Diarrhea in Nontravelers: Risk and Etiology

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Acute diarrheal illnesses in nontravelers are common and represent a significant health and economic burden in the United States and other developed countries. The likelihood of experiencing diarrhea is increased many fold during travel to developing countries. Extensive overlap exists in the pathogens that cause diarrhea in travelers and nontravelers, although proportions differ and show variation by geographic area and by season, and they change over time. Rates of infection are highest in infants and young children, in whom viral pathogens predominate. Person-to-person transmission may account for more than one-half of cases. In contrast, in many studies, bacterial infections predominate in travelers, who often acquire infection from contaminated food and water. Because of the globalization of the food supply, clinicians in developed countries should expect to continue to see sporadic cases and outbreaks of diarrhea caused by unusual pathogens, such as *Cyclospora* species.

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Traveler's diarrhea is defined by the circumstances of acquisition, not by the specific microbial agent causing it. Nontravelers are also at risk for acute gastrointestinal infections that cause diarrhea. Extensive overlap exists in the pathogens that cause diarrhea in travelers and in nontravelers, although the relative importance of various microbes that cause diarrhea in nontravelers may vary by geographic region of residence, age, and host characteristics and may change over time. Dozens of studies have assessed causes of diarrhea in travelers; relatively few studies have analyzed the entire range of pathogens that cause diarrhea in large populations of nontravelers over time. Much of what is known about diarrhea in nontravelers comes from the study of outbreaks, which may not accurately reflect the usual causes of diarrhea in a population. Such studies also do not allow an estimate of background rates of diarrhea in a population. It is worth noting that, in a world that is extensively interconnected by trade, diarrhea resulting from exposures at home may be associated with ingestion of imported food. Many outbreaks, including those due to infection with *Cyclospora* species [1] and *Salmonella* species [2], have been traced to imported foods. Imported foods may become contaminated with microbes at many different points before they reach the marketplace (e.g., at the time of growth, or during harvesting, processing, packaging, or distribution). This article will examine the following questions:

1. What is the morbidity and mortality associated with diarrhea in nontravelers?
2. What is the etiology of diarrhea in nontravelers?
3. Do causes and consequences differ by country?

CAUSES, SOURCES, AND TRANSMISSION

It is important to bear in mind that many published studies of diarrhea in the United States do not exclude data pertaining to travelers or estimate the contribution of diarrhea in recent travelers to the overall burden of diarrhea. In general, traveler's diarrhea has a short incubation period, so many persons who experience it will experience improvement or will have recovered by the time they return home. Many of the studies that assess diarrhea look specifically at foodborne and waterborne infectious diseases, yet not all infections that cause diarrhea are transmitted by food and water. The source may also be direct person-to-person contact or exposure to animals. Although diarrhea is a common consequence of foodborne and waterborne infections,

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in fact, not all foodborne and waterborne infections cause diarrhea as the main clinical finding (e.g., brucellosis, legionellosis, and hepatitis A).

Ingestion of contaminated food and water is considered to be the cause of most cases of traveler's diarrhea. It should be noted that swallowing of contaminated water, at home or abroad, can also occur during recreational activities in water, such as swimming. In the United States in 2001–2002, a total of 30 (46.2%) of 65 outbreaks attributed to exposure to contaminated water during recreational activities manifested clinically as gastroenteritis [3]. The most common causes were cryptosporidia (50%), in sites with treated water (such as a swimming pool), and toxigenic *Escherichia coli* and norovirus, in freshwater sites.

Although research on traveler's diarrhea has focused on identifying microbial causes, chemical contamination of water can also cause diarrhea. This phenomenon is well documented in the United States and, presumably, occurs elsewhere as well. Data from surveillance of waterborne disease outbreaks associated with drinking water in the United States in 2001–2002 showed that chemicals were the cause of gastroenteritis symptoms in 5 (20.8%) of 24 outbreaks for which a cause was identified [4]. Among the chemicals implicated were copper, ethylene glycol, and ethyl benzene.

Routes of acquisition of diarrhea-causing pathogens are similar in travelers and nontravelers, although a higher proportion of cases of diarrhea occurring in travelers visiting developing areas may be related to contaminated food and water, compared with the proportion of such cases in nontravelers. In the United States, it has been estimated that more than one-half of cases of acute gastroenteritis result from pathogens that have been transmitted from person to person (e.g., rotaviruses and astroviruses) [5].

Few studies have assessed the rates of diarrhea in travelers to the United States. In the 1970s, investigators studied the incidence of new diarrheal illness in persons attending a large meeting held in Miami, Florida [6]. Acute diarrhea developed in 3 (2%) of 147 foreign participants and in 1 (2%) of 51 US participants. *Salmonella* organisms were isolated from one ill participant. In another study, performed in 1975–1984, researchers gathered data through interviews of 20,000 European travelers (primarily Swiss and German travelers) who had returned from 15 different destinations [7]. The mean duration of travel was 2–3 weeks. Although the overall incidence of diarrhea was >30% (range, 4%–51%, depending on the destination), 4% of persons traveling to the United States and Canada reported having experienced diarrhea.

MORBIDITY AND MORTALITY ASSOCIATED WITH DIARRHEA

Studies that can help to define the burden of diarrhea in a population come from multiple sources, but many studies provide only a small part of the overall picture. Many studies focus on a specific population (e.g., a particular age group or persons in a specific location), a specific pathogen or group of pathogens, or one point in time. Various studies use different inclusion criteria (e.g., different definitions of diarrhea and inclusion or exclusion of vomiting and other symptoms) and different terminology (e.g., "diarrhea," "gastroenteritis," "infectious intestinal disease," or "enteritis"). A number of community-based studies have assessed how common diarrhea is in a population. Some of these studies were done decades ago. Some included laboratory studies; others included only verbal histories.

In developing countries and areas, children <5 years old experience a median of 3.2 episodes of diarrhea/child-year [8], and diarrhea accounts for 21% of all deaths among children <5 years old. Substantially lower rates are found in developed countries. In several prospective community-based studies done in the United States in the past, rates of acute gastroenteritis were remarkably similar: 0.63 episode/person-year in Tecumseh, Michigan, in 1965–1971 [9, 10], 0.83 episode/person-year in Cleveland, Ohio, in 1948–1957 [11], and 1.5 episodes/person-year in Charlottesville, Virginia, in 1976 [12].

In the United States, a telephone survey of 12,755 people in the general population was performed in 1998 and 1999 to assess the burden of acute diarrhea [13]. After the researchers excluded subjects with chronic diarrhea, they found that 10% of subjects reported having experienced any episode of diarrhea in the past 4 weeks and that 6% of subjects reported having an episode of an acute diarrheal illness (rate, 0.72 episode of acute diarrhea/person-year). Children <5 years old had the highest rates of illness (1.1 episodes/person-year), and adults ⩾65 years old had the lowest rates of illness (0.32 episode/person-year). Overall, 21% of subjects sought medical care for their illness, 9% visited a health care provider, and 2% were hospitalized for at least 1 night. Among subjects who sought medical care, 16% were asked to provide a stool specimen. The reported prevalence of diarrhea was similar in men and women, in urban and rural areas, and in different geographic areas. The prevalence of diarrhea, its severity, and the presence of concomitant vomiting were highest in the winter months. Not surprisingly, children <5 years old and adults ⩾65 years old were more likely to seek medical care than were subjects in other age groups. These results were similar to those of a survey performed in the United States in 1996–1997, in which the estimated annual incidence of acute diarrhea was 0.75 episode/person-year [14].

When the authors used these estimates of background rates of diarrhea, they projected that 195 million episodes of acute diarrheal illness occurred in the United States in 1999 and that 3.6 million persons were hospitalized at least overnight [13]. As noted above, foodborne infections are one cause of diarrhea. In a study published in 1999, Mead et al. [15] estimated that

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foodborne infections in the United States caused ∼76 million illnesses, 325,000 hospitalizations, and 5000 deaths each year. More recent estimates suggest that 211–375 million episodes of acute diarrhea occur each year in the United States and lead to >900,000 hospitalizations and 6000 deaths annually [14].

A population-based community cohort study of infectious intestinal disease in England involved 70 general practices that were chosen to be representative of all general practices nationally; each practice participated for a year [16]. One in 5 persons reported infectious intestinal disease per year (19.4 episodes/100 person-years). Of those with gastrointestinal illness, 1 in 6 sought medical care from a general practitioner. On the basis of these figures, the authors estimated that 9.4 million cases occur in the community each year in England and that 1.5 million patients seek medical care. In a separate study based on data from 1991 to 1994, it was estimated that infectious intestinal disease was responsible for >300 deaths and 35,000 hospitalizations annually in England [17]. Children <5 years old accounted for more than one-half of the hospitalizations in that study.

In a population-based study conducted in 4 areas of The Netherlands, among participants who completed questionnaires and submitted stool samples over a 17-week period (between March and July) in 1991, the incidence of first episodes of gastroenteritis was 45 episodes/100 person-years or 0.45 episode/person-year [18]. Participants consulted a physician (by telephone or by visit) for 22% of the episodes. Children <10 years old had a higher incidence of gastroenteritis than did older persons. Among schoolchildren, 34% of those with gastroenteritis missed school. Medications were used for 52% of the episodes.

CAUSES OF DIARRHEA

Other studies have tried to identify the causes of acute diarrhea in the general population. In a prospective study in 1996–1997, researchers in Sweden studied adult patients who sought medical care for diarrhea ($n = 851$) and control subjects ($n = 203$) [19]. Overall, enteropathogens were identified in 56% of patients and 16% of control subjects. In adults with acute diarrhea (duration, <1 week) and travelers, they identified an enteropathogen in 65% of cases. The most commonly identified pathogens were *Campylobacter* species (13% of subjects), *Clostridium difficile* (13%), enterotoxigenic *E. coli* (8%), *Salmonella* species (7%), *Shigella* species (4%), calicivirus (i.e., norovirus; 3%), rotavirus (3%), enteroaggregative *E. coli* (2%), *Aeromonas* species (2%), *Giardia* species (2%), *Cryptosporidium* species (2%), and astrovirus (2%). Among the patients included in the study, 50% were hospitalized, suggesting moderately severe illness in the study population. Among the ill adults, 50% had visited a country other than Sweden during the previous 2 weeks. The majority of subjects infected with viruses (66%) and *C. difficile* (75%) had not traveled, but a high percentage of other enteropathogens were found in persons who had traveled recently (e.g., 71% of subjects infected with *Salmonella* species, 88% of subjects infected with *Shigella* species, 70% of subjects infected with *Campylobacter* species, 61% of subjects infected with *Giardia* species, 83% of subjects infected with *Cryptosporidium* species, and 81% of subjects infected with enterotoxigenic *E. coli*). In this industrialized country, persons who had traveled recently made a considerable contribution to the overall burden of diarrhea, although they were more likely to be infected with certain bacterial and protozoan pathogens than were the sick nontravelers.

A prospective population-based cohort study with a nested case-control study was done in The Netherlands to estimate the incidence and causes of gastroenteritis in a general population over a 12-month period (December 1998–December 1999) [20]. The study included an age-stratified random sample of persons registered in sentinel general practices. Participants completed a questionnaire at baseline and, on a weekly basis, sent in a card reporting on gastrointestinal symptoms. Those who developed gastroenteritis symptoms were asked to submit stool specimens, which were tested for pathogenic bacteria, viruses, parasites, and bacterial toxins. Almost 5000 persons participated; 1050 case episodes of gastroenteritis occurred during the study. The overall incidence of gastroenteritis was 28.3 episodes/100 person-years (0.28 episode/person-year). A pathogen was identified for 46% of cases. Viral pathogens were the most common causes of gastroenteritis in the community, accounting for 21% of the cases, with the largest percentage of cases attributable to Norwalk-like virus (norovirus) (11% overall). Bacterial pathogens were found in 5%, bacterial toxins in 9%, and parasites (predominantly *Giardia* species) in 6% of cases. The article includes no mention of testing for *C. difficile.* On the basis of their findings, the authors estimate that 4.5 million episodes of gastroenteritis occur annually in The Netherlands.

In The Netherlands, patients who visited a general practitioner for acute gastroenteritis and an equal number of patients with nongastrointestinal illnesses were invited to participate in a case-control study performed during 1996–1999 through a network of general practitioners that covered ∼1% of the Dutch population [21]. Stool samples were tested for usual bacterial pathogens, viruses (rotavirus, norovirus, and adenovirus), and intestinal parasites (eggs, cysts, and trophozoites). A pathogen was identified in ∼40% of patients (bacteria, 16% of patients; viruses, 15% of patients; and parasites, 8% of patients) and in 9.8% of control subjects. The overall incidence of gastroenteritis was 79.7 episodes/10,000 person-years. *Campylobacter* species was the most common bacterial pathogen detected (10% of cases); *Giardia* species, rotaviruses, and noroviruses were found in 5% of cases each, and *Salmonella* species were found in 4% of cases. The incidence of diarrhea was highest in the youngest

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age groups. For patients included in the study, the median duration of symptoms before consulting a general practitioner was 6 days.

Using the same database described above, researchers studied the association between specific pathogens and age and clinical symptoms [22]. Children <5 years old had the highest rates of infection with rotavirus (21%) and noroviruses (15%), and the percentage of patients who tested positive for these pathogens decreased with increasing age. *Campylobacter* species were the most common type of pathogen in all age groups >5 years old. The most common pathogens in patients with febrile gastroenteritis were *Campylobacter* species (in 15% of patients), rotavirus (9.5%), and *Salmonella* species (6.8%).

In a study of 202 adults (only 2 of whom had recently traveled to Mexico) with acute diarrhea who were sick enough to seek care at a hospital in Chicago between June 1985 and September 1987, investigators assessed the etiology of diarrhea and the potential role for empirical antimicrobial therapy in the treatment of diarrhea in nontravelers [23]. Patients were randomly assigned to receive ciprofloxacin, sulfamethoxazole-trimethoprim, or placebo after stool specimens were obtained for culture. Studies revealed a potential pathogen in 34% of the patients, with the most common pathogens being *Campylobacter, Shigella,* and *Salmonella* species. Treatment with ciprofloxacin shortened the duration of diarrhea, compared with placebo, and increased the percentage of participants who showed improvement or were cured on each of the follow-up days. Patients from whom *Campylobacter, Shigella,* or *Salmonella* isolates were recovered had more-severe illness, compared with other patients. Of note, ciprofloxacin-treated patients who did not have cultures positive for pathogens also had a shorter duration of diarrhea than did untreated patients. The laboratory studies included evaluation for *E. coli* O157 but not for other diarrheogenic *E. coli.* The response to ciprofloxacin suggests that bacteria not sought in this study may be significant contributors to diarrhea in nontravelers with moderate-to-severe diarrhea. Whether similar results would be observed today is unclear given increasing rates of quinolone resistance among *Campylobacter* isolates.

A national study that focused on 281 outbreaks of gastroenteritis in The Netherlands in 2002 found that norovirus was the most common pathogen (54% of cases), followed by *Salmonella* species (4%), rotavirus group A (2%), and *Campylobacter* species (1%) [24]. In outbreak-associated gastroenteritis, the predominant route of transmission overall was person to person (78%), and the most common location for outbreaks was homes for the elderly (57%). An increase in norovirus outbreaks in April and May of 2002 coincided with the emergence of a new norovirus variant, which also caused outbreaks in several other European countries [25].

The Foodborne Diseases Active Surveillance Network (FoodNet) of the Centers for Disease Control and Prevention, with support from the US Department of Agriculture (Food Safety and Inspection Service) and the US Food and Drug Administration, was established in 1996 and provides active surveillance for laboratory-diagnosed foodborne diseases in the United States [26, 27]. As of 2003, the network covered 41.5 million persons (14% of the US population) and involved >450 laboratories. It has provided valuable data on the frequency and severity of foodborne infections and their trends in the United States. Through the network and the system of typing pathogens, investigators have been able to identify connections between laboratory-confirmed cases in different geographic regions that previously would not have been made. The FoodNet system includes surveillance for *Campylobacter* species, Shiga toxin–producing *E. coli* O157, *Listeria monocytogenes, Salmonella* species, *Shigella* species, *Vibrio* species, *Yersinia enterocolitica, Cryptosporidium parvum, Cyclospora cayetanensis,* and the hemolytic-uremic syndrome. Hence, it includes many pathogens that commonly cause diarrhea, but is also misses many others, including other *E. coli, Giardia lamblia, C. difficile, Entamoeba histolytica,* and, importantly, all of the viral pathogens (noroviruses, rotaviruses, adenoviruses types 40 and 41, and astroviruses).

In 2003, a total of 15,600 laboratory-diagnosed infections were reported from the surveillance sites [27]. There are some geographic variations in incidence and predominant organisms, but infections with *Campylobacter, Salmonella,* and *Shigella* species predominate. For these infections, the burden of diarrhea varies by age, with the youngest subjects having the highest rates of infection. For example, the incidence of infection with *Salmonella* species was 122.7 infections/100,000 children <1 year old, 50.6 infections/100,000 children 1–4 years old, and 10.8 infections/100,000 children ⩾5 years old. The system also allows tracking of trends over time and shows, for example, a striking decrease in the incidence of infection with *Campylobacter* species in California [27].

Over time, additional pathogens have been recognized as causes of diarrhea in nontravelers, and specific testing for them has been added in some studies. In a study of community-acquired gastroenteritis in Melbourne, Australia, atypical strains of enteropathogenic *E. coli* were the most frequently identified pathogens (found in 12.8% of patients with acute symptoms and in 2.3% of asymptomatic patients) [28].

The appearance of new strains or novel genetic variants of microbes can also be associated with a shift in the epidemiological profile of infections. Increases in the number of outbreaks of norovirus-associated gastroenteritis were observed in at least 10 different European countries in 2002 [25], including The Netherlands, as described above. Further analysis identified that the increases coincided with the appearance of a new norovirus variant, which had a consistent mutation in the poly-

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merase gene. The biological characteristics of the novel variant that allowed it to spread widely and cause multiple outbreaks are still being investigated.

In a recently published study, researchers in Cincinnati, Ohio, examined the prevalence of diarrheogenic (enterotoxigenic, enteroinvasive, enterohemorrhagic, enteropathogenic, diffusely adherent, and enteroaggregative) *E. coli,* as well as other viral and bacterial pathogens, in children with acute enteritis [29]. The study included 1327 children (643 inpatients $\leqslant$18 years old and 684 children $\leqslant$5 years old seen in the emergency department) with diarrhea and/or vomiting, as well as 555 healthy control children. Usual bacterial pathogens were found in 2.1% of the ill children and in 0.5% of the control subjects; rotavirus was found in just >20% of both inpatient and emergency department patients, versus 1.1% of control subjects. Diarrheogenic *E. coli* was found in 24.4% of emergency department patients and 14.1% of control subjects. Enteroaggregative *E. coli,* the most commonly identified diarrheogenic *E. coli,* was significantly more common in emergency department patients than in control subjects. The researchers concluded that diarrheogenic *E. coli* may account for up to 10% of all cases of acute gastroenteritis in children in the United States.

Because diarrhea is relatively common in travelers to developing countries, can disrupt travel plans, and may occur where access to medical treatment may be limited or of uncertain quality, many studies have examined ways to prevent or limit the effect of traveler's diarrhea. One approach has been self-treatment with antimicrobial agents for acute diarrhea. For nontravelers, self-treatment with antimicrobials is generally not recommended. Diarrhea in nontravelers is much less common overall and may be more likely to be caused by viruses than is diarrhea in travelers, and medical care is widely available and may include antimicrobials. Among participants interviewed by telephone in the study by Imhoff et al. [13], 33% of those with acute diarrhea received antidiarrheal medication, and 12% received an antibiotic. Among the 21% overall who sought medical care, 38% received an antimicrobial.

Looking to the future, there are several factors that could lead to an increase in diarrhea in nontravelers. These include factors that make the host more vulnerable (e.g., expansion of populations of people who are elderly, HIV infected, or immunocompromised because of disease or chemotherapy) and increased ingestion of contaminated food (e.g., more imported produce, mass produced and processed foods that may lead to mass contamination, and more meals eaten outside the home).

In conclusion, diarrhea occurs at home, as well as during travel, but the likelihood of diarrhea is increased many fold during travel to developing countries. Acute diarrheal illnesses in nontravelers are common and represent a significant health and economic burden in the United States and other developed countries, but associated mortality is low. Extensive overlap exists in the types of pathogens seen in travelers and nontravelers, although proportions of pathogens differ and show variation by geographic area and season and change over time. Rates of infection are highest in infants and young children, in whom viral pathogens predominate. Person-to-person transmission may account for more than one-half of cases. In contrast, bacterial infections predominate in many studies in travelers, who often acquire infection from contaminated food and water. Recent studies suggest that diarrheogenic *E. coli* may be more common in developed countries than previously was thought. This observation deserves broader study because of its implications for treatment. Given the globalization of the food supply, clinicians in developed countries should expect to continue to see sporadic cases and outbreaks of diarrhea caused by unusual pathogens, such as *Cyclospora* species.

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