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Pathogens That Cause Travelers' Diarrhea in Latin America and Africa

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With the advent of rapid and convenient means of transportation, millions of persons travel each year from industrialized to developing countries in the tropics and subtropics. These travelers are at risk for a variety of infectious diseases that are endemic in these areas; the most frequently occurring of these is diarrhea. Studies of groups of travelers to Latin America and Africa have found that approximately one-half develop diarrhea during their stay abroad. Etiologic investigations of these illnesses have demonstrated that the important agents that cause travelers' diarrhea are similar to those that cause diarrhea in children in the developing countries. One-third of the cases are associated with enterotoxin-producing strains of *Escherichia coli*. Smaller proportions appear to be due to rotavirus, Norwalk virus, *Shigella*, *Salmonella*, *Giardia lamblia*, and *Entamoeba histolytica*. Although they have not been fully evaluated in travelers' illnesses in Latin America or Africa, *Campylobacter jejuni*, *Aeromonas hydrophila*, other viruses, and *Cryptosporidium* probably cause some of the currently unexplained cases of diarrhea.

In areas where infectious diseases are highly prevalent, the burden of morbidity falls most heavily on the young. Surviving adults are largely immune to the endemic diseases and become ill only from contact with infectious microorganisms that are novel to them.

With the development of rapid and convenient means of transportation, approximately 12 million persons a year travel from industrialized countries to developing countries in the tropics and subtropics. Because of their limited previous exposures, these travelers are at risk for a wide variety of infectious diseases during their stay abroad. The most frequent illness, regardless of the destination, is diarrhea. The incidence of travelers' diarrhea reflects the extent of exposure to the contaminated environment found in developing countries. This exposure to conditions of contaminated water supplies, inadequate disposal of feces, and nonhygienic food preparation practices allows the traveler to briefly share with the children of these countries a high risk for infectious diarrheal diseases.

The discovery of several important enteric pathogens in the last decade has led to the search for these organisms in childhood diarrhea and to the elucidation of the cause of a majority of episodes of the disease in children in developing countries [2]. Similarly, in the last 10 years, some of these same agents have been found to be important causes of diarrhea in travelers to developing countries. Studies of the etiologic agents of travelers' diarrhea that were conducted from 10 to 20 years ago were able to report an enteropathogen in fewer than 20% of the cases [3]. However, studies begun by Shore et al. [4] and confirmed by Gorbach et al. [5] and Merson et al. [6] determined that enterotoxin-producing strains of *Escherichia coli* are the predominant enteropathogens of travelers' diarrhea.

Because of the importance of the role of enterotoxigenic *E. coli* (ETEC) in this setting, only studies conducted in the 10 years since the role of ETEC was first recognized will be reviewed. At present there are 15 published studies that have been done in Latin America [4–20] and three studies, in Africa [21–23]. Some of these studies were specifically designed to determine the etiology of travelers' diarrhea, whereas others were done to evaluate an intervention for the prevention or treatment of diarrhea. From the latter studies, only the results on the control or placebo-treated subjects were included in this review of the pathogens associated with travelers' diarrhea.

For the studies of trips to Latin America of not more than six weeks' duration, the median attack rate for diarrhea was 52%, with a range of 21%–100% (table 1). In the African studies, the median attack rate was 54% (range, 36%–62%). These attack rates are comparable to those seen in previous studies with small sample sizes but are somewhat higher than the median attack rate of 28% (range, 26%–49%) noted for various parts of Latin

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Table 1. Characteristics of travelers' diarrhea for travelers to Latin America and Africa.

Region, country (year)	Reference	Study population	*N*	Duration of stay (days)	Attack rate (%)	Percentage of cases in which diarrhea was associated with indicated enteropathogen			
						ETEC	*Shigella*	*Salmonella*	Rotavirus
Latin America									
Mexico (1974)	4	Adult tourists	28	19–38	39	36	0	0	NR
Mexico (1975)	5	Students	133	18	29	72	0	0	NR
Mexico (1976)	6	Physicians and family members	121	7	49	45	4	16	4
Mexico (1976, 1977)	7, 8	Students	55	30	40	46	22	0	NR
Mexico (1978)	9	Students	24	28	29	NR	NR	NR	NR
Mexico (1978)	10	Students	NR	NR	NR	NR	NR	NR	26
Mexico (1979)	11	Students	76	21	54	NR	NR	NR	NR
Mexico (1979)	12	Students	164	21	66	NR	NR	NR	24
Mexico, Central America, Caribbean (1980)	13	Students	35	30	71	56	0	0	0
Mexico (1980)	14	Students	66	21	61	39	18	13	21
Honduras (1981)	15, 16	Peace Corps volunteers	22	42	55	28	0	0	36
Mexico (1982)	17	Students	80	29	55	50	10	10	NR
Mexico (1983)	18	Sailors	70	2–3	21	NR	NR	NR	NR
Mexico (1983)	19	Students	30	14	33	50	30	10	NR
Honduras (1984)	20	Peace Corps volunteers	22	21	100	44	0	0	NR
Africa									
Kenya (1977)	21	Peace Corps volunteers	39	35	36	75	0	0	0
Kenya (1978)	22	Peace Corps volunteers	21	28	62	36	0	0	0
Morocco (1979)	23	Peace Corps volunteers	24	28	54	31	15	0	0

NOTE. Abbreviations: ETEC = enterotoxigenic *Escherichia coli*; NR = not reported.

America, the Caribbean, and Africa in the more broadly based studies that have been conducted by Steffen [24]. This discrepancy may not be surprising in that the studies detailed in table 1 were conducted in populations that differ from those consisting of average tourists or business travelers, i.e., in groups of students or Peace Corps volunteers, who generally stay in one location or a few locations for three to five weeks. In other studies, such young adult travelers have been found to have the highest incidence of diarrhea, perhaps because of their more limited previous travel experience and their more adventurous style of travel. Furthermore, although the incidence of diarrhea is usually highest in the first two weeks, the attack rate also increases with the duration of the trip. Thus, the studies reviewed may have overestimated the incidence of diarrhea among the more typical tour group or business traveler.

Ten of the Latin American studies had sufficiently complete reporting of methodology for detection of enteropathogens to permit a comparison of the enteropathogens that were found (table 1). In these studies, enterotoxin-producing *E. coli* were associated with a median of 36% of diarrheal episodes. These organisms were the most commonly identified pathogens in all of the studies, accounting for 28%–72% of cases.

Shigellae were isolated from 0–30% of patients with diarrhea, and salmonellae, from 0–16%. In only a few studies in which adequate culture methods were reported were other bacterial pathogens sought. Invasive *E. coli*, *Vibrio paraheaemolyticus*, and *Campylobacter jejuni* were all identified in stool samples from at least one patient. *Yersinia enterocolitica* and *Aeromonas hydrophila* were not identified, but it appears that none of the studies used optimal methods to isolate these organisms.

Protozoa, namely *Giardia lamblia* and *Entamoeba*

histolytica, were found in 0–9% of the few studies in which they were sought. Another potentially important parasite—*Cryptosporidium*—was not sought in any of the studies.

Rotaviral infection was investigated in six studies by use of a variety of techniques. A median of 22% (range, 0–36%) of the diarrheal illnesses were said to be associated with rotaviruses. The etiologic significance of rotaviruses in these illnesses is unclear, since some studies also found that a high proportion of asymptomatic controls had evidence of rotaviral infection and since all studies noted that patients with rotavirus were commonly (up to 50% of such patients) infected with other pathogens. The only study that looked for serologic evidence of infection due to Norwalk virus during the traveler's stay abroad found that 10% of ill subjects had a significant rise in antibody titer [15].

In the African studies, ETEC were found in a median of 36% of ill travelers. As was found in the Latin American studies, these agents were predominant in all of the etiologic studies (range of identification, 28%–72%). Among other enteropathogens, shigellae were found in 15% of illnesses in one of the three studies and salmonellae were not found in any. Increases in antibody titers to rotavirus were not detected in any ill travelers in the three studies. Rises in antibody titer to Norwalk virus were seen in four of 31 ill persons in one study [23]. Again, other potentially important enteropathogens were not systematically evaluated.

Thus, in the etiologic studies of travelers' diarrhea for travel to both Latin America and Africa, there is a remarkable similarity in the incidence of the disease and in the association with specific enteropathogens. ETEC accounted for the largest proportion of cases, followed, in descending order of identification, by rotavirus, Norwalk virus, *Shigella*, *Salmonella*, *G. lamblia*, and *E. histolytica*. This leaves a small proportion of diarrheal illnesses without a recognized enteropathogen. It is worthwhile to speculate on the possible causes of these illnesses.

(*1*) A proportion of the important enteropathogens may be missed because the laboratory methodologies for their detection are insensitive. For example, ETEC must be detected by specific testing of five to 10 selected *E. coli* from the entire stool flora. This method is relatively insensitive, especially in milder illnesses, in which the enteropathogen constitutes only a fraction of the aerobic stool flora. Likewise, *G. lamblia* colonizes the small bowel, and examination of a single stool specimen, as was done in these etiologic studies, is known to miss a substantial fraction of infections. Thus, it is likely that more sensitive methods would detect higher proportions of the known important agents.

(*2*) Some enteropathogens that are now known to be frequently associated with diarrhea in children in developing countries were not sought with the use of appropriate methods in these studies. Of particular importance may be *C. jejuni*, a common pathogen in such children and a cause of diarrhea and dysentery [25]. *C. jejuni* has been reported to be associated with 15% of cases of travelers' diarrhea occurring in Bangladesh [26] and has also been recognized in stool samples from ill persons returning to Finland from trips to many developing countries, including those in Latin America and Africa [27]. Also of interest is *Aeromonas hydrophila*, which has been found to be significantly associated with diarrhea in children in Australia and Peru ([28], author's unpublished observations). *Aeromonas* has been reported in association with travelers' diarrhea in Asia [29, 30]. *Vibrio* strains have also been associated with diarrhea and should be sought more carefully in stool samples from travelers [26]. *Cryptosporidium* is a parasite that has recently been recognized to cause ~5% of acute childhood diarrheas in developing countries, such as Costa Rica and Peru [31, 32]. It has also been found in the stool samples from Finnish travelers with diarrheal illnesses [33].

(*3*) There may be enteropathogens that are not yet recognized as causes of some of the illnesses. Some agents, such as adenoviruses [34], astroviruses [35], and coronaviruses [36], have been thought to cause diarrhea in children. If this proves to be true, it is likely that they will cause a portion of the illnesses in travelers as well. Still other enteropathogens must exist, since extensive community-based etiologic studies of diarrhea, both in developed and developing countries, can identify an enteropathogen in only ≤50% of cases of acute diarrhea [37].

(*4*) It is possible that a portion of the mild illnesses do not have an infectious etiology. It is likely that this portion is small, since the studies of antibiotic prophylaxis of travelers' diarrhea demonstrate substantial protection against even the diarrheas for which no pathogen was isolated, a finding which suggests that they are actually infectious in etiology [22].

Some limitations of the studies reviewed herein should be noted. The almost exclusive concentration on young adult students and Peace Corps volunteers

provides no information on the pathogens associated with diarrhea that occurs among older or younger (children) travelers. These may be the groups for whom particular concern would be warranted if a serious illness develops during a stay abroad. It is also difficult to generalize from the countries in which the studies have been done to all of Latin America or Africa. Nearly all of the Latin American studies have been conducted in Mexico or Central America; no etiologic information is available on travelers to South America. Likewise, detailed etiologic studies have been done in only two countries in Africa, a sample that does not permit generalization to the entire continent. Nevertheless, the similarities of the findings of the studies that have been performed suggests that we have a reasonably accurate picture of many of the important enteropathogens. Furthermore, the observation that travelers from industrialized countries often become ill from the same enteropathogens that cause childhood diarrhea in developing countries leads us to surmise that several other agents are also likely to be important causes of travelers' diarrhea.

Although fluid replacement of diarrheal stool losses does not depend on the etiology of diarrhea for the patient in question, more specific prophylactic or therapeutic measures may. Knowledge about the enteropathogens associated with travelers' diarrhea and about the changes over time in their identity should greatly facilitate the assessment of the need for, and the likelihood of success of, attempts to prevent or manage this illness.

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