. Routine dilution of cow's milk formula in infants younger than 6 months who are solely milk-fed does not seem to convey any clinical benefit.[107,108] Caution with early refeeding, however, is advised in this age group and in children with severe diarrhoea.[109] In developed countries, the premorbid state of nutrition is likely to be normal, but malnutrition in developing countries is associated with marked structural changes in the gut[110] so refeeding might be expected to be less successful. However, the limited data available suggest that severe cases of persistent diarrhoea can be safely and effectively treated with locally available diets.[111]

Breastfeeding

In 1985, Khin and colleagues[112] reported that continued breastfeeding during infant diarrhoea reduced diarrhoeal losses and requirements for oral rehydration. This finding has been confirmed by results from other studies, including data suggesting that non-breastfed infants are 14–25 times more likely to die from diarrhoea than are infants who are exclusively breastfed.[113,114] Breastmilk contains many protective factors that act at the intestinal

Pathogens	Particular group of patients	Suggested antibiotics
Campylobacter spp	Severe dysentery/systemic symptoms/ immunocompromised	Macrolides/quinolones
Salmonella spp	Enteric fever, immunocompromised and infants under 3 months	Chloramphenicol, ampicillin, TMP-SMX, 3rd generation cephalosporins, quinolones
Enteroinvasive and enteropathogenic *E coli*	Severe dysentery and prolonged diarrhoea	TMP-SMX, quinolones
Shigella spp	Severe dysentery	Nalidixic acid, TMP-SMX, quinolones
C difficile	Diarrhoea severe or non-responsive to withdrawal of causative antibiotic	Metronidazole, vancomycin
V cholerae	Severe cases	Tetracycline, TMP-SMX, macrolides, quinolones
Giardia lamblia		Metronidazole
Entamoeba histolytica		Metronidazole

TMP-SMX=trimethoprim-sulphamethoxazole (co-trimoxazole).

Table 2: **Infectious causes of diarrhoea in which antibiotics may be useful**[19,126,127]

mucosal surface to prevent microbial infection and enhance development of the immune system.[115] Evidence strongly supports the promotion of breastfeeding for the first 4–6 months of life and its continuation during diarrhoeal illnesses.

Micronutrients and vitamins

In view of the association between poor nutrition and recurrent diarrhoeal illness, it is not surprising that many of these unfortunate children show deficiencies in vitamins and trace elements.[116] Zinc and vitamin A are especially relevant to diarrhoea. Zinc has important roles in immunity and wound healing and vitamin A participates in the maintenance of epithelium.[117] Zinc supplementation of children who are malnourished or zinc deficient reduces the incidence, frequency, severity, and persistence of diarrhoeal illnesses.[118–121] The effects seem independent of vitamin A[118–120,122] although deficiencies often coexist and zinc is involved in the release of vitamin A and production of retinol-binding protein. There is conflicting evidence about the efficacy of simultaneous supplementation of zinc and vitamin A in children with diarrhoea.[116,118] The benefit of vitamin A supplementation alone is more modest than that of zinc supplementation.[123,124]

Drugs

Use of drugs is largely limited to the treatment of specific congenital and chronic diarrhoeal disorders and is not recommended for routine treatment of acute infectious diarrhoea. Despite widespread dissemination of this message, drugs are still often prescribed for acute diarrhoea. Mittal and Mathew[125] argue that in addition to exposure of children to potential toxic effects, this practice diverts attention from ORT and appropriate feeding. Results of various studies across the world show that antidiarrhoeal drugs, including antimicrobials, were prescribed in up to 94% of children with diarrhoea. Physicians who defend this practice refer to parental pressures to prescribe drugs, beliefs that drugs are effective in diarrhoea, and concerns about the efficacy of and compliance with ORT. Furthermore, drugs are easy to prescribe and there is a tendency to extrapolate adult treatment regimens to children.

Antibiotics

Antibiotics eliminate pathogens and limit their carriage and systemic effects; however, in most diarrhoeal illnesses they do not alter the disease substantially, and in some, such as infection with *E coli* O157:H7, they make matters worse.[19] Their main use remains in the management of dysentery. Table 2 summarises infections for which antimicrobials might be useful, but this does not mean that they should be used in every case.

Motility and other antidiarrhoeal agents

This group of drugs includes loperamide, opiates, bismuth subsalicylate, kaolin, smectite, and anticholinergic medications. Although some data exist for their efficacy, side-effects are substantial or effects are not reliable. None of these medications is recommended for use in children with acute diarrhoea.[125,128,129]

Immunomodulators

These agents modulate harmful and disordered immune responses, and include steroids and immunosuppresants such as azathioprine, ciclosporin, and methotrexate. Uses include severe enteropathies secondary to food allergy and autoimmunity and idiopathic inflammatory bowel disease.

Novel agents for secretory diarrhoea

Research on the interaction of enterotoxins with enterocytes and the enteric nervous system has yielded possible targets for pharmacological therapy to inhibit the augmented secretion or return the intestine to a net absorptive state.[74,75]

5HT-receptor antagonists reverse the fluid and chloride secretion seen with cholera toxin and these receptors could act as potential targets in diarrhoea. However, other bacterial enterotoxins do not seem to use 5-HT pathways, and the receptor antagonists have little effect once the secretory state is established. Sigma receptor agonists (eg, igmesine) seem to reverse effects of VIP and reduce the secretion induced by both cholera toxin and *E coli* enterotoxins. Enteric nerves have sigma receptors.

Somatostatin analogues such as octreotide are thought to function in the treatment of neuroendocrine tumours (eg, vipomas) by inhibiting the release of secretogogues such as VIP and 5-HT. They also seem to be effective without measurable reductions in VIP, suggesting direct effects on the enteric nervous system or enterocytes. Furthermore, somatostatin is present in neurones of the enteric nervous system thought to be proabsorptive. The enkephalinase inhibitor racecadotril prevents the rapid degradation of endogenous enkephalins, which act as proabsorptive preganglionic neurotransmitters in the enteric nervous system right down to the level of enterocytes, and are able to reduce cholera toxin induced secretion. Racecadotril has been shown to be effective in the clinical management of acute diarrhoea in children.[130–132]

Enzyme supplementation

Cystic fibrosis and chronic pancreatic disorders result in decreased intraluminal digestion secondary to deficiencies in digestive enzymes, and in these conditions enzyme supplementation is required.

Binding and replacement of bile salts

When bile salts are not reabsorbed in the distal ileum, as happens in congenital defects in the ileal sodium-dependent bile acid transporter and, more commonly, in Crohn's disease or ileal resection, the bile pool is depleted and the non-absorbed bile salts can inhibit sodium and water absorption in the colon to cause diarrhoea. This difficulty can be prevented by bile salt binders such as colestyramine.

Special diets

Specific food allergies, congenital transport defects, and coeliac disease will require specific avoidance or elimination diets,[133] but care must be taken to avoid compromising overall nutrition and causing specific deficiencies of, for example, trace elements and fat-soluble vitamins. Some symptoms may have to be accepted if nutrition and growth are to be preserved. The use of paediatric dieticians and careful education is essential. Specific diets such as elemental and polymeric feeds in Crohn's disease are thought to act by promoting healing as well as via direct anti-inflammatory effects.

Probiotics

The intestine's complex bacterial ecosystem provides both nutritional benefit and protection against pathogens, and is vital in modulating interactions with the environment and the development of beneficial immune responses.[134–136]

Probiotics are live microbes characteristic of healthy normal human gut microflora, and include strains of lactobacillus (eg, *L rhamnosus* (lactobacillus GG), *L acidophilus*, and *L casei*), bifidobacterium (eg, *B bifidum* and *B breve*), and streptococcus (eg, *Strep thermophilus*). *Saccharomyces boulardi* is the exception, as a yeast of non-human origin.[46,137] These microbes are designed to improve intestinal microbial balance, and partake in normal bacterial-epithelial crosstalk. They create an unfavourable environment for pathogens by the production of antimicrobials, competition with pathogens for essential nutrients and binding sites in the intestinal mucosa, and the metabolism of nutrients and bile acids. The most important mechanism of probiotic action, however, relates to the development, maturation, and regulation of mucosa-associated immune defences.[46,135–137]

Results of two meta-analyses, one of which looked specifically at *L rhamnosus*, showed that probiotics reduced both the frequency and duration of diarrhoea in people with acute infectious illness.[138,139] The risk of diarrhoea of more than 3 days' duration was also significantly reduced, which is of relevance to developing countries where persistence of diarrhoea in already malnourished and dehydrated children carries substantial risks of mortality. There are data supporting a preventive role in reducing the frequency of diarrhoeal illnesses, possibly by stimulation of specific humoral responses, such as the production of specific IgA.[46] The effect seems to be most prominent in diarrhoea with a viral cause, usually rotavirus, rather than a bacterial cause. Duration of rotaviral shedding is reduced, as is gut permeability. There are increased numbers of IgA secreting cells.[46,140,141] The stabilisation of indigenous microflora by probiotics is underlined by the beneficial effects of probiotics, in conditions where the resident microflora are disturbed by environment (such as traveller's diarrhoea)[44,45] or use of antimicrobials,[142,143] irrespective of the presence of *Clostridium difficile*. *Sacc boulardi* seems to have a specific protective mechanism against *C difficile*.[144]

Probiotics might also be beneficial in several atopic disorders including food allergies and eczema.[52,53,145] Probiotics such as *L rhamnosus* seem capable of reducing the immunogenicity of food antigens by partial hydrolysis. Elimination diets for such disorders supplemented with probiotics result in substantial improvements in both clinical outcomes and markers of local and systemic inflammation. This effect could be caused, in part, by modulation of the immunological response to prevent activation of T-helper-2 cells and future IgE dominant inflammation driven by immunological memory.[46] Probiotics also seem to possess inherent anti-inflammatory components, which might be useful in both allergic disorders and inflammatory bowel diseases with or without bacterial overgrowth.[146]

Interest surrounds the use of certain nutrients such as the fructan and galactan carbohydrates, which on fermentation within the intestinal lumen seem to selectively stimulate the growth of beneficial bacteria such as bifidobacteria and lactobacilli.[147,148] These nutrients are termed prebiotics and in certain practices given routinely with probiotics to enhance efficacy. This approach might be more viable to implement on a global scale than probiotics; however, research is preliminary and more studies are needed.

However, caution should be heeded: there has been an explosion of so-called probiotic preparations available for purchase, many of which are of doubtful effectiveness. Furthermore, some published studies on probiotics are partly funded by commercial companies with vested interests in the success of their products.

Prevention of diarrhoea

While prevention mainly relates to avoidance of infectious agents, it is recognised that the apparent upsurge in allergic and immune-mediated gut disorders might, ironically, be the result of an environment with fewer pathogens. With respect to morbidity and mortality from diarrhoea, the developed world has benefited enormously from substantial improvements in hygiene, sanitation, health, and nutrition with severe disease mostly confined to agents capable of adapting to or resisting these changes. In developing countries, such prevention measures are largely hindered by climatic, social, and economic factors and resultant morbidity remains high. Global discussion has done little to improve the situation, despite evidence that appropriate water, hygiene, and sanitation interventions can reduce diarrhoea incidence by 26% and mortality by 65%.[149] The situation is much the same for malnutrition, which requires an urgent and concerted action. Although research in vaccines and probiotics seems to be done mostly with developed countries in mind, findings from these areas of investigation could herald a more positive approach to diarrhoeal diseases in the developing world.

Vaccines

Significant resources are being directed to the development of mucosal immunisation against a range of pathogens responsible for infectious diarrhoea. Such vaccines would act to interfere with one or more of the pathogenic steps such as attachment, colonisation, penetration, or replication, or would block the action of elaborated toxins. However, work has been hampered by problems related to antigen delivery systems and adverse reactions in recipients.[150]

Rotaviral vaccines

Improvements in hygiene, sanitation, and access to clean water have not greatly affected the incidence of rotaviral diarrhoea, as shown by the similarity between prevalence

in developing and developed countries. Except for supportive measures, no treatment exists for rotaviral diarrhoea, leaving prevention measures such as vaccination to tackle this global disease.

The epidemiology of rotaviral infections corresponds with the loss of the passive immunity acquired in utero and progressive acquisition of protective immunity following repeated exposures thereafter. There is evidence in children and adults that rotavirus infection results in both serum and intestinal antibody responses, which protects against severe diarrhoea on reinfection. Higher serum levels of both IgA and IgG seem to be protective, and researchers have noted that patients with rotaviral diarrhoea have much lower concentrations of these antibodies.[28,30,151] In the course of immunological studies and epidemiological work, specific rotaviral epitopes (VP7 and VP4) for the production of serotype specific or cross-reactive neutralising antibodies were identified.[152] Such antibodies were shown to be protective, which has aided the progress of rotaviral vaccines including a live attenuated reassortant oral vaccine developed by Albert Kapikian of the National Institute of Allergy and Infectious Diseases.[153] In August, 1998, after a number of successful trials,[21,153,154] Rotashield, a tetravalent human-rhesus vaccine (RRV-TV), was licensed by the US Food and Drug Administration for use in the USA. It was given to about 1 million children before it was withdrawn from the market in October, 1999. Reports from early in the vaccination programme suggested an increased risk of intussusception in vaccinated children, although no deaths were reported.[155] After public-health organisations withdrew their recommendations for the vaccine, Wyeth Pharmaceuticals stopped manufacturing Rotashield. However, as the dust settled several researchers began to question the validity of the reported increased incidence of intussusception in children who had been vaccinated.[156] More importantly, the entire debate seems to have ignored the cost/benefit ratio of the vaccine. In view of the data from trials, it was suggested that the vaccine could have saved up to half a million lives every year in the developing world for one case of intussusception for every 4670–9474 infants vaccinated. Despite renewed interest in the original vaccine, it is unclear whether the manufacturers will relaunch the vaccine given its tarnished profile. Currently, trials of other rotaviral vaccines, including phase III drug trials of a human-bovine reassortant vaccine, and of attenuated human monovalent vaccine are underway.[157,159]

Bacterial vaccines

Trials are underway to assess the efficacy as vaccines of genetically modified enterotoxigenic *E coli* and *Salmonella typhi*, whose virulence genes have been deleted.

Challenges for the future

WHO predicts that there will still be about 5 million deaths in children younger than five years by 2025. 97% of these will be in the developing world and mostly caused by infectious diseases, within which diarrhoea will continue to play a prominent part.[160] In 1995, more than a quarter of children under the age of 5 years were malnourished, accounting for half of all deaths.[160] Poor hygiene, sanitation, and access to safe drinking water drive mortality even higher, representing in the developing world an unacceptable but potentially reversible struggle between life and death.

It is clear from the experience in the developed world that even if such inequalities were addressed, the burden of diarrhoeal disorders would shift, albeit positively, from mortality to morbidity. Rotaviral diarrhoea will remain a focus of prevention, with vaccines providing some hope in the ever-present struggle between humans and viruses. The new challenges of immune-related gut diseases are likely to become globally prominent with continued attention needed to focus on the interaction between host and bacteria and the evolution of immunity. Probiotics go some way to addressing this shift in disease pattern, but are unlikely to provide a magical solution on their own. The tremendous scientific inroads in molecular biology and our understanding of the mechanisms of diarrhoea are likely to be the key in advancing our progress towards preventing and treating the disease—they have already resulted in the development of novel anti-secretory agents and identification of more candidate targets.

Education of health-care providers and recipients will always remain the vital final pathway for dissemination of any interventions. Despite the benefits of ORT being known for some decades, low uptake of the therapy and widespread and inappropriate use of medication for diarrhoea remain common. Interventional programmes on local and national scales have been successful, but they need to maintain momentum to promote education.

All these challenges share one requirement—that global, economic, and political barriers are lifted to allow the most important and urgent challenges to be addressed. In view of the enormous progress that has taken place in the developed world with respect to the prevention and treatment of diarrhoeal illness, it is now unacceptable that so many people continue to die from the disease.

Conflict of interest statement

The centre for adult and paediatric gastroenterology at the authors' institution received a developmental award from Acambis, a company undertaking trials of bacterial vaccines.

Acknowledgments

We thank Paul Kelly, Barts and the London, Queen Mary School of Medicine and Dentistry, University of London, and University of Lusaka, Zambia, for helpful comments.

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