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DIARRHOEAL DISEASES: AETIOLOGIC AGENTS AND THEIR MODE OF TRANSMISSION

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1. INTRODUCTION.

Diarrhoeal diseases are one of the leading causes of morbidity and mortality in the developing world. In some countries 40% of deaths in children up to 5 years of age are related to diarrhoeal illnesses. Until recently, the aetiology could be determined in less than one-third of these illnesses. Pathogens recognized in the laboratory included Salmonellae, Shigellae, Vibrio cholerae and enteropathogenic Escherichia coli. Within the past five years additional aetiologic agents have been identified such that under optimal laboratory conditions a diagnosis can now be made in 85% of diarrhoeal cases. In approximately 15% multiple aetiologies are present.

This paper will review the epidemiology of the presently recognized diarrhoeal disease agents. Emphasis will be placed on pathogens that are the most important recognized causes of diarrhoea in the developing world including enterotoxigenic E. coli and rotaviruses which, in areas where they have been studied, are responsible for as many as 50% of diarrhoea cases. In summary, it can be said from an epidemiologic perspective that all the diarrhoeal diseases are spread primarily by the faecal-oral route. This simple explanation serves, in large part, to explain the vast difference in the incidence of diarrhoeal diseases between the developed countries where appropriate sanitary facilities are available to the majority of the population and the developing countries where food and water hygiene are often inadequate and safe sewage disposal systems are frequently lacking. A summary of the information presented is given in Table 1.

2. AGENTS KNOWN TO BE IMPORTANT CAUSES OF DIARRHOEA IN DEVELOPING COUNTRIES

2.1 Vibrio cholerae

V. cholerae has two recognized biotypes: classical and El Tor, and these biotypes are each separated into Ogawa and Inaba serotypes. Its site of infection is the small intestine, primarily the jejunum, where the organism elaborates an enterotoxin. This enterotoxin causes fluid loss in the bowel through activation of the intracellular enzyme adenyl cyclase, which results in an isotonic sodium and water deficit, a base deficit acidosis, and potassium depletion.

From 1817-1923 cholera spread worldwide in six pandemics. The seventh pandemic, caused by the El Tor biotype, began in Indonesia in 1961 and by 1978 has spread to most of the South-East and and South Asia, the Middle East, West and East Africa, Southern Europe, the Far East and the Western Pacific.

Endemic and epidemic cholera often have a seasonal pattern which varies for unknown reasons in different geographic areas. For example, the cholera season generally peaks during the hot dry season in March, April and May in Calcutta, after the monsoon season in Bangladesh, and during the rainy season in the Philippines. In endemic areas cholera is predominantly a disease of children; in rural Bangladesh attack rates are ten times greater in children aged 1-4 than in adults, and two-thirds of cases are in children below the age of ten (Mosley, 1969). In contrast, when cholera spreads to a previously uninfected area, attack rates are usually equal in all age-groups exposed and are usually highest in adult males. Cholera is rare in children under one year of age.

Contaminated water and food, especially shellfish and raw, leafy vegetables which have been "freshened" with contaminated water, play a major role in transmission of the disease. In Africa the disease has often spread at large gatherings of people (e.g., fairs, festivals, market places and especially funerals). Transmission through direct person-to-person contact is rare because of the large infectious dose required to cause disease and the gastric acid barrier in the stomach that kills ingested vibrios. V. cholerae is host-specific for man; animals play no role in transmission. Persons with asymptomatic or mild infection play an important role in spread of the disease. The ratio of asymptomatic or mild infections to severe disease is about 5:1 in classical cholera and greater than 10:1 in El Tor cholera. Family contacts of hospitalized patients are frequently infected. A prolonged gall bladder carrier state has been documented in adults. Studies from Calcutta (Sinha et al., 1968) suggest that the disease is transmitted at low levels during interepidemic periods in endemic areas by persons who are asymptomatic or have mild disease.

Antibiotic resistance of V. cholerae occurs rarely. Isolates of V. cholerae that are non-toxigenic under in vitro assay conditions but produce toxin under in vivo conditions such as in the rabbit ileal loop have been isolated from man and environmental sources; their role in the epidemiology of cholera is unknown. Another recent microbiologic enigma has been the isolation of V. cholerae from river water in 4 countries in the absence of recognized disease despite intensive surveillance for cases.

2.2 Vibrio parahaemolyticus

V. parahaemolyticus was first recognized as an important diarrhoeal pathogen in Japan in the 1960's as a result of surveillance for V. cholerae. V. parahaemolyticus organisms have distinct O and K antigens but serologically identical H antigens. Some strains produce a heat-stable direct haemolysin which lyses human red blood cells (the Kanagawa phenomenon). These strains are usually isolated from ill persons but not from environmental sources or contaminated foods.

The organisms cause two distinct clinical syndromes. The one most commonly observed is that of watery diarrhoea; recent evidence suggests that this diarrhoea may be enterotoxin-mediated. The second syndrome, consisting of bloody diarrhoea with severe abdominal cramps and fever, is possibly due to an inflammatory lesion related to the heat-stable direct haemolysin.

Information on the epidemiology of V. parahaemolyticus diarrhoea is limited. The organism is an important cause of diarrhoea in the Far East, South and South-East Asia, the Indian subcontinent, Panama, Togo, the United States of America and Europe. In these areas it has been isolated from sea-water and marine life, usually when water temperatures are highest. The vehicle of human infection is usually shellfish that is raw, inadequately cooked, or contaminated after cooking and stored at suitable

temperatures for bacterial growth (15-45°C) before consumption. The generation time of vibrios may be as short as 10-12 minutes. Secondary cases do not occur.

2.3 Non-cholera vibrios (NCV)

These organisms, also referred to as non-agglutinable vibrios (NAG), possess the same biochemical properties as V. cholerae except that they do not agglutinate with group O antiserum. The pathogenic mechanism by which these organisms cause diarrhoea is unclear. A few strains have been shown to produce a heat-labile enterotoxin that has properties similar to those of cholera enterotoxin. Diarrhoea caused by these organisms resembles cholera except that it is of a milder severity, and is more often associated with abdominal pain and low-grade fever.

Little data is available on the epidemiology of these organisms. They have been isolated on a seasonal basis from diarrhoea patients and coastal waters in Africa, Czechoslovakia, the Indian subcontinent and the United States of America. They are also frequently found in stools of persons without diarrhoea, suggesting that they are not always pathogenic. Food and water undoubtedly play the primary role in transmission of these organisms. Secondary cases have not been observed

2.4 Enterotoxigenic Escherichia coli (ETEC)

ETEC are E. coli that are capable of producing a heat-labile (LT) enterotoxin (LT strains), a heat-stable (ST) enterotoxin (ST strains) or both of these enterotoxins (LT-ST strains). LT activity is destroyed after treatment at 56°C for 30 minutes. Its mechanism of action is similar to that of cholera toxin (adenyl cyclase activation in the small intestine) to which it is antigenically related. ST activity is present after treatment at 100°C for 15 minutes. Its mechanism of action is probably through activation of guanyl cyclase in the small intestine and it is not antigenically related to cholera. LT production is detected by tissue culture assay systems (Sack, 1975) or by an ELISA assay (Yolken, 1977a). ST production is measured only through a relatively cumbersome infant mouse assay. Toxin-production is plasmid-mediated. LT-ST strains appear to be restricted to a limited number of serotypes (e.g., O6: K15: (H16), O8: K40: H9, O78:K-:(H11)) with identical biotypes (Orskov and Orskov, 1977). Plasmid-mediated colonizing factors (CF) are essential for establishment of ETEC strains in the small intestine but their characteristics are not well understood.

ETEC are a frequent cause of diarrhoea in areas where diarrhoeal diseases are common. Travellers to these areas are often infected by these organisms. In persons living on the Indian subcontinent infection with this organism frequently results in an illness indistinguishable from cholera; it is unknown whether this syndrome occurs in other endemic areas. The relative frequency of LT-ST, LT and ST producing strains appears to vary with geographic location. In Bangladesh, where the disease is seasonal, occurring before and after the monsoon season, LT-ST strains are more commonly isolated from hospitalized adult patients, while ST strains are more frequently found in children less than 2 years of age who have milder disease

ETEC diarrhoea in travellers is caused most commonly by consumption of contaminated food (Merson et al., 1976). In endemic areas food and water are thought to be vehicles of infection. LT-ST and ST ETEC strains are also frequent causes of diarrhoea in young calves but there is no evidence to date to indicate that animal strains are pathogenic for humans or that animals provide a reservoir for human strains. Other gram-negative organisms, including strains of Aeromonas, Klebsiella, Enterobacter and Citrobacter, have been reported to produce one or both of these or similar toxins but the significance of these findings is unclear.

2.5 Rotavirus

This virus was first detected in humans in 1973 in duodenal biopsies from ill children in Australia (Bishop, 1973). It has been called human reovirus-like agent (HRVL), duovirus, orbivirus and infantile gastroenteritis virus, but most investigators now accept the name rotavirus. The virus is a 70nm particle; it has now been cultivated in tissue culture and has been detected in most studies by electron-microscopic examination of diluted 2% diarrhoeal stool filtrates. A recently devised ELISA procedure has simplified detection of the virus in stool and measurement of antibody (Yolken, 1977 b). The virus causes a typical clinical syndrome of diarrhoea preceded or followed by vomiting and fever; the illness generally lasts from 3-7 days and in the most severe cases results in total fluid loss of about 250 cc/kg body weight. In animals the virus infects the small intestine causing shortening of villi with denudation of tips and distortion of epithelial cells.

In most studies of rotavirus diarrhoea which to date have been carried out in hospitalized patients in developed countries, the virus has been found responsible for 50-70% of diarrhoea cases in children between 6 and 24 months of age. Most cases have been observed during the colder months. Disease is uncommon in children less than 6 months of age, although nursery outbreaks have been described in which, for unknown reasons, asymptomatic infection is common. Disease in adults is rare; this has been confirmed by serologic studies demonstrating the presence of serum antibody to rotavirus in as many as 80% of persons over the age of two (Kapikian et al., 1976). However, 40% of adult contacts of cases have serologic conversions, presumably from subclinical infection. Carriage of rotavirus in the stool in healthy persons is very uncommon.

Data from studies presently under way or completed have shown the importance of rotavirus as a diarrhoea pathogen in infants and young children in developing countries. There is some evidence to suggest that the disease, while most common in the colder months, may be frequent all year round. In Bangladesh, the peak incidence of the disease is at the end of the first year of life and 95% of cases are below the age of two. The protective role of breast milk in the disease is under study.

The mode of transmission of the disease has not been conclusively demonstrated but the faecal-oral route is most likely. Stools of diarrhoea patients with rotavirus infection can contain $10^9 - 10^{10}$ particles per gram of faeces. Respiratory transmission has also been proposed because of accompanying pulmonary symptoms, although preliminary observations from Bangladesh demonstrated rotavirus antigen in nasal washings or throat swabs from only 1% of diarrhoea cases. Because rotavirus is a common cause of neonatal diarrhoea in calves and lambs and human rotavirus strains can cause disease in animals, the question has arisen whether animals can provide a reservoir for human rotavirus strains. Recent evidence indicates that there are at least two serotypes of human rotavirus strains; this finding may have important epidemiologic implications.

2.6 Shigellae

Four serotypes of Shigellae are known: Shigella dysenteriae (Shiga), S. flexneri, S. sonnei, and S. boydii. All may produce a watery diarrhoea syndrome and dysentery but disease caused by S. dysenteriae is generally more severe and associated with higher mortality. An antigentically similar enterotoxin is produced by all except S. boydii; this enterotoxin may account for the small bowel watery diarrhoea syndrome that often precedes the dysentery symptoms which are due to invasion of the large bowel. Persons with shigellosis are often thought to have amoebiasis because of their similar clinical presentations and the large number of leucocytes in their stool which are mistaken for amoeba.

S. flexneri is the most common isolated serotype in the developing countries. S. sonnei is most commonly isolated in developed countries and is associated with a higher incidence of multiple antibiotic resistance. The ability of S. sonnei strains to produce inhibitory substances called colicins has been helpful in epidemiologic studies of this organism. Although the incidence of S. dysenteriae has declined in the developing countries, outbreaks caused by S. dysenteriae type I with plasmid-mediated multiple antibiotic resistance patterns occurred recently in Central America (Mata et al., 1970) and parts of Asia. Of interest was the rapid termination of these outbreaks presumably related to improvement in food availability and other economic conditions.

Shigellae are host-specific for man. As few as 10 organisms can cause disease. Thus the organisms can be readily spread by direct person-to-person contact, although water and food-borne transmission also occur. Studies in developing countries have demonstrated that 5-10% of normal persons and 20% of contacts of dysentery cases are asymptomatic carriers. The disease is most common in children less than 5 years of age, especially in males, and in their siblings aged 5-9; adult females are often infected, which is probably a reflection of close contact with their children. Studies have shown that as the amount of water used in the home increases, the incidence of shigellosis decreases illustrating the fact that it is a water-washed disease. Persons with recent measles infection are at particularly high risk of developing shigellosis.

2.7 Salmonellae

The genus Salmonellae consists of about 2 000 serotypes. Except for S. typhi which is host-specific for man, these organisms are pathogens for animals and man. S. typhimurium, one of the more common serotypes, can be lysed by a number of recognized phages which has been helpful for epidemiological studies of this organism. Salmonellae can cause acute febrile gastroenteritis, enteric fever, bacteraemia or localized metastatic infections. While the pathogenesis of salmonella gastroenteritis is believed to be intracellular invasion of small intestinal (primarily ileum) epithelial cells, a salmonella enterotoxin has recently been described which may play a role in the disease.

The incidence of salmonellosis is highest in children and in persons with certain underlying diseases (e.g., schistosomiasis, chronic liver disease, blood dyscrasias, carcinoma, bartonellosis, etc.) Convalescent carriage frequently occurs; as many as 80% of infected persons may excrete the organism for 6 weeks to 2 months after symptoms cease. Chronic carriage is rare; it is most common in those infected with S. typhi who have gallbladder disease. Salmonellae are frequently resistant to many antibiotics through plasmid acquisition. This is thought to be due in part to indiscriminate use of antibiotics in man and animal feed and has created significant problems in the treatment of salmonella non-gastrointestinal illness.

The incidence of salmonellosis caused by different serotypes varies greatly among countries. This may be related to the fact that the main reservoir of Salmonellae is animals and the primary mode of transmission is contaminated foods, usually of animal origin, which are consumed more frequently by some populations than by others. Water-borne and person-to-person transmission, especially in institutional settings, also occur. The infectious dose of Salmonellae in volunteers is 10^5 organisms but disease can occur after ingestion of food containing fewer organisms.

3. AGENTS WHOSE IMPORTANCE AS A CAUSE OF DIARRHOEA IN DEVELOPING COUNTRIES IS PRESENTLY UNKNOWN

3.1 Escherichia coli

3.1.1 Invasive Escherichia coli. Strains of E. coli that are capable of invading the large intestine may cause watery diarrhoea or dysentery syndrome. These strains are

estricted to certain O serogroups (Groups 28, 112, 115, 124, 136, 143, 144, 147 and 152). Recognition of these strains requires testing of E. coli by the Sereny test, i.e., for their ability to produce Kerato-conjunctivitis after inoculation of 10^9 organisms in the eye of a guinea-pig. Because of the in vivo assay required for its recognition, this organism has been looked for in only a few reported studies. One large outbreak due to consumption of French cheese has been described (Marier, 1973).

3.1.2 Enteropathogenic Escherichia coli. Beginning in 1945 it was recognized that certain O serogroups of E. coli (O groups 26, 55, 86, 111, 119, 124-128) caused outbreaks of diarrhoea in infants, especially in nurseries where person-to-person transmission presumably occurred. Evidence from human volunteer studies with strains from two such outbreaks has recently demonstrated that these organisms are pathogenic by an as yet unrecognized mechanism. It is not clear, however, whether isolation of E. coli of one of these serotypes from a sporadic case of diarrhoea indicates that this organism is responsible for disease since these organisms are often isolated from normal persons (Gangarosa and Merson, 1977).

3.2 Other foodborne pathogens

3.2.1 Clostridium perfringens. C. perfringens is a spore-forming bacillus that is widely distributed in the soil and frequently found in the intestinal tract of man and animals. Anaerobic techniques are required for its isolation. Strains of C. perfringens are classified into 5 toxigenic types (A to E). Classic C. perfringens is caused by type A organism; type C organisms have caused outbreaks of necrotizing enteritis (Pig bell) in Europe, South America, Africa and New Guinea. Illness caused by C. perfringens type A organisms is due to a heat-labile enterotoxin that is synthesized in the large intestine during sporulation of ingested vegetated cells and released upon lysis of sporangia. The precise mechanism of action of this enterotoxin is unknown though it is not through adenyl cyclase activation. The reason why resident C. perfringens strains do not cause illness is not known. Disease produced by C. perfringens consists primarily of abdominal cramps and watery diarrhoea. Foods transmitting the disease are primarily those of animal origin (e.g., beef, poultry and their gravies) which are usually contaminated with C. perfringens prior to cooking. During cooking vegetative cells are usually destroyed but spores survive. When this cooked food is then stored at suitable temperature (15-45°C) for a sufficient time period (4-6 hours), the spores germinate into vegetative cells which rapidly multiply.

Ingestion of approximately 10^8 organisms produces symptoms. Since C. perfringens is a common inhabitant of the intestinal tract, confirmation of C. perfringens as a cause of diarrhoea requires isolation of organisms of the same serotype from ill persons and epidemiologically implicated food.

3.2.2 Staphylococcus aureus. S. aureus foodborne illness is caused by ingestion of food containing enterotoxin produced by certain coagulase-positive strains. This enterotoxin induces vomiting and diarrhoea which are classical symptoms of the disease. The main reservoir of S. aureus is man and the principle source is the nose. As many as 50% of normal persons have this organism in their nose, throat or faeces or on their skin. Disease occurs when foods such as meat products, pastries and salads (e.g., potato, chicken, etc.) which are capable of supporting the growth of these organisms are handled and contaminated by such persons and stored at a suitable temperature (15-45°C) for a sufficient time period (4 to 6 hours) to permit multiplication of the organisms with subsequent enterotoxin production during their exponential and transitional phases of growth. Food contaminated with staphylococcal enterotoxin tastes and smells normal. Since the enterotoxin is relatively heat stable, holding foods at high temperature (70°C) does not prevent illness. Confirmation that illness has been caused by S. aureus requires detection of enterotoxin in food, isolation from the faeces of ill persons of enterotoxin-producing S. aureus of the same phage type as S. aureus isolated

from the incriminated food and food handler, or, less optimally, demonstration of more than 10^5 coagulase-positive S. aureus organisms per gram of incriminated food.

3.2.3 Bacillus cereus. B. cereus is an ubiquitous organism; it is readily isolated from soil and is a frequent contaminant of soil-grown food products (e.g. spices, sauces, potatoes, vegetables, cereal products) and milk products. The organism causes two distinct clinical syndromes. One is characterized by diarrhoea and abdominal cramps; the other is characterized by nausea and vomiting simulating staphylococcal food poisoning. There is some evidence that enterotoxins are responsible for each of these syndromes (Melling, 1976). The diarrhoea syndrome has been described most commonly in outbreaks in Europe after the ingestion of various soil-grown food products; the vomiting syndrome has been reported primarily after the consumption of fried rice. B. cereus spores survive high temperatures, including boiling, and multiply rapidly in food stored at room temperature. Confirmation of B. cereus as a pathogen requires isolation of 10^5 organisms per gram of implicated food.

3.3 Newly recognized bacterial pathogens

3.3.1 Yersinia enterocolitica. Y. enterocolitica (previously called Pasteurella pseudotuberculosis, Pasteurella X) is now considered to be a member of the family Enterobacteriaceae. Unlike other enteric pathogens, the organism grows optimally at 22-29° C and poorly at 37° C. Because of this unusual requirement, the reported rate of isolation of the organism is greatly influenced by procedures used by laboratory workers.

It has been found as an important diarrhoea pathogen in many European countries, Japan and North America. The symptoms caused by the organisms are related to the age of the patient. Infants characteristically have febrile diarrhoea, older children have acute mesenteric lymphadenitis, and adults may present with enteritis and fever; arthritis and erythema nodosum are seen especially in older women. The pathogenic mechanism of Y. enterocolitica diarrhoea is unknown.

The organism has been isolated from swine and dogs, from foods such as beef, milk and ice cream, and from non-chlorinated well-water (Morris & Feeley, 1976). There is limited information on how Y. enterocolitica spreads. Foodborne outbreaks have been well described but person-to-person or direct animal to human transmission may also occur. Serotyping and phage typing systems have been developed which are helpful for epidemiologic studies. In some countries a few serotypes predominate, while in others multiple serotypes have been found. Some Y. enterocolitica found in the environment are not pathogenic for man.

3.3.2 Campylobacter jejuni. C. jejuni has very recently been described as an enteric pathogen in humans. The organism has very specific isolation requirements. Workers in Belgium and England who have the most experience in isolation inoculate stools on sheep blood agar containing multiple antibiotics and incubate the plates at 43° C for 48 hours in an atmosphere containing oxygen, carbon dioxide and hydrogen (Skirrow, 1977). Disease caused by the organism is characterized primarily by watery diarrhoea sometimes of more than 2 weeks' duration; fever and abdominal pain are common and vomiting, dysentery and bacteraemia occur. The sites of infection are the ileum and jejunum.

Few data are available on the epidemiology of this organism. In recent studies in Africa, England, and Belgium C. jejuni was isolated from 6-11 % of diarrhoea cases. The organism has been found in contacts of confirmed cases and in healthy persons.

Nursery outbreaks have also been described. The mode of transmission is unknown; there is evidence that poultry may be the reservoir of the organism.

3.4 Parvovirus

These small viruses (approximately 27 nm) were first demonstrated in faecal filtrates by immunoelectronmicroscopy. The virus infects the upper small intestine and causes watery diarrhoea. Different serotypes (e.g., Norwalk agent, Hawaii agent, Montgomery agent) have been identified which have partial cross-reactivity (Wyatt & Kapikian, 1977). Since infection with one parvovirus does not necessarily protect against infection with an antigenically different parvovirus, diarrhoeal disease from this virus occurs at any age. Disease to date has been observed primarily in outbreaks involving older children and adults. More readily applicable techniques for detection of the virus are being developed.

Other small viruses (e.g., coronavirus, astrovirus, calcivirus, minirotavirus) have been reported as causes of diarrhoea but more research in required to establish them as definite diarrhoeal pathogens.

4. Parasites

4.1 Entamoeba histolytica. E. histolytica invades the large bowel and produces a dysenteric syndrome. Complications include amoebomas, intestinal perforation, and hepatic disease which may occur in the absence of intestinal symptomatology. The presence of trophozoites containing ingested red blood cells in the stool of a patient with dysentery suggests a diagnosis of amoebic dysentery. Almost all human infections are from cysts passed by asymptomatic human carriers. Encystment does not occur outside the body so patients passing only trophozoites in their stools are not infectious. Cyst passage may continue for years. Man is the reservoir of E. histolytica and passes the infection to other primates. Food, especially uncooked fruits and vegetables, and water can be vehicles of infection. Direct person-to-person transmission also occurs.

2 Giardia lamblia. G. lamblia may be associated with a variety of diarrhoeal mptoms including explosive, watery diarrhoea, loose, foul-smelling stools, and eatorrhea. Abdominal cramps, anorexia and bloating are common. The parasite inhabits e duodenum and upper jejunum but does not invade intestinal cells. Its pathogenesis unknown. The majority of patients with giardiasis are asymptomatic cyst carriers. estic and wild animals can also be infected and excrete cysts. Cysts have recently n demonstrated in water, confirming the importance of water as a vehicle of nsmission. Foodborne transmission, especially from raw fruits and vegetables, and son-to-person spread, particularly among siblings within a family group also occur.

DIRECTIONS FOR FUTURE EPIDEMIOLOGIC RESEARCH

There are great deficiencies in our knowledge of the incidence and epidemiologic acteristics of the diarrhoeal disease agents in the developing world. The following ies are considered to be of particular importance for implementation:

Studies to define the epidemiology of rotavirus and enterotoxigenic E. coli hoea: These pathogens are two of the most common causes of diarrhoea in infants oung children. These studies should be community based so that the entire spectrum sease is observed. The relationship between these pathogens, infant feeding ns and malnutrition requires intensive study. Through the use of newly developed, fied laboratory techniques, such as ELISA assays, these studies can be performed atively unsophisticated laboratories.

5.2 Studies to determine the vehicles of spread of cholera, especially in newly infected areas: while it is recognized that in a cholera outbreak multiple sources of infection may be present, such studies may elucidate vehicles that account for a high proportion of cases.

5.3 Longitudinal studies in various geographic areas to determine the relative importance of watery diarrhoea and dysentery as causes of morbidity and mortality, especially in young children. These studies should include populations from different socioeconomic groups living under different climatic and environmental (e.g., rural, urban) conditions. Whenever possible, these studies should include isolation of newly recognized pathogens (e.g., Yersinia, Campylobacter, parvovirus), and a case-control assessment of the importance of enteropathogenic E. coli as a cause of diarrhoea; this may initially require collaboration with laboratory workers from other countries. Such studies can provide community-based rates on the incidence of watery diarrhoea and dysentery so that if intervention measures (e.g., improved water sources) are applied, their impact can be readily measured.

Information derived from the studies described above is important for the development of national programmes for prevention and control of diarrhoeal diseases.

TABLE 1 - SUMMARY OF IMPORTANT CHARACTERISTICS OF DIARRHOEAL PATHOGENS

A. AGENTS KNOWN TO BE IMPORTANT CAUSES OF DIARRHOEA IN DEVELOPING COUNTRIES

Agent	Pathogenesis	Reservoir	Mode of transmission	Distinguishing characteristics
Vibrio cholerae	enterotoxin	man	water; food (especially shellfish and raw, leafy vegetables); person-to-person transmission rare	Clinical manifestations can be severe but this form of disease is uncommon; seasonal pattern; disease occurs primarily in children in endemic areas and in adults in newly infected areas
Vibrio parahaemolyticus	enterotoxin (?) invasive	sea-water marine life	inadequately cooked and improperly handled foods of marine origin (fish, shellfish)	Can produce watery diarrhoea or dysentery; only Kanagawa-positive strains isolated from humans
Non-cholera vibrios	(?) enterotoxin	sea-water; marine life; (?) man	water; food	Cholera-like illness of milder severity
Enterotoxigenic Escherichia coli	heat-labile (LT) and heat-stable (ST) enterotoxins	(?)	water; food	Strains may produce one or both toxins; may mimic cholera in clinical presentation; disease common in young children; probably seasonal; common cause of travellers diarrhoea
Rotavirus	invasive	(?)	(?) person-to-person	Vomiting common with diarrhoea; peak incidence during colder months; almost all cases in children less than 2 years of age; asymptomatic infection frequent in adults and in neonates.

Agent	Pathogenesis	Reservoir	Mode of transmission	Distinguishing characteristics
Shigellae: S. dysenteriae, S. flexneri, S. boydii, S. sonnei	invasive (?) enterotoxin	man	person-to-person; water; food	Dysentery symptoms common but watery diarrhoea can occur. S. flexneri most common in developing countries; low infectious dose; contacts of cases often infected; water-washed disease
Salmonellae (about 2 000 serotypes known)	invasive (?) enterotoxin	animals; man; S. typhi only serotype host-specific for man	food (especially animal products); water; person-to-person transmission in institutional settings	Febrile gastroenteritis; diarrhoea rare in typhoid fever; highest incidence in children; serotypes vary from country to country; multiple antibiotic resistance common; chronic carriage rare

B. AGENTS WHOSE IMPORTANCE AS A CAUSE OF DIARRHOEA IN DEVELOPING COUNTRIES IS PRESENTLY UNKNOWN

Invasive E. coli (specific serotype)	invasive	(?)	food	Produces dysentery and watery diarrhoea; detected by Sereny test
Enteropathogenic Escherichia coli (specific serotype)	(?)	(?)	(?) person-to-person	Institutional outbreaks in infants well documented; relationship to sporadic disease unknown.

Agent	Pathogenesis	Reservoir	Mode of transmission	Distinguishing characteristics
Clostridium perfringens (Type A organisms)	enterotoxin	human and animal intestinal tracts	food (especially cooked meat and poultry and their gravies)	Produces watery diarrhoea and abdominal cramps; common inhabitant of large intestine.)
Staphylococcus aureus (Coagulase-positive strains)	enterotoxin	human nose, skin, faeces	food (especially meat products, pastries, salads)	Produces vomiting and diarrhoea; enterotoxin is heat-stable
Bacillus cereus	enterotoxins	soil	food (especially cereal products, gravies)	Organisms cause two distinct clinical syndromes; one primarily of vomiting and one primarily of diarrhoea.
Yersinia entercolitica	(?) invasive	man; animals	food; water (?) (?) person-to-person;	Clinical syndrome varies with age; high incidence reported in some countries; unusual isolation requirements
Campylobacter jejuni	(?) invasive	(?) poultry	(?) food	Produces febrile gastroenteritis which can be of long duration; unusual isolation requirements
Parvoviruses	invasive	(?)	person-to-person	Cause of diarrhoea in older children and adults; probably many serotypes.

C. PARASITES

Agents	Pathogenesis	Reservoir	Mode of transmission	Distinguishing characteristics
Entamoeba histolytica	invasion	man	food (especially raw vegetables and fruits); water; person-to-person	Dysenteric symptoms - may be confused with shigellosis
Giardia lamblia	(?)	man; animal	water; food (especially raw vegetables and fruits); person-to person	Can produce persistent diarrhoea and malabsorption

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