Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter 50

C. Anthony Hart

Introduction to Acute Infective Diarrhoea

Diarrhoeal disease is a major cause of morbidity and mortality worldwide. In a global estimate of causes of death in 1990, diarrhoeal disease was the fourth commonest after ischaemic heart disease (6.25 million deaths), cardiovascular disease (4.4 million) and respiratory tract infections (4.3 million).[1] It was responsible for approximately 3 million of the total 50.5 million deaths.

Although the burden of diarrhoeal disease is greatest in children under 5 years, and especially in developing countries, causing approximately 2 million deaths per annum,[2] adults and especially the elderly are also at risk. In general, viral enteropathogens are more important in childhood gastroenteritis in developed and developing countries alike, whereas bacterial and protozoal enteropathogens predominate in adults.[3]

In developing countries, estimates of the annual incidence of diarrhoea in children vary from 3.3 episodes,[4] to 7.9 episodes,[5] to 10 episodes in urban Lima, Peru.[6] In contrast, the incidence is much less in children in developed countries. For example, children in Winnipeg, Canada, were reported to experience 0.8 diarrhoeal episodes per year,[7] and the overall incidence for all ages in Holland was also 0.8 per annum.[8] The contrast between paediatric diarrhoea in developed and developing countries is shown in Table 50.1. The relative importance of the various viruses, bacteria and protozoa in developing and developed countries is shown in Table 50.2. However, it must be remembered that the relative importance of the various enteropathogens will depend on a variety of factors, including the pathogens sought and the sensitivity and specificity of the diagnostic tools used, the age group studied, the duration and season of study, geographical location, and whether the survey is hospital or community based. For example, improved diagnostic methods have increased the detection rates of astrovirus and caliciviruses (noroviruses and sapoviruses) and, in community-based studies, astrovirus, which causes a milder diarrhoea, assumes greater importance than rotavirus,[10] which is the converse to the situation in hospital-based studies. In addition to the morbidity and mortality associated with diarrhoeal disease, it is also a major drain on health resources in developing countries. For example, in Indonesia it was estimated that US$2.50 was spent per annum per child on diarrhoeal disease, against a yearly per capita health budget of US$5.41 at 1990 costs.

There are over 40 different enteropathogens able to cause gastroenteritis and even in the best-funded laboratories not all are sought. To arrive at an aetiological diagnosis in all cases is neither possible nor necessary, except for epidemiological purposes, for example when a vaccine has been introduced, or when large epidemics occur. However, it is possible to subdivide diarrhoeal disease into two major categories, inflammatory and non-inflammatory. There are of course areas of overlap, but this classification does provide a framework for discussing diarrhoeal disease (Table 50.3). In addition to those in Table 50.4, there are enteropathogens that produce vomiting with no or very little diarrhoea. This usually results from ingestion of emetic toxins liberated by certain strains of *Staphylococcus aureus* or *Bacillus cereus*.

NON-INFLAMMATORY DIARRHOEA

The pathogens causing non-inflammatory diarrhoea are shown in Table 50.4. For the majority of these, their principal site of action is the upper small intestine. Since the transit time is so rapid through the small intestine, an important pathogenic factor is the ability to adhere to the small-intestinal mucosa. The mechanisms most commonly employed in producing diarrhoea are osmotic and secretory. In the former there is an inability to degrade, for example disaccharides to monosaccharides. Since only monosaccharides can be absorbed by enterocytes, the disaccharides pass down the intestine, taking water with them. In secretory diarrhoea the enterocyte is stimulated to secrete fluid into the gut lumen.

INFLAMMATORY DIARRHOEA

Although there is some overlap (e.g. *Salmonella* spp. and *Campylobacter* spp. can both cause non-inflammatory diarrhoea), the pathogens causing inflammatory diarrhoea form a distinct group (Table 50.4). Their site of action is usually the distal ileum and colon and they produce disease by destroying parts of the enteric mucous membranes, leading to an inflammatory response. This in turn leads to the excretion of neutrophils and erythrocytes in faeces, which can be detected by simple wet film microscopy or myeloperoxidase by ELISA.

EPIDEMIOLOGICAL ASPECTS

The prevalence of different enteropathogens varies with the age of the individual, how the diarrhoea is acquired (e.g. food poisoning or traveller's diarrhoea), between acute and chronic diarrhoea, and with the state of the host's immunity (Table 50.2).

Age

In general, paediatric diarrhoea is most often due to viral enteropathogens (see Chapter 45). Up to 60% of cases in most hospital-based surveys are due to viruses, with rotavirus accounting for a large proportion of cases, followed by adenovirus 40/41 and then astrovirus, but it is now clear that noroviruses are important causes of outbreaks of disease. Bacterial enteropathogens such as enteropathogenic *Escherichia coli* (EPEC), enteroinvasive *E. coli* (EIEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAggEC), salmonellae, *Campylobacter jejuni* and shigellae and the protozoan *Cryptosporidium parvum* and *C. hominis* are responsible for the majority of the remaining cases where a pathogen is found.

In adults, bacteria assume greater importance, although viral gastroenteritis does occur, due, for example, to unusual serogroups of rotavirus, norovirus or astrovirus.[18,19] For instance, it is estimated that *C. jejuni* is responsible for 17–20% of episodes of adult diarrhoea.

Table 50.1 Paediatric diarrhoea in developed and developing countries

Feature	Developed countries	Developing countries
Episodes per annum	<1	3–10
Seasonality	Winter	None
Severe dehydration	Rare	Frequent
Nutritional sequelae	Rare	Usual
Measles associated	Non-existent	15–63%
Epidemic	Rare	Frequent
Polymicrobial	Unusual	>20%
Case fatality rate	<0.01%	0.6%

After Kumate & Isibasi.[9]

Environmental factors

In temperate countries, viruses, except for noroviruses, produce peaks of disease in the cold dry weather of winter,[20] whereas in tropical Africa the seasonality is blurred but with an upsurge in cases in the dry season.[21] In contrast, bacterial and protozoal diarrhoeas tend to occur in the wetter seasons in the tropics and summer in temperate countries. In temperate countries, cryptosporidiosis peaks in spring with a lesser peak in autumn, but, for example, in Gaza, most cases occur in the hottest and driest parts of the year, perhaps when water availability and quality is compromised.[22] On a more global scale, during the 1997–1998 El Nino, when mean ambient temperatures were 5°C higher than normal, in Peru the number of daily hospital admissions with gastroenteritis doubled.[23]

Table 50.2 The relative importance of enteropathogens in childhood diarrhoeal disease

	Mexico	Multicentre	China	Philippines	Malawi	Canada	Chile	Australia
Reference	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
No. of subjects	271	3640	186	236	168	206	90	4637
Survey duration	4.5 months	24 months	22 months	25 months	2 months	24 months	12 months	13 years
Setting	Community	Out-patient	In-patient	In-patient	Out-patient	In-patient	Out-patient	In-patient
	% Positive	% Positive	% Positive	% Positive	% Positive	% Positive	% Positive	% Positive
Rotavirus	3.7	16	56	65	42	3.9	1.1	39.6
Astrovirus	61	NT	8.5	0.4	1.2		5.6	NT
Adenovirus 40/41	12.9	4	2.5	0.4	4.2	} 3.9	1.1	6%
Caliciviruses*	NT	3	7.6	0.4	1.2		NT	NT
Toroviruses	NT	NT	NT	0	0	3.5	NT	NT
Total viruses	77.6	23	74.6	66.2	48.6	42.8	7.8	45.6
Total bacteria	20.3	51	NT	23.4	NT	NT	32.2	9.2
Total protozoa	NT	3.3	NT	2.1	4.2	NT	3.3	NT
Mixed infection	7.4†	0	0	7†	0	NT	30†	0
No pathogen detected	NA	22.7	25.4	1.2	NA	NA	42	43.5

NT, not tested; NA not applicable.
* Includes noroviruses and sapoviruses.
† Predominantly viruses.

Table 50.3 Clinical features of inflammatory and non-inflammatory diarrhoea

	Non-inflammatory	Inflammatory
Symptoms	Nausea, vomiting, abdominal pain, but fever not a major feature	Abdominal pain, tenesmus, fever
Stool	Voluminous, watery	Frequent, small volume; blood-stained, pus cells present, mucus
Site	Proximal small intestine	Distal ileum, colon
Mechanism	Osmotic or secretory	Invasion of enterocytes leading to mucosal cell death and inflammatory response

Table 50.4 Pathogens in inflammatory and non-inflammatory diarrhoea

	Inflammatory	Non-inflammatory
Viruses (see Chapter 45)	Nil	Rotavirus Adenovirus 40/41 Astrovirus Norovirus Sapovirus Coronavirus Torovirus Bredavirus Picobirnavirus
Bacteria (see Chapter 51)	Enteroinvasive *E. coli* (EIEC) Enterohaemorrhagic *E. coli* (EHEC), e.g. 0157 Enteroaggregative *E. coli* (EaggEC) *Aeromonas hydrophila* *Campylobacter* spp. *Salmonella* spp. *Shigella* spp. *Yersinia enterocolitica* *Clostridium difficile* *Laribacter hongkongensis*	Enterotoxigenic *E. coli* (ETEC) Enteropathogenic *E. coli* (EPEC) *Vibrio cholerae* *Vibrio parahaemolyticus* *Campylobacter* spp. *Salmonella* spp. *Plesiomonas shigelloides* *Bacillus cereus* *Clostridium perfringens* *Clostridium difficile*
Protozoa (see Chapter 79)	*Entamoeba histolytica* *Balantidium coli*	*Cryptosporidium hominis* *Giardia intestinalis (lamblia)* *Cyclospora cayetanensis* *Blastocystis hominis* *Isospora belli* *Enterocytozoon bieneusi* (Microsporidia)

Food poisoning

Diarrhoeal disease following ingestion of food or water contaminated by bacteria, toxins or protozoa is still an important problem in both developed and developing countries. Although high-intensity animal rearing is important in the maintenance of human enteropathogens in developed countries, in developing countries human-derived enteric pathogens such as *Salmonella* spp. and *C. jejuni* and enterohaemorrhagic *E. coli* (EHEC) may still be implicated in outbreaks of food poisoning. Recently, water-borne outbreaks of *C. parvum* have been assuming greater importance.

Traveller's diarrhoea (turista, Aztec two-step, Montezuma's revenge, Delhi belly, etc.)

It is estimated that approximately 16 million people will travel annually from their domicile in industrialized countries to less-developed countries. Approximately one-third of these will develop diarrhoeal disease and in the majority of cases this will be due to an infective agent.[24] A large number of different enteropathogens have been implicated, but in most surveys ETEC are the predominant pathogens (Table 50.5), followed by *C. jejuni* and *Salmonella* spp. The aetiological agents vary considerably according to the countries visited; for example, *C. parvum* and *C. hominis* have recently been shown to be important in visitors to the Caribbean[25] and Africa.[26] Viral enteropathogens can cause traveller's diarrhoea but have, for example, been more frequently associated with shipboard epidemics, in which astrovirus and norovirus have been implicated.

Immunocompromised host

In tropical countries, the immune compromises due to malnutrition and HIV are of major importance; both affect the frequency

Table 50.5 Enteropathogens in traveller's diarrhoea

Pathogen	Prevalence (%)
Enterotoxigenic *E. coli*	30–80
Campylobacter jejuni	*c.* 20
Shigella spp.	5–15
Salmonella spp.	3–15
Giardia lamblia	0–3
Cryptosporidium spp.	?
Entamoeba histolytica	0–3
Rotavirus	10
Astrovirus	1
Norovirus	1
Unknown	10–15

Table 50.6 Clinical assessment of rehydration

Severity	Body weight loss (%)	Clinical state	Signs
Mild	<5	Not unwell	Thirsty, mucous membranes dry
Moderate	5–10	Apathetic	Sunken eyes, sunken fontanelle, tachypnoea, oliguria, loss of skin turgor
Severe	10–15	Shocked	Hypotensive, peripheral circulatory failure
Critical	>15	Moribund	Severely shocked, comatose

and severity of diarrhoeal disease. With the appearance of AIDS, diarrhoeal disease due to previously unrecognized pathogens, such as *C. parvum*, *Isospora belli*, *Enterocytozoon bieneusi* and *Mycobacterium avium-intracellulare*, has assumed increasing importance, albeit more often causing chronic diarrhoea.[27] Interestingly, rotavirus—the major cause of infantile gastroenteritis—appears to be no more severe in HIV-infected than in HIV-uninfected children.[28]

MANAGEMENT OF ACUTE DIARRHOEA

The mainstay of management of diarrhoeal disease is the assessment of dehydration (Figure 50.1) and the appropriate replacement of fluid and electrolytes.[29] Although diarrhoeal disease can produce dehydration at any age, its impact is greatest in those under 5 years old. This is because, as a result of their relatively greater surface area and thus greater fluid loss through skin, infants require 2.5 times more water per kilogram body weight than older individuals. Fluid and electrolyte loss is also greatly exacerbated by vomiting. Both the initial degree of dehydration and the response to rehydration therapy should be monitored clinically (Table 50.6).

Originally, rehydration was exclusively intravenous. This resulted in a tremendous drop in fatality rates – for example, in cholera, from 40% to less than 1% when properly administered. A major advance was made when an effective oral rehydration regimen was devised.

Oral rehydration therapy

Early oral rehydration solutions (ORS) contained only electrolytes and water and it was not until it was realized that glucose or sucrose was required to enhance sodium absorption that effective oral rehydration therapy became available. Glucose and sodium transport into enterocytes are coupled. Sucrose, a dimer of glucose and fructose, must be cleaved by brush-border sucrase for it to be absorbed. Nevertheless, glucose and sucrose seem to be equally effective in ORS,[30] although there may be minor advantages with glucose.[31]

There is also some debate over the use of bicarbonate or citrate to correct acidosis. Both are equally effective, but citrate is more

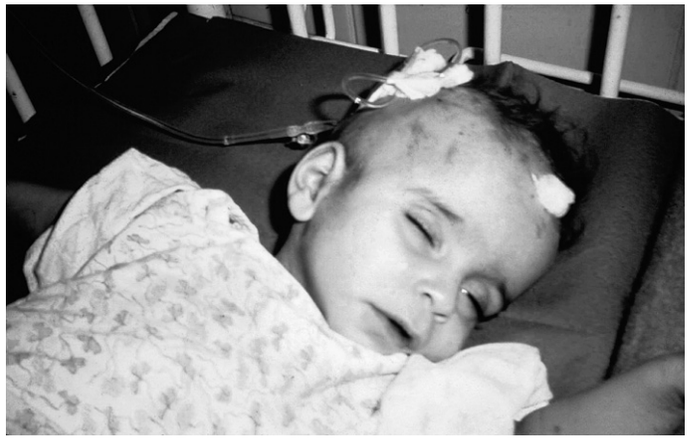

Figure 50.1 A child with severe dehydration being rehydrated intravenously.

stable and has replaced bicarbonate in World Health Organization (WHO) solutions. A further modification has been the incorporation of glycine, which is taken into the enterocyte by a specific amino acid transport system. Glycine, when present in ORS at a concentration of 111 mmol/L, was found to decrease both duration of diarrhoea and stool volume.[32] The composition of various ORS is shown in Table 50.7. ORS can be obtained in packets from UNICEF or can be made up locally. They should contain sodium chloride (3.5 g), potassium chloride (1.5 g) and glucose monohydrate (22 g), made up to 1 L with potable water (sucrose, 40 g, may replace glucose, and trisodium citrate dehydrate, 2.9 g, sodium bicarbonate). To be fully effective ORS should be available at the village level so therapy can be initiated as rapidly as possible. This will require the solution(s) to be available either prepacked or in bulk, with appropriate measuring spoons, a method of providing the correct volume of potable water, and instructions on use as well as to discard unused solution within 24 hours. Studies have shown that when properly instructed 98% of mothers can prepare ORS with a sodium range of 30–110 mmol/L.[33] Recently, rice powder-based ORS have been investigated, since

these are more readily available. Rice powder at 30–50 g/L is an effective substitute for glucose. It tastes better than simple electrolyte–glucose ORS and is thus more acceptable to children. A recent meta-analysis of 13 randomized trials of rice-based versus glucose-based oral rehydration therapy demonstrated the superiority of the rice-based solution in cholera diarrhoea, although the benefit was considerably smaller for children with acute non-cholera diarrhoea.[34] During the initial phase of oral rehydration therapy, while the patient is dehydrated, adults can consume 750 mL/h and children up to 300 mL/h. Maintenance therapy of 20 mL solution per kilogram body weight should be started as soon as signs of dehydration have gone. ORS are suitable for rehydration of all except severely dehydrated infants and those with shock (Table 50.8). Decreased-osmolarity ORS (178–268 mmol/L) has been shown to be as safe and effective as conventional ORS (311 mmol/L).[35]

Intravenous rehydration

Approximately 98% of children will respond to oral rehydration therapy. The remainder are generally infants with severe dehydration or those with profuse vomiting or a high purging rate. These will require rehydration by the intravenous route. Suitable solutions include: Ringer's lactate (Hartman's), consisting of NaCl 6.2 g, KCl 0.4 g, Na lactate 2.3 g and 2 mL 50% glucose per litre of solution; Dacca solution (NaCl 5 g, $NaHCO_3$ 4 g, KCl 1 g and 2 mL 50% glucose per litre of solution); or acetate solution (NaCl 5 g, KCl 1 g, Na acetate 6.5 g and 2 mL 50% glucose per litre of solution). Oral rehydration therapy should be started as soon as possible following institution of intravenous rehydration; however, if signs of severe dehydration persist, it may be necessary to continue using Ringer's lactate at 100 mL/kg body weight per 4 hours.

Table 50.7 Composition of oral rehydration solutions

	CONCENTRATION (MMOL/L WATER)		
Component	**Citrate ORS**	**Bicarbonate ORS**	**Glycine ORS***
Sodium	90	90	90
Potassium	20	20	20
Chloride	80	80	80
Citrate	10	—	—
Bicarbonate	—	30	30
Glucose	111	111	111
Glycine	—	—	111

* May contain either bicarbonate or citrate.

Adjunctive therapy

Other potential therapeutic interventions include antimicrobial agents, antimotility drugs and antisecretory drugs. They have varying degrees of efficacy and some are absolutely contraindicated for certain conditions.

Antimicrobial drugs

In general, infants with acute watery diarrhoea are best managed without recourse to antibiotics. However, if there is evidence of systemic spread, cholera or dysentery, then antimicrobials will shorten the course of diarrhoea and ameliorate its effects. With the advent of the fluoroquinolones such as ciprofloxacin and ofloxacin, the debate on the use of antimicrobials has been reopened. First, there is no doubt that the widespread indiscriminate use of antimicrobials, often in subtherapeutic regimens, encourages resistance in both pathogens and normal enteric flora.[36] On the other hand, even with ETEC, early treatment with co-trimoxazole[37] or ciprofloxacin can decrease the severity of diarrhoea. This is preferred to the widespread prophylactic use of these antimicrobials, which will certainly produce resistant bacteria.

In cholera, tetracycline or ciprofloxacin decreases the duration of diarrhoea and shedding of bacteria. In countries where *Shigella* spp. dysentery is endemic or when epidemics occur, antimicrobials are of benefit, but development of resistance during the course of epidemics occurs with monotonous regularity.[36] Metronidazole (or tinidazole) is valuable in the treatment of giardiasis or amoebic dysentery.

Antimotility drugs

These should be avoided.

Antisecretory drugs

These will of course only be effective if there is a secretory component to the diarrhoea. The value of loperamide as an adjunct in treating diarrhoea in well-nourished children has been demonstrated[38] but these authors warned against its use in malnourished children.

Compounds such as kaolin or charcoal which, it is postulated, act by absorbing toxins, have had little effect in controlled trials.

Table 50.8 Guidelines for rehydration

Degree	Age group	Type of fluid	Volume (mL/kg body weight)	Timing
Mild	All	ORS	50	Every 4 hours
Moderate	All	ORS	100	Every 4 hours
Severe	Infants	i.v. (Hartman's)	70	Every 4 hours
Severe and shock	All	i.v. (Hartman's)	70–100	Every 4 hours

Nutritional supplements

Micronutrient deficiencies have been associated with increased incidence, severity and duration of diarrhoeal and other diseases. Micronutrient supplementation trials have yielded varying results. For example, a trial of vitamin A supplementation in Haiti demonstrated an increased 2-week prevalence of diarrhoea post supplementation,[39] whereas a trial of zinc supplementation in India has demonstrated clinically important decreases in the severity and duration of diarrhoea.[40]

There is increasing interest in the value of administering commensal bacteria (probiotics) to ameliorate diarrhoeal disease.[41] In trials in Pakistan and Thailand, administration of one such probiotic, *Lactobacillus casei* GG, decreased the duration of diarrhoea and reduced stool frequency in children with acute watery diarrhoea.[42,43]

CONTROL OF DIARRHOEAL DISEASE

In industrialized countries, it has been the separation of human and animal excreta from potable water and foodstuffs that has contributed to the great decline in the incidence of diarrhoeal disease. In addition, improvements in facilities for personal hygiene within the home have decreased the intrafamilial spread of enteropathogens. To implement these measures in developing countries will need a massive input from industrialized countries. Other simpler and more locally applicable measures to prevent diarrhoeal disease include development of technologies and practices that interrupt disease transmission by muscid flies.[44,45] Recently it has been shown that exposure of drinking water (in plastic bottles) to tropical sunlight decreased diarrhoeal disease in Maasai children in Kenya.[46]

There is little doubt that measles and malnutrition increase the morbidity and mortality of diarrhoeal disease, and control of measles by immunization should be possible. Finally, it is unlikely that spread of some enteric pathogens, such as rotavirus, can be prevented completely by public health and good hygiene. A safe and effective vaccine would be of major benefit.

Morbidity

Malnutrition greatly affects immunity[47,48] and the incidence and severity of diarrhoeal disease. Similarly, diarrhoeal disease will greatly exacerbate malnutrition, thus creating an inexorable downward spiral. Acute diarrhoeal disease can become chronic, and chronic diarrhoea, for example that due to *C. parvum* or *C. hominis*, can become greatly prolonged.[49] Disaccharide (principally lactose) intolerance following certain types of diarrhoea has been a source of great controversy. Certain pathogens such as rotavirus or EPEC produce a great decrease in small-intestinal disaccharidase levels. Some consider that infants should not be given their normal diet because of the problem of disaccharide intolerance. Most evidence now suggests that infants should return to their normal diet within 24 hours of onset of diarrhoea unless there are specific contraindications.[50]

CONCLUSIONS

Diarrhoeal disease is still a major cause of mortality even though it has been shown that introduction of oral rehydration therapy can decrease mortality to less than 0.5% in defined study areas.

Editors regret to announce the untimely death of Professor Tony Hart whose contributions to Manson's were invaluable.

REFERENCES

1. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet* 1997; 349:1269–1276.
2. Bern C, Martines J, de Zoysa I, et al. The magnitude of the global problem of diarrhoeal disease: a ten year update. *Bull World Health Organ* 1992; 70: 705–714.
3. Hart CA, Cunliffe NA. Diagnosis and causes of viral gastroenteritis. *Curr Opin Infect Dis* 1996; 9:333–339.
4. WHO/CDD/VID/84.4 *Diarrhoeal Disease Control Programme. Report of the Third Meeting of the Scientific Working Group on Viral Diarrhoeas. Microbiology, Epidemiology, Immunology and Vaccine Development.* Geneva: WHO; 1984:8–14.
5. Mata L, Simhon A, Urrutia J, et al. Epidemiology of rotavirus in cohort of 45 Guatemalan Mayan Indian children from birth to age 3 year. *J Infect Dis* 1984; 148:452–461.
6. Black RC, Lopez de Romana G, Brown KH, et al. Incidence and etiology of infantile diarrhea and major routes of transmission in Huascar, Peru. *Am J Epidemiol* 1989; 129:785–799.
7. Gurwith M, Wenman W, Hinde D, et al. A prospective study of rotavirus infection in infants and young children. *J Infect Dis* 1981; 144:218–224.
8. de Wit MAS, Koopmans MPG, Kortbeek LA, et al. Gastroenteritis in sentinal practices, The Netherlands. *Emerg Infect Dis* 2001; 7:82–91.
9. Kumate J, Isibasi A. Pediatric diarrheal diseases: a global perspective. *Pediatr Infect Dis J* 1986; 5(suppl):S21–S28.
10. Maldonaldo Y, Cantwell M, Old M, et al. Population-based prevalence of symptomatic and asymptomatic astrovirus infection in rural Mayan infants. *J Infect Dis* 1998; 178:834–839.
11. Hulian S, Zhen LG, Mathan MM, et al. Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries. *Bull World Health Organ* 1992; 69:549–555.
12. Qiao HP, Nilsson M, Abreu ER, et al. Viral diarrhea in children in Beijing, China. *J Med Virol* 1999; 5:390–396.
13. Pajé-Vilar E, Co BG, Caradang EH, et al. Non-bacterial diarrhoea in children in the Philippines. *Ann Trop Med Parasitol* 1994; 88:53–58.
14. Pavone R, Schinaia N, Hart CA, et al. Viral gastroenteritis in children in Malawi. *Ann Trop Paediatr* 1990; 10:15–20.
15. Jamieson FB, Wang EL, Bain C, et al. Human torovirus: a new nosocomial gastrointestinal pathogen. *J Infect Dis* 1998; 178:1263–1269.
16. Gaggero A, O'Ryan M, Noel JS, et al. Prevalence of astrovirus infection among Chilean children with acute gastroenteritis. *J Clin Microbiol* 1998; 36: 3691–3693.
17. Barnes GL, Uren E, Stevens KB, et al. Etiology of acute gastroenteritis in hospitalized children in Melbourne, Australia from April 1980 to March 1993. *J Clin Microbiol* 1998; 36:133–138.
18. Krishnan T, Sen A, Choudhury JS, et al. Emergence of adult diarrhoea rotavirus in Calcutta, India. *Lancet* 1999; 353:380–381.
19. Glass RI, Noel J, Mitchell D, et al. The changing epidemiology of astrovirus-associated gastroenteritis: a review. *Arch Virol* 1996; 12(suppl):287–300.
20. Hart CA, Cunliffe NA. Viral gastroenteritis. *Curr Opin Infect Dis* 1999; 12: 447–457.
21. Cunliffe NA, Kilgore PE, Bresee JS, et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. *Bull World Health Organ* 1998; 76:525–537.

22. Sallon S, El Showaa R, El Masri M, et al. Cryptosporidiosis in children in Gaza. *Ann Trop Paed* 1990; 11:277–281.
23. Checkley W, Epstein LD, Gilman RH, et al. Effects of El Nino and ambient temperature on hospital admissions for diarrhoeal diseases in Peruvian children. *Lancet* 2000; 355:442–450.
24. Steffan R, van der Linde F, Gyre K, et al. Epidemiology of diarrhea in travellers. *JAMA* 1983; 249:1176–1180.
25. Ma P, Kaufman DC, Helmick CG, et al. Cryptosporidium in tourists returning from the Caribbean. *N Engl J Med* 1985; 312:647–648.
26. Soave R, Ma P. Cryptosporidium: traveller's diarrhea in two families. *Arch Intern Med* 1985; 145:70–72.
27. Smith PD. Gastrointestinal infections in AIDS. *Ann Intern Med* 1992; 116: 63–77.
28. Cunliffe NA, Gondwe JS, Kirkwood CD, et al. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. *Lancet* 2001; 18:550–555.
29. Cash RA. Oral rehydration therapy. In: Farthing MJG, Keusch GT, eds. *Enteric Infection*. London: Chapman & Hall; 1989:441–451.
30. Sack DA, Chowdhury AMAK, Eusof A, et al. Oral rehydration in rotavirus diarrhoea: a double blind comparison of sucrose with glucose electrolyte solution. *Lancet* 1978; ii:280–283.
31. Nalin DR, Levine MM, Mata L, et al. Comparison of sucrose with glucose in oral therapy of infant diarrhoea. *Lancet* 1978; ii:277–279.
32. Mahalanabis D, Patra FC. In search of a super oral rehydration solution: can optimum use of organic solute-mediated sodium absorption lead to the development of an absorption promoting drug? *J Diarrhoeal Dis Res* 1983; 1:76–81.
33. Bhatia S, Cash RA, Cornaz I. Evaluation of the oral therapy expansion program (OTEP) of the Bangladesh rural advancement committee (BRAC). *Swiss Development Cooperation and Humanitarian Aid* 1983; January 24–February 12.
34. Gore SM, Fontaine O, Pierce NF. Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. *BMJ* 1992; 304:287–291.
35. Murphy C, Hahn S, Volmink J. Reduced osmolarity oral rehydration solution for treating cholera. *Cochrane Database Syst Rev* 2004; (4):CD003754.
36. Kariuki S, Hart CA. Global aspects of antimicrobial resistant enteric bacteria. *Curr Opin Infect Dis* 2001; 14:576–586.
37. DuPont HR, Randall RR, Galindo E, et al. Treatment of traveller's diarrhea with trimethoprim/sulfamethoxazole and with trimethoprim alone. *N Engl J Med* 1982; 307:841–844.
38. Diarrhoeal Diseases Study Group (UK). Loperamide in acute diarrhoea in childhood: results of a double blind placebo controlled multicentre clinical trial. *BMJ* 1984; 298:1263–1267.
39. Stansfield SK, Muller P-L, Lerebours G, et al. Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; 342:578–582.
40. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation in young children with acute diarrhea in India. *N Engl J Med* 1995; 333:839–844.
41. MacFarlane GT, Cummings JH. Probiotics and prebiotics: can regulating the activities of intestinal bacteria benefit health? *BM J* 1999; 318: 999–1003.
42. Raza S, Graham SM, Allen SJ, et al. *Lactobacillus* GG promotes recovery from acute non-bloody diarrhea in Pakistan. *Pediatr Infect Dis J* 1995; 14:107–111.
43. Pant AR, Graham SM, Allen SJ, et al. *Lactobacillus* GG and acute diarrhoea in young children in the tropics. *J Trop Pediatr* 1996; 42:162–165.
44. Chavasse DC, Shier RP, Murphy OA, et al. Impact of fly control on childhood diarrhoea in Pakistan: community randomised trial. *Lancet* 1999; 353:22–25.
45. Emerson PM, Lindsay SW, Walraven GEL, et al. Effect of the fly control on trachoma and diarrhoea. *Lancet* 1999; 353:1401–1403.
46. Conroy RM, Elmore-Meegan M, Joyce T, et al. Solar disinfection of drinking water and diarrhoea in Maasai children: a controlled field trial. *Lancet* 1996; 348:1695–1696.
47. Chandra RK. Nutrition, immunity and infection: present knowledge and future directions. *Lancet* 1983; i:688–691.
48. Dowd P, Heatly R. The influence of undernutrition on immunity. *Clin Sci* 1984; 66:241–248.
49. Sallon S, Deckelbaum RJ, Schmid II, et al. *Cryptosporidium,* malnutrition and chronic diarrhea in children. *Am J Dis Child* 1988; 142:312–315.
50. Committee on Nutrition. Use of oral fluid therapy and posttreatment feeding following enteritis in children in a developed country. *Pediatrics* 1985; 75:358–361.