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# Epidemiology of Infectious Diarrhea

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## Basic Concepts

Diarrhea is a symptom of very diverse causes, and it is characterized by three circumstances: consistency, number, and volume of waste excretions. The consistency of the feces is liquid, or pastelike, adapting to the form of its receptacle. The frequency and volume of the excretions can be seen to increase within a highly variable range, starting with very slight diarrhea up to that which can put the patient's life at risk. The volume of feces in a healthy adult is almost 300 ml. Diarrhea's pathogenic mechanism is responsible for an acceleration of intestinal transit.

The World Health Organization (WHO) defines diarrhea as "the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual. It is usually a symptom of gastrointestinal infection, which can be caused by a variety of bacterial, viral and parasitic organisms. Infection is spread through contaminated food or drinking-water, or from person to person as a result of poor hygiene." Dr. Sherwood L. Gorbach states: "Acute diarrhea is often defined as the occurrence of three or more unformed bowel movements a day or any number of such movements when accompanied by fever, abdominal cramps, or vomiting." While carrying out studies epidemiologists can use other operative definitions adapted to the objectives of each study, taking into account the sensitivity and specificity of the definitions in each case.

From this three clinical syndromes can be described:

- a. Acute watery diarrhea: Beginning abruptly, it consists of the passing of a great amount of liquid feces without blood. Main symptoms usually remain for less than 7 days (but can persist up to 2 weeks at most); it can be accompanied by vomiting and fever, but it also presents a greater problem, the possibility of dehydration. It is a result of the alteration of absorption and secretion balance. Causal agents include rotavirus, *Campylobacter*, nontyphoidal *Salmonella*, enterotoxigenic *Escherichia coli*, *Vibrio cholerae*, and so on.
- b. Dysentery: When diarrhea is accompanied by visible traces of blood in the feces, it is called dysentery. It is a result of damage suffered by intestinal mucus in the colon ravaged by an external agent, such as *Shigella dysenteriae*, nontyphoidal *Salmonella*, *Entamoeba histolytica*, and *Campylobacter*. Rapid weight loss is the most frequent consequence.
- c. Persistent diarrhea: With a duration of more than 14 days, it can start as acute diarrhea or dysentery. It should not be confused with chronic diarrhea due to noninfectious causes. It can produce noticeable weight loss and a risk of dehydration. Causal agents include *Shigella*, enteroaggregative *E. coli*, *Cryptosporidium*, and *Giardia*.

The consequent effects of diarrhea can be highly variable: from a slight and transitory condition that spontaneously resolves itself to its more severe incarnations where loss of water and electrolytes can be an important factor. The resulting hypovolemic shock can cause renal failure, disorders in other organs, and in the most vulnerable patients it can prove to be fatal.

The appearance of diarrhea results from confrontation between aggressive external elements (a causal agent's toxicity or virulence, the quantity of the inoculant dose) and the body's own defense mechanisms. Among the defense mechanisms combating infectious agents, the following can be highlighted: gastric acid, gastrointestinal mucus, intestinal motility, bile salts, regular intestinal bacteria, macrophage cells, lymphocyte cells, and type IgA immunoglobulin in the mucus. Additionally, there are genetic factors that can affect resistance to particular infections; for example, blood group 'O' individuals are at greater risk of suffering from cholera, whereas the so-called nonsecretory individuals, with certain FUT 2 gene mutations, are partially resistant to norovirus infection. Other specific external circumstances such as the ingestion of alcohol or (nonvolatile) red wine could act as protective factors against infection by *Salmonella* when the ingestion of the microorganism and those kind of drinks is almost simultaneous. There are few vaccines effective against diarrheal diseases. Recently, a vaccine against rotavirus has been authorized, which is expected to show positive results.

Occasionally, diarrhea presents itself as an accompanying symptom of chronic conditions, such as the collateral effect of some medicines or a sign of malnutrition. However, this article discusses diarrhea as the principal effect of infections and poisoning by microorganisms, ingestion of animals, plants, or compound chemical toxins.

In this context, it is very common to associate diarrhea with the ingestion of food that is either contaminated or well past its best. But infections and food poisonings do not always present themselves as the clinical profile in which diarrhea is predominant. For example, in botulism or some marine biotoxins the essential factors are the neurological signs – diarrhea may or may not be present.

Infant mortality from acute diarrhea has reduced throughout the last years of the twentieth century, essentially due to improvements in sanitation and the implementation of Oral Rehydration Therapy programs by the WHO. Even so, in the year 2000, it caused approximately 2 million deaths. The vast majority was related to avoidable causes.

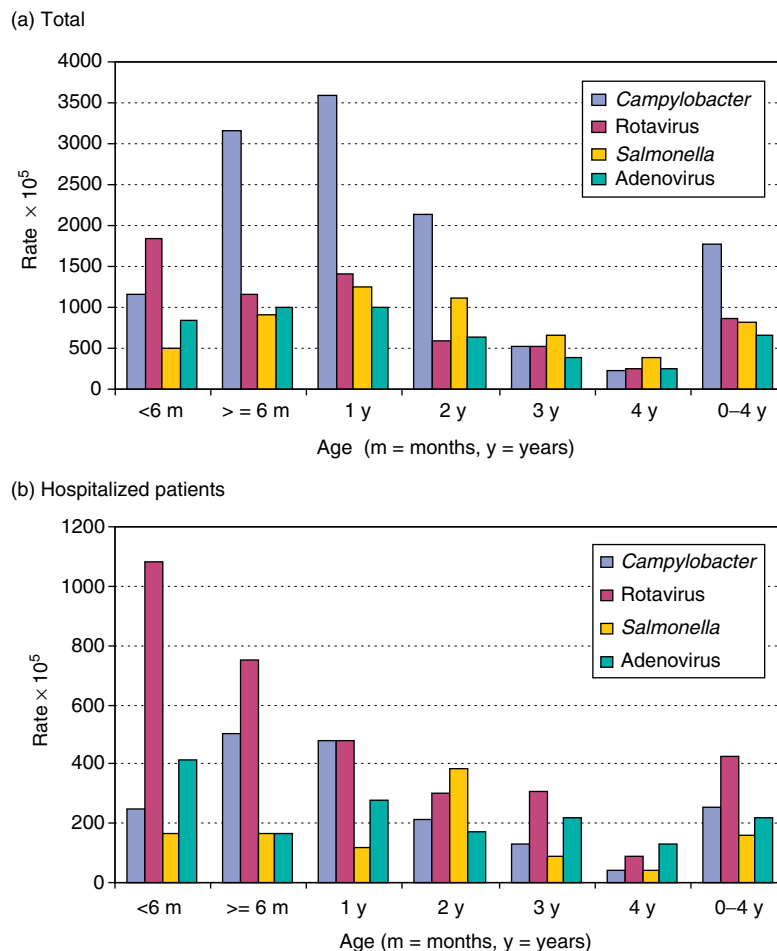
In the distribution of diarrhea cases there are geographic and age-related differences. With as much respect to etiology as to the seriousness of the cases, somewhat different patterns have been found, according to whether the countries are industrialized or not. Certain parasites and cholera, for example (of whom the WHO is continuously in international pursuit), are still frequent in some underdeveloped regions where favorable conditions for their propagation exist. Bad conditions of individual hygiene, nutrition,

and existing public sanitation in many poor countries favor the presence of diarrhea. Even when incidences of the infection do not display such great geographic differences, in the case of some viruses, the indicators in terms of its lethality are noticeably different; for example, rotavirus is very frequent in all types of countries, but its severity (mortality rate) is greater in poor countries. In England and Wales, the microorganisms that most frequently cause diarrhea are *Campylobacter*, rotavirus, norovirus, *Salmonella*, *Giardia*, and *Cryptosporidium*.

Since means have been available for the virological diagnosis of gastroenteritis, it has been seen that viruses are the most common cause of diarrhea in Western countries. Generally they do not cause very serious illnesses at the individual level, but they are responsible for a considerable social burden in the form of hospital admissions and scholastic and employee absenteeism.

The age of patients, the seriousness of the illness, and the capabilities of laboratories are factors that determine the scope of the etiological diagnosis. Age also relates to the etiology of diarrhea (Figure 1) and to the probability of fecal analyses. Faced with a similar clinical profile, a child does not have the same probability as an adult of receiving an etiological diagnosis: in the child's case it is more likely. The same happens with serious conditions in comparison to slight ones. The slight diarrheas often go without etiological diagnosis. This is also the case with conditions caused by agents that are not detected by the laboratory participating in the analysis. Age bias, age, and technical ability need to be considered when analyzing epidemiological statistics. However, epidemiological studies were performed in England and Holland at the end of 1990s and in the United States in 2001 and 2002, in which a thorough fecal examination of all patients was undertaken, independent of their age and the seriousness of their condition, including those patients who no longer showed symptoms of diarrhea. In these studies, fecal examination was also carried out in healthy control subjects, so that the frequency in which specific microorganisms appeared could be compared with asymptomatic subjects.

Usually the etiological diagnosis of acute infectious (or toxic) diarrhea is obtained by fecal analysis: wet mount, coproculture, antigen detection, toxin detection, or other analyses. Specialized laboratories can use more complex techniques that, generally, prove to be more sensitive and specific, but are also more expensive and difficult. Nevertheless, many of the coprocultures a standard laboratory requests and examines are negative. A negative result can be the consequence of the following reasons: diarrhea is not



**Figure 1** Annual incidence of sporadic cases of diarrhea by etiology among children 0–4 years old (total population of 0–4 years old: 11 800; Castellón, Spain: EDICS, 2004). *Source:* Internal reports of the Public Health Center of Castellón, data elaborated for the authors.

actually infectious, it is caused by an agent for which the laboratory has no data, there is a failure in the test sensitivity, the patient may have taken antibiotics, or there may have been problems in fecal transport. Cases that have returned negative results are a mixture of etiologies, and for that reason further investigation makes little sense. In the EDICS study (Study of Infectious Diarrhea in Castellón) of risk factors in infantile diarrhea, no risk factors were found associated to the cases with a negative fecal analysis result. On the contrary, risk factors were found in cases of campylobacteriosis, salmonellosis, or rotavirus. This indeed suggests that the group of negatives is a mixture of different etiological cases without common origin and with few shared risk factors. The appearance of vomit as an initial symptom, the absence of fecal blood (macro- or microscopic,) and low PCR (reactive C protein) are signs suggestive of viral etiology, especially in children.

### The Epidemiological Point of View: Sporadic and Epidemic Cases

Faced with an epidemiological case of diarrhea two questions arise: one, if the etiology is already known; two, if there are more cases related to the original. These two elements are represented in **Table 1**, where each cell signifies a distinct epidemic concern.

There are noticeable differences in modes of approaching the epidemiological study of diarrhea cases according to their sporadicity or pertinence to an outbreak. Certain microorganisms have a preference to appear fundamentally as one of these forms. As such, *Campylobacter* or rotavirus constitutes the majority of sporadic cases, not excluding the possibility of producing outbreaks. On the contrary, *Salmonella* and, especially, norovirus more characteristically present themselves in the form of outbreaks. From the epidemiological point of view, it could be said that epidemic cases 'come' to the investigator as one, whereas the investigator 'goes' in search of the sporadic cases and reunites them for their studies.

Among the sporadic cases there is a group, which in fact belongs to small clusters, that escapes common systems of epidemiological monitoring and needs special investigations. This group of apparently sporadic cases (but which, in fact, are not sporadic) can only be detected by the existence of an exceptionally good monitoring system or by performing specific studies. Steen Ettenberg and other collaborators performed a specific study on cases registered throughout Denmark in the 1990s and found that 13.3% of *Salmonella enteritidis*, 10.4% of *Shigella sonnei*, 5.6% of *Salmonella* serotype *Typhimurium*, 3.2% of *Campylobacter*, and 2.0% of *Yersinia enterocolitica* cases belonged to this type of clusters, which is a large majority unknown to epidemiological monitoring systems. In absolute terms, the cases of campylobacteriosis were the most numerous due to the large amount of patients diagnosed with the infection in the last years of the study. In a much smaller study in Castellón (Spain), 10 clusters of this type were identified after systematic investigation of coprocultures in an area of 250 000 inhabitants. Small family clusters of *Campylobacter*, *S. enteritidis*, rotavirus, and intestinal adenovirus were found.

In addition to the etiology and level of aggregation, a third question arises: the source of infection and its mechanism of transmission. When the etiology is well known, the epidemiology of the agent involved is generally known. **Table 2** summarizes some epidemiological characteristics of five infection sources and significant mechanisms of transmission. **Figures 2 and 3** represent two outbreaks of diarrhea by norovirus in residential homes for the elderly; these charts clearly demonstrate two mechanisms of transmission. **Figure 2** shows a specific outbreak transmitted by foods (foodborne point source outbreak), and **Figure 3** shows an outbreak, beginning gradually and progressively exacerbating, in which the transmission mechanism was predominantly 'person to person' and environmental (surfaces, fomites). **Figure 4** represents a simple theoretical diagram for the investigation of transmissible disease cases by using the ARMIGO system (agent, reservoir, mechanism of transmission, individual, groups, other people).

Following an outline inspired by the epidemic cases of **Table 1**, three situations can be distinguished according to the characteristics of the affected population. First, a defined, open population with a specific exposure, which refers to people who only momentarily shared an exposure factor, for example, attending a shared dinner or banquet. Second, a defined, closed population with lasting exposure factors, for example, permanent residents within a closed institution, who continually share meals, places, and activities. And third, an indefinite population, with or without specific exposure, which occurs when there is no obvious relationship between people and they are implicated in an outbreak, solely by sharing an exposure factor distributed throughout the population. In the case of laboratory analysis, an epidemic is identified where some rare microorganism in unusually large numbers of people is detected in a fairly prolonged time frame. For example, an outbreak that occurred in the United States in the first half of 2008 was

**Table 1** Epidemiologic first approach to a case of diarrhea

			<i>Etiology</i>	
			<i>Known</i>	<i>Unknown</i>
Aggregation	Sporadic	Usual	A	B <sup>a</sup>
		Unusual in the area	C	D <sup>a</sup>
Epidemic		Small cluster	E	F
		Outbreak cohort defined <sup>b</sup>	G	H
		Epidemic cohort undefined	I	J

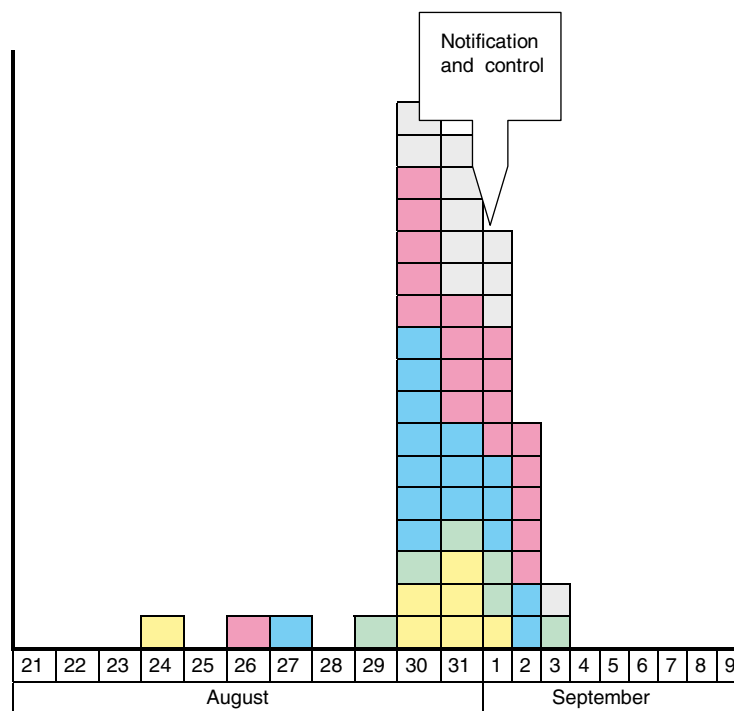
<sup>a</sup>Defined by clinical symptoms, i.e., clinical diarrhea and fecal specimens of usual or unusual characteristics.

<sup>b</sup>Open cohort in an 'open' setting (i.e., banquet) or in a 'closed' setting (i.e., nursing home).

**Table 2** Source and mechanisms of transmission in epidemic and sporadic cases of diarrhea

<i>Point source food water</i>	<i>Sustained source – food/water (localized or scattered)</i>	<i>Person–person</i>	<i>Environmental surfaces – fomites</i>	<i>Animal</i>
Outbreak	Outbreak, sporadic	Outbreak, sporadic	Sporadic and outbreak	Sporadic or little outbreak
Epidemic curve, cases clustered	Epidemic curve, cases scattered	Epidemic curve, cases occur in waves	Epidemic curve, irregular	
Urgent notification	Maybe urgent notification	Delayed notification	Delayed	Delayed
Cases shared same kitchen or food supplier	Cases shared same kitchen or food supplier	Cases shared same house/ward at the same time	Cases shared same ward at same and different times	Cases shared same animals
Food handles affected	Food handlers affected	Household members, contacts affected	Household, roommates, affected	Persons in contact with animals
Agent predominantly spread via food/water	Agent predominantly spread via food/water	Agent predominantly spread via person to person	Agent predominantly spread via environment	Agent predominantly spread via animal contact
<i>Bacillus cereus</i> , <i>C. perfringens</i> , <i>Salmonella</i> , norovirus	<i>Cryptosporidium</i> (tap water), <i>Salmonella enterica</i> (scattered distributed in the food chain), <i>Campylobacter</i> (sporadic)	Rotavirus, norovirus, <i>Shigella</i>	Norovirus	<i>Campylobacter</i> , <i>Salmonella</i> (i.e., some serotypes very indicative of reptiles)

Note: Mixed mechanisms of transmission may be present. Endogenous infection, as may be the case of *Clostridium difficile*, is not included.

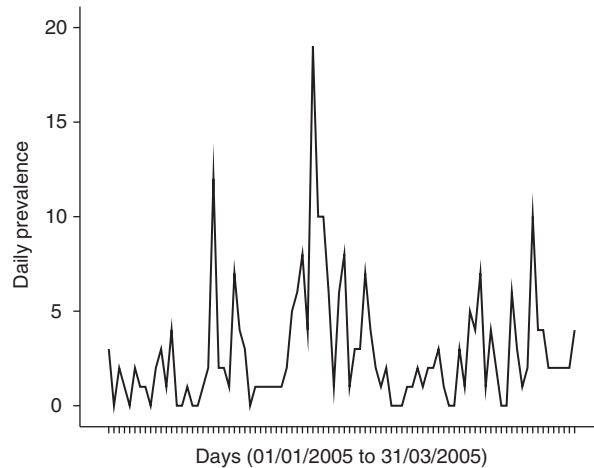


**Figure 2** Epidemic curve of a point source foodborne outbreak of norovirus (Castellón, Spain, 2004). Colored blocks represent different wards of residents and gray blocks represent workers. Source: Internal reports of the Public Health Center of Castellón, data elaborated for the authors.

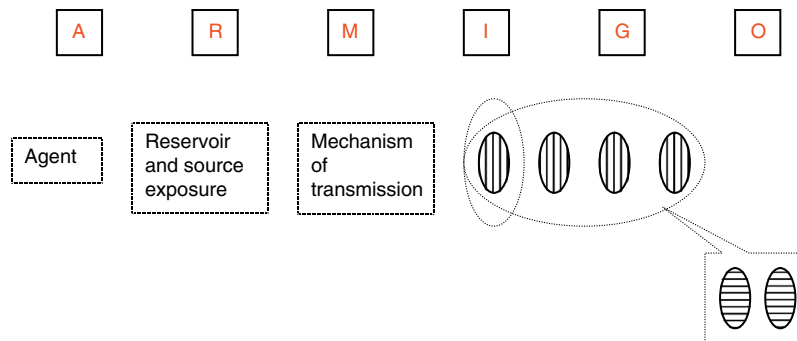
produced by *Salmonella* Saintpaul with the same genetic fingerprint that affected more than 500 people in 32 states. The epidemic was related to the consumption of tomatoes distributed throughout the country.

### Some of the Microorganisms Capable of Producing Diarrhea and Their Principal Features

Table 3 shows the agents that most frequently cause diarrhea, and Table 4 summarizes the more relevant epidemiological features of the diarrhea caused by these agents. Some of these microorganisms are discussed below.



**Figure 3** Daily prevalence of cases of diarrhea and vomiting during a 90-day period, in a nursing home where a person-to-person and environmental transmission outbreak occurred in February 2005 (Castellón, Spain, 2005). *Source:* Bellido-Blasco JB, Rubert-Escrig C, Salvador-Ribera MM, et al. (2009) Outbreaks of acute viral gastroenteritis in geriatric homes: threshold detection system for prevalence (SiDUP). *Rev Esp Salud Publica* 83(5): 669–678.



**Figure 4** A schematic theoretical diagram of a communicable transmissible disease, for example, diarrhea, obtained by using ARMIGO system. *Agent:* bacterial, viral, other (biotoxin, chemical); *reservoir and exposure source:* animal, soil, surfaces, water, food, ill person, carriers; *mechanism of transmission:* food, water, hands, aerosol, or dust swallowed via mouth; *individual at risk:* age, earlier health status, genetic susceptibility; *group at risk:* same opportunity to exposure; *other related people:* contact with primary ill or asymptomatic person.

## Viruses

### Rotavirus

This was identified by Ruth Bishop in 1973 and was named as such because of its ‘wheel-like’ form. There are various groups of rotavirus capable of producing infections in humans. The vast majority of cases are children infected by group A rotavirus. Group B is related to diarrheas in adults and group C to slight diarrheas at any age. Other serogroups are zoonotic and are possibly transmitted by some animals. Rotavirus is the main etiological agent for serious diarrheas in children all over the world. At a very young age, a large number of children have already been infected or reinfected.

Rotavirus has limited capabilities for producing outbreaks. The most important problems it constitutes are sporadic and hospital cases. Many cases are relatively serious infections that require hospitalization. According to a study of common rotaviral diarrhea in children under 5 years of age, carried out in 2000 and again in 2004 in Castellón, almost half of the patients were hospitalized. In nonindustrialized countries, hospitalizations are fewer because welfare services are less accessible; mortality rates, however, are greater. Year 2006 saw the authorization of two new oral vaccines that promise to be effective: RotaTeq® and Rotarix®.

### Norovirus

Previously known as ‘Agent Norwalk,’ this virus was identified by Albert Kapikian in 1972. It is related to the *Caliciviridae* family, of which only norovirus and sapovirus cause diarrhea in humans – the former preferentially causing epidemic cases (outbreaks) and the latter causing sporadic ones. Norovirus, especially genogroups I and II, actually constitutes the most frequent cause of viral diarrhea epidemics in industrialized countries.

If rotavirus is characterized by producing sporadic cases, norovirus characteristically produces outbreaks; especially in semi-enclosed spaces such as residential homes for the elderly. The infection originates from diverse sources: foods, water, patients,

**Table 3** Infectious agents that commonly cause acute diarrhea (infectious and others)

<i>Viruses</i>	<i>Bacteria</i>	<i>Parasites</i>	<i>Others (some examples)</i>
Rotavirus ( <i>Reoviridae</i> )	<i>Campylobacter</i>	<i>Giardia</i>	Scombroid fish
Norovirus ( <i>Caliciviridae</i> )	<i>Salmonella</i>	<i>Cryptosporidium</i>	Diarrhetic shellfish
Sapovirus ( <i>Caliciviridae</i> )	<i>Shigella</i>	<i>Entamoeba histolytica</i>	Mushroom
Adenovirus ( <i>Adenoviridae</i> )	<i>Yersinia</i>	<i>Cyclospora</i>	<i>Robinia pseudoacacia</i>
Astrovirus ( <i>Astroviridae</i> )	<i>Escherichia coli</i>	<i>Balantidium coli</i>	Chemicals
Torovirus ( <i>Coronaviridae</i> )	<i>Clostridium difficile</i>	<i>Isospora belli</i>	
Coronavirus ( <i>Coronaviridae</i> )	<i>Clostridium perfringens</i>	<i>Blastocystis hominis</i> <sup>a</sup>	
	<i>Bacillus cereus</i>		
	<i>Vibrio parahaemolyticus</i>		
	<i>Vibrio cholera</i>		
	<i>Staphylococcus aureus</i>		
	<i>Clostridium botulinum</i>		

<sup>a</sup>Controversial pathogenicity. High fecal concentration of *B. hominis* may be a pathogenicity criterion.

and environment. The fingers are easily contaminated. A small dose of inoculant is sufficient to produce symptoms in susceptible people. On wood, metal, or plastic surfaces, the virus can survive for hours or even days. It has been proven that transmission is possible through typical hand-to-surface contact, such as door handles, telephone receivers, or taps. An experimental study found that contaminated fingers could transfer the virus to the clean surfaces they touch by up to seven times, and at least 14 people could be contaminated by touching the same surface.

Alternatively, it is known that certain subjects are genetically resistant to infection by norovirus. The polymorphism of gene FUT 2 divides into secretory and nonsecretory individuals, who are susceptible and resistant, respectively. Approximately 20% of Caucasian subjects are nonsecretory. However, recently it has been seen that nonsecretory subjects are not totally resistant, suggesting some norovirus strains use alternative routes of infection. The characteristics of norovirus make it difficult to produce a vaccine against it.

### Adenovirus

This belongs to the *Adenoviridae* family. Within the adenovirus genus, serotypes 40 and 41 are responsible for cases of diarrhea. It is possible to identify them in feces by ELISA techniques or latex agglutination, but serologic determinations useful for the diagnosis of respiratory infections by adenovirus do not have the same use in gastroenteritis profiles.

These serotypes generally cause cases of infantile diarrhea throughout the year. The only demonstrated mechanism of infectious transmission is direct contact between people. Perhaps they have a limited epidemic potential. The infectious capacity of this virus is not accurately known.

### Astrovirus

This was first identified in 1975 in a fecal examination among children with diarrhea. The *Astroviridae* family, to which it belongs, was established in 1993, and was named after its star-shaped appearance.

It causes diarrhea in children and adults, with a slight seasonal pattern of predominance in cold months in regions with a temperate climate. The infectious capacity is high, perhaps very few viral particles can produce disease. Epidemiological data suggest that immunity does not last and is serotype specific. Few laboratories can diagnose the routine of this infection. It is believed that the virus can be an important factor in hospital diarrheas as much as in external cases.

### Torovirus and coronavirus (RNA virus)

These belong to the *Coronaviridae* family. Among the viruses that cause diarrhea in humans, they are the only ones that possess envelopes. It is believed that the torovirus produces acute diarrhea in children and can also be an important factor in nosocomial diarrhea. Coronavirus occasionally produces diarrhea, but it gained importance as a result of severe acute respiratory syndrome (SARS) outbreaks, originated by coronavirus with a great capacity for environmental and person-to-person dissemination. The elimination of the virus in feces is less at the beginning of the illness. However, viral particles have been found several months after the symptoms first started.

## Bacterias

### *Campylobacter*

*Campylobacter*, especially *Campylobacter jejuni*, is responsible for the majority of bacterial gastroenteritis cases in the industrialized countries. It is a germ that grows little or nothing in foods. This is the probable cause of its limited epidemic potential and the scarcity of known outbreaks. Some relationships to the ingestion of milk or public drinking water have been described. However, the majority of diagnosed cases are sporadic, essentially occurring in very small children and with little evidence of any seasonal pattern.

**Table 4** Information relevant to infectious agents that commonly cause acute diarrhea

<i>Virus</i>	<i>Usual symptoms</i>	<i>Duration</i>	<i>Diagnostic methods</i>	<i>Reservoir</i>	<i>Transmission</i>	<i>Incubation period</i>	<i>Period of communicability (human duration of shedding)</i>	<i>Susceptibility</i>	<i>Outbreaks versus sporadic cases</i>
Rotavirus	Fever, vomiting, diarrhea (infants)	4 days (3–9 days)	EIA, latex agglutination	Human (animal?)	Human (fecal–oral) (aerosol?)	2 days (1–3 days)	4 days (2–7 days)	Children (infants, toddlers)	Sporadic (sometimes epidemic), nosocomial
Norovirus	Diarrhea, malaise, vomiting	1–3 days (1–8 days)	EIA RT–PCR	Human (animal?)	Human (fecal–oral), food, water, surfaces, aerosol from vomitus	24 h (6 h–48 days)	3 days (1 day to weeks)	All ages, elderly; genetic resistance (FUT 2 polymorphisms)	Epidemic more than sporadic
Adenovirus	Diarrhea, vomiting, low-grade fever	2–4 days (1–7 days)	EIA, latex agglutination	Human	Human (fecal–oral)	2–3 days (2–10 days)	5 days (3–11 days)	Children, all ages	Sporadic
Astrovirus	Diarrhea, malaise, vomiting, low-grade fever	2–5 days (1–14 days)	EIA RT–PCR	Human	Human (fecal–oral) (aerosol?)	1–2 days (0.5–4 days)	1–4 days (1 day to weeks)	Children (infants, toddlers)	Sporadic nosocomial
<i>Bacteria</i>	<i>Usual symptoms</i>	<i>Duration</i>	<i>Diagnostic methods</i>	<i>Reservoir</i>	<i>Transmission</i>	<i>Incubation period</i>	<i>Period of communicability (human duration of shedding)</i>	<i>Susceptibility</i>	<i>Outbreaks versus sporadic cases</i>
<i>Campylobacter</i>	Diarrhea (bloody), abdominal pain, fever	3 days (1–7 days)	Fecal culture	Animals (poultry and cattle), raw poultry meat	Poultry, milk, tap water	3 days (1–7 days)	Variable (50% negative after 3 weeks)	Children, all ages	Frequent sporadic, rare outbreaks
<i>Salmonella</i> (nontyphoidal)	Diarrhea, fever, abdominal pain, malaise	2–4 days	Fecal culture	Animal reservoirs (poultry–eggs, cattle, pigs, turkey, others)	Foods (poultry, eggs), human contact, water	24 h (8–24 days)	5 weeks (rarely carriers for some years)	All ages	Both; foodborne, others outbreaks, sporadic
<i>Shigella</i>	Diarrhea, fever, abdominal pain, malaise	3–4 days (2–6 days)	Fecal culture	Human	Human contact, food, water	3 days (1–7 days)	Days to weeks	All ages (children in day care centers)	Yes, foodborne, day care
<i>Yersinia enterocolitica</i>	Diarrhea, fever	2–3 days (2 weeks)	Fecal culture (CIN medium)	Animal (asymptomatic carriage in pigs and cattle)	Foods, water, contact (human and animal)	3–7 days (2–11 days)	2–3 weeks (rarely months)	Young children aged <5 years, all ages	Sporadic cases and rarely outbreaks (households)

(Continued)



**Table 4** Information relevant to infectious agents that commonly cause acute diarrhea—cont'd

<i>Virus</i>	<i>Usual symptoms</i>	<i>Duration</i>	<i>Diagnostic methods</i>	<i>Reservoir</i>	<i>Transmission</i>	<i>Incubation period</i>	<i>Period of communicability (human duration of shedding)</i>	<i>Susceptibility</i>	<i>Outbreaks versus sporadic cases</i>
<i>Yersinia pseudotuberculosis</i>	Fever, abdominal pain (mesenteric adenitis), diarrhea		Fecal culture (CIN medium)	Animal (rodent and wild birds); not still clear	Foods (fresh: lettuce, raw carrots) water; not still clear	3–7 days (2–11 days)	2 days after the symptoms	Children, all ages	Sporadic and epidemics in some countries
Enterotoxigenic <i>Escherichia coli</i> (ETEC)	Diarrhea (watery) cramps	3–5 days (0.5–5 days)	Fecal culture (not conventional)	Animals	Fecal–oral (food, water, person to person)	10–72 h	May be prolonged	Adults, infants, children	Both (travelers diarrhea)
Enteropathogenic <i>E. coli</i> (EPEC)	Diarrhea (watery) vomiting, fever	2–6 days (2–14 days)	Fecal culture (not conventional)	Animals	Fecal–oral (nurseries)	9–12 h	May be prolonged	Infants, children	Sporadic, outbreaks
Enteroinvasive <i>E. coli</i> (EIEC)	Diarrhea (watery, bloody), fever	1–2 weeks	Fecal culture (not conventional)	Animals	Food?	10–18 h	As long as excretion persists	Adults, all ages	Foodborne
Enteraggregative <i>E. coli</i> (EAEC)	Variable (cramps, vomiting, diarrhea, fever)	Acute and chronic (>14 days)	Fecal-specific analysis (PCR)		Fecal–oral; food and water	8–18 h (or 20–48 h)	1 week (more in children)	Children, adults, HIV infected; genetic resistance (IL-8 polymorphisms)	Outbreaks (travelers diarrhea)
Enterohemorrhagic <i>E. coli</i> EHEC (including VTEC O157)	Diarrhea (bloody), vomiting (hemolytic uremic syndrome; HUS)	1–9 days (1–12 days)	Fecal culture (specific) and PCR	Gastrointestinal tract of animals (cattle and others)	Food, direct contact, secondary cases, water (farm dust?)	1–3 days (0.5–12 days) (HUS 5–10 days after diarrhea)	Asymptomatic carries, ill people	Children, all ages	Sporadic and outbreaks
<i>Clostridium difficile</i>	Diarrhea, abdominal pain, fever pseudomembranous colitis	Improvement after discontinuation of antibiotics	Toxin and culture (fecal samples), histological	Human (children <2 years) and environment (spores)	Fecal–oral, from patients or environment (spores)	Not well determined; 4–9 (of starting antibiotics) (1 day–6 weeks)	Endogenous infections, and transient infectiousness in diarrhea cases	Elderly, hospitalized, debilitated people	Both, hospital outbreaks
<i>Clostridium perfringens</i>	Diarrhea, nausea	=< 24 h	Fecal cultures (10 <sup>6</sup> per gram), enterotoxin in stool	Human (healthy) and animals, soil, sewage	Food (stored cooked meat)	10–12 h (6–24 h)	Not communicable from person to person	All ages	Foodborne outbreaks
<i>Bacillus cereus</i>	Nausea and vomiting or colic and diarrhea	=< 24 h	Fecal cultures: + in 2 cases and – in controls (outbreaks)	Soil, environment, foods	Food (rice, cereals, pasta, spices, dried food)	0.5–6 h (vomiting) 6–24 h (diarrhea)	Not communicable from person to person	All ages	Foodborne outbreaks

<i>Vibrio cholerae</i> (O1 or O139)	Profuse painless watery diarrhea and vomiting	Severe diarrhea	Fecal culture	Human, and maybe in brackish water	Human contact, food, water	2–3 days (1–5 days)	Few days after recovery (rarely months, carriers)	All ages; genetic ABO blood groups	Yes, forborne, water (pandemic)
<i>Vibrio parahaemolyticus</i>	Diarrhea, abdominal cramps	1–7 days	Fecal culture	Marine water, fish, shellfish	Seafood, water	12–24 h (4–96 h)	Not normally communicable from person to person	All ages	Foodborne outbreaks
<i>Staphylococcal</i> (food poisoning)	Vomiting, nausea, cramps, diarrhea	1–2 days	Culture (feces, vomit – food)	Human (food handlers)	Foods (enterotoxin)	2–4 h (1–7 h)	Not communicable from person to person	All ages	Foodborne outbreaks
Parasitic	Usual symptoms	Duration	Diagnostic methods	Reservoir	Transmission	Incubation period	Period of communicability (human duration of shedding)	Susceptibility	Outbreaks versus sporadic cases
<i>Giardia</i>	Abdominal discomfort, diarrhea	1–8 weeks to months or years	Microscopical examination of feces	Humans (and other animals)	Tap water, human contact	9 days (3–25 days)	3 weeks to 6 months	All ages, children	Both (day care, waterborne)
<i>Cryptosporidium</i>	Diarrhea, abdominal pain, headache, fever	12–12 days (3–60 days)	Microscopical examination of feces	Humans, cattle, and other animals	Fecal–oral, water (and person-to-person, animal-to-person, food)	7 days (1–14 days)	7 days (oocystin freshly stools are infectious and survive in moist environment)	All ages	Outbreaks (swimming venues, tap water)
<i>Entamoeba histolytica</i>	Diarrhea (mucous, blood) abdominal pain	Weeks–months	Microscopical examination of feces	Human (chronically ill, asymptomatic passer)	Food, water; sexually (oral–anal contact)	2–3 weeks	Not communicable when symptoms	All ages, young adults (rarely among <2 years old)	Sporadic and clustering
<i>Cyclospora</i>	Diarrhea, weight loss (relapses)	Few days–months (variable)	Microscopical examination of feces	Human (animal?)	Fresh fruits and vegetables, water	1 week (1–14 days)	Oocystin freshly stools are immature not infectious (only after become infectious)	Children, adults	Outbreaks, foodborne, waterborne
<i>Balantidium coli</i>	Diarrhea (mucous, blood), abdominal pain	Unknown	Microscopical examination of feces; sigmoidoscopy	Swine and other animals?	Food, water, fecal	Few days?	As long as infections persist	Unknown (low incidence)	Low incidence, waterborne, outbreak
<i>Isospora belli</i>	Diarrhea	2–3 weeks	Microscopical examination of feces	Humans?	Fecal–oral, water?	9–15 days	?	Adults HIV positive	Sporadic

It is possible – as happens with other microorganisms – that this predominance of diagnosed cases in children may be the consequence of a diagnostic age bias. Studies on intestinal infection where adult participants were asked to provide fecal cultures revealed that *Campylobacter* is also frequent in adolescents, adults, and the elderly. The majority of diagnosed intestinal infections do not require hospital admission. According to the authors of this article, only 15% of cases resulted in patients being hospitalized.

Reservoirs of *Campylobacter* are not only found in farm animals, essentially avian, but also found in bovine livestock. Companion animals, if they have diarrhea when very young, can pose an infection risk to their owners. The study of risk factors in *Campylobacter* infection presents difficulties given that the majority of cases are sporadic and in children under the age of 2 years. Exposure to avian or bovine meat products has been related to infection. Exposure is not necessarily by direct consumption; the presence of these products in home kitchens presents a risk factor, probably by cross-contamination due to poor hygienic practices. The existence of other diarrhea cases in the patient's nearby surroundings implies that there are small groupings, small outbreaks not identified by conventional systems of epidemiological monitoring.

### **Salmonella (nontyphoidal)**

*Salmonella* owes its name to the North American Veterinarian Daniel Elmer Salmon, who was one of the pioneers of microbiology toward the end of the nineteenth century. Diarrhea by *Salmonella* is a very common zoonosis all over the world. The clinical profile in many patients consists of diarrhea with fever and an exaggerated variable state of health. In the nontyphoidal *Salmonella* group, there are more than 2500 serotypes that can cause gastroenteritis in humans, most common are *S. enteritidis* and *S. typhimurium*, although many others have been identified on numerous occasions. When available, the serotype and fagotype are laboratory data that aid in the investigation of epidemiological factors and the infection source (eggs, birds, and other animals).

Some serotypes have a preference to form reservoirs in specific animals. Chickens and hens are principal reservoirs of *S. enteritidis*; however, pigs and cattle transmit *S. typhimurium*. Other serotypes such as *S. hadar*, *S. virchow*, and *S. heidelberg* are also present in chickens and hens. Reptiles are transmitters of some less frequent serotypes. Hen eggshells can also be contaminated. But a remarkable fact is the vertical transmission of *Salmonella* in hens, laying eggs that are internally contaminated. Adequate data about the prevalence of contaminated eggs do not exist. At the beginning of the 1990s, random sampling was carried out for a study in Castellón, the estimation was little more than 1 in a 1000.

Also, common vegetables (tomatoes, watermelon) and foods with little water activity such as chocolate or powdered milk have been implicated in outbreaks. An outbreak was even transmitted by marijuana consumption. In 2008, an outbreak in the United States transmitted by tomatoes affected more than 500 people in some 30 states. When investigating outbreaks, the possibility of secondary cases has to be taken into account.

It is not believed that there are chronic carriers as with *S. typhi*, but the feces of some patients can remain contagious for months, especially in children. These situations and the cases with few symptoms are particularly important when they occur in food handlers.

The infectious dose, the conditions surrounding its ingestion (accompanying food, antacid medication, etc.) and some characteristics of the host can act as factors that greatly modify the incubation period and the severity of the clinical profile. Symptoms can start from 6 h up to 3 days after the ingestion of contaminated produce. Some greasy foods facilitate *Salmonella*'s crossing the stomach without being eliminated by the extreme acidity of the gastric juices. It has been suggested, when faced with infection by *S. ohio*, that the simultaneous ingestion of alcohol (or red wine) has a protective effect.

### **Shigella**

Several serotypes of *Shigella* exist. Of them, *S. dysenteriae* type 1 is responsible for the most serious cases, bacillary dysentery, due to the Shiga toxin. Other serotypes are *S. sonnei*, *S. flexneri*, and *S. boydii*, which in general produce less severe profiles, accompanied by watery diarrhea. The geographic distribution of each serotype is different. In industrialized countries the impact is diminished. In Asia, it seems that incidents of shigellosis maintain a presence but tend to be less serious. Little is known about incidents in Africa. The infectious dose is very low (from 10 to 100 bacilli); therefore, secondary cases are very frequent due to easily contaminated hands. *Shigella* produces outbreaks and sporadic cases. The incubation period of *S. dysenteriae* is longer, up to a week. Carriers can be asymptomatic for weeks, and with antibiotic treatment they could reduce the time needed for elimination of *Shigella* in the feces. However, the appearance of antibiotic resistance has been observed. The protection from natural infection it offers is type specific.

### **Yersinia (intestinal)**

Within the *Yersinia* genus there are numerous nonvirulent environmental strains. Those that most frequently cause intestinal infection are *Y. enterocolitica* and *Y. pseudotuberculosis*. The former (whose taxonomic classification has undergone important changes from its initial description in 1934 as *Flavobacterium pseudomallei* to the denomination *Yersinia* at the beginning of the 1960s) produces a diarrhea profile that includes abdominal pain and, sometimes, fever; the latter (whose first identification dates from many years earlier, in 1883) produces a clinical profile in which it is worth mentioning the symptoms of *Mesenteric adenitis*, which can sometimes simulate an appendicitis. Not all strains of *Y. enterocolitica* are pathogenic in humans; furthermore, different pathogenic serotypes and biotypes are unequally distributed among the population.

Specific culture media are required for the identification of *Yersinia* from human fecal samples; standard culture mediums are not usually sufficient. Changes in laboratory practice have been considered an explanation for observed increases in the 1980s and some geographical differences.

The large majority of *Y. enterocolitica* cases are sporadic. In many countries with temperate climates, the patients are usually small children diagnosed in winter months. The percentage of total diagnosed cases of diarrhea is small. The *Y. pseudotuberculosis* species is less frequent and little knowledge exists regarding its mechanisms of transmission. There have been cases grouped in spatiotemporal clusters without a commonly identified nexus. In these clusters no secondary cases were observed, suggesting the source was most probably environmental.

*Y. enterocolitica* is frequently found in pig's tonsils. In the case of *Y. pseudotuberculosis*, the reservoirs are wild rodents and birds. There is a possibility that some humans may be carriers of *Y. enterocolitica*. Also, *Yersinia*, from these reservoirs, may contaminate foods or water, which will then infect those who consume them.

In the case of *Y. pseudotuberculosis*, there are recorded outbreaks transmitted by 'iceberg' lettuce and radishes. It is postulated that initially the infection is caused by waters contaminated by animal reservoirs, which indicates that the washing of fresh vegetables is a method to prevent infection. But an outbreak that occurred in Finland in 1998 experimentally demonstrated the possibility of internal contamination of the lettuces, with the result that in such an eventuality external washing would have little effect.

### ***Escherichia coli***

*Escherichia coli* is a bacterium that forms part of the normal intestinal flora in humans and other warm-blooded animals. Nevertheless, in the 1960s, it was discovered that certain strains of *E. coli* had a pathogenic capacity in humans. There are many serotypes. Their capacity to produce different clinical syndromes and affect different age groups is a factor unique to each serotype, ranging from 'traveler's diarrhea' to a serious profile of hemorrhagic colitis. The serotypes able to cause diarrhea are enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), and most virulent of all enterohemorrhagic *E. coli*, also named verocytotoxic *E. coli* (EHEC or VCEC) of the serotype O157:H7. The geographic distribution and transmission channels vary between serotypes. Among the clinical characteristics of these infections, it is worth mentioning a serious complication of serotype O157:H7, hemolytic-uremic syndrome (HUS), which appears mainly in children, and can be exacerbated by taking antidiarrheal or antibiotic medicines. This virulent stock of *E. coli* is transmitted mainly through ingestion of contaminated meat from bovine livestock, but it is also possible that there are other environmental routes of contagion by contact with surfaces or dust and sawdust in farms and zoological parks.

Recent studies suggest that EAEC can cause both traveler and chronic diarrhea. Furthermore, the inflammatory response to this infection depends on human genetic factors linked to interleukin-8.

### ***Clostridium difficile***

This is a microorganism that can cause serious diarrhea, occasionally as pseudomembranous colitis, especially in hospitalized and debilitated patients. Usually, it is triggered by taking antibiotics for therapeutic or preventive purposes. Nevertheless, slight cases exist that are not diagnosed and are only detected in specific studies. The asymptomatic carrying and elimination of bacterial spores is relatively frequent in small children, but it is only patients with established diarrhea who are contagious. The origin of diarrhea from microorganisms previously present in the same individual can be endogenous. These microorganisms are stimulated when intestinal flora is altered as a result of taking antibiotics; this can happen for 4–9 days at the beginning of an antibiotic course and even later, up to 6 or 8 weeks after starting. In these cases, it is difficult to speak of an incubation period in the classic sense. There may also be exogenous contagion from environmental spores or *C. difficile* excreted by another patient.

In some countries improvement in diagnostic methods has contributed to the increased number of diagnoses, especially in hospitalized patients. It is rare that it produces communal outbreaks. When it appears in an epidemic form it usually does so in hospitals.

### ***Vibrio cholerae***

According to what is known of its clinical and epidemiological characteristics, cholera only produces the *V. cholerae* serogroups O1 and O139, the latter confined to Southeast Asia. Other serogroups, denominated 'non-O1' and 'non-O139,' usually present themselves as sporadic cases or small outbreaks with an incubation period of 12–14 h. As per epidemiological characteristics of cholera, it is easily spread through water or foods but not from person to person. In countries where there is overcrowding, poor nutrition, and poor environmental hygiene, cholera remains a very serious problem. People with blood group O are generally more susceptible to severe diseases.

### ***Clostridium perfringens*, *Bacillus cereus*, and *Vibrio parahaemolyticus***

All these cause diarrhea through the consumption of contaminated food. The first two have the capacity to form spores and are found in terrestrial environments (the ground, for example). *V. parahaemolyticus* is halophilic and is found in marine environments and seafood products. Person-to-person transmission, if it exists, would be rare.

### **Parasites**

Diarrheas caused by parasites usually have a more prolonged and insidious course. Relapses and chronic forms are frequent and cause weight loss. They are usually resistant to the levels of chlorination in drinking water.

*Entamoeba histolytica* is frequent in tropical and subtropical countries. Patients with diarrhea dispose of the parasite in trophozoite form, a form with little infectious potential due to its environmental fragility. In contrast, a significant number of infected people remain asymptomatic for months or years, eliminating cysts that have a greater infectious capacity than trophozoite.

*Giardia lamblia* is distributed by people all over the world. Outbreaks caused by *Giardia* are relatively common in day-care centers, especially when there are poor hygienic conditions that facilitate person-to-person transmission. Foods and water can also provide vehicles of transmission. The reservoir is human and, perhaps, some animals such as beavers. People can remain carriers for months.

*Cryptosporidium parvum* produces diarrhea in humans and can also affect systems other than the digestive system. They are parasites resistant to the levels of chlorination used to disinfect drinking water; therefore, hydric transmission outbreaks occur without requiring failures in chlorination. Water filtration is a preventive method to avoid propagation. It has a good survival capacity in the aquatic environment of continental waters. It is responsible for 57% of gastroenteritis outbreaks related to swimming venues in the EU, although hyperchlorination can inactivate cysts present in the water. It has been diagnosed with relative frequency throughout 2007 and 2008 in Ireland, England, and Belgium, and with less frequency in Germany. There have been outbreaks from tap water contamination.

Parasites such as *Cyclospora cayentanensis*, *Balantidium coli*, and *Isospora belli* have less importance than the ones mentioned earlier. There are even doubts about their capacity to produce symptomatic infection in humans.

### Other Agents

There is a very diverse range of agents that cause, or can cause, diarrhea (Table 3). They are characterized by short incubation periods following ingestion (minutes or hours). They have a very broad clinical spectrum. Notable among the biotoxins is scombroid fish poisoning, which can take place after ingestion of certain scombroid fish (such as tuna and herring) in certain circumstances. The symptomatology simulates an allergic reaction that presents itself in an epidemic form. Ciguatoxin, tetrodotoxin, and gempilotoxin are marine biotoxins that can produce very serious digestive and neurological symptoms. Especially striking is gempilotoxin poisoning, in which diarrhea with orange colored feces has been observed. Among vegetables, mushroom poisoning can cause serious consequences. Less well known is the diarrhea from *Robinia pseudoacacia* poisoning, which can be observed after chewing the bark of common trees.

### Long-Term Effects of Gastrointestinal Infections

As consequences of the intestinal infections, complications and long-term aftereffects are distinguishable. The former occurs in the acute phase and the latter appears 3 weeks or 1 year after resolving the clinical profile, sometimes even later.

Studies used by epidemiologists to investigate aftereffects are:

- Point source outbreaks studies
- Prospective cohort studies of sporadic cases
- Retrospective cohort studies.

### Long-Term Effect of Bacterial Gastrointestinal Infections

The etiology of inflammatory bowel disease (IBD) is not known, but cohort studies carried out in the United Kingdom and Sweden indicate that previous bacterial intestinal infections by *Salmonella*, *Campylobacter*, or diarrheagenic *E. coli* and other agents of acute gastroenteritis double or triple the risk of suffering from some IBD variants, with incidences reaching almost 70 per 100 000 person-years.

Irritable bowel syndrome (IBS) can develop after infectious gastroenteritis by *Campylobacter*, *Shigella*, *Salmonella*, or *E. coli* O157:H7. By case-control studies, a statistically significant odds ratio of 4.8 has been estimated. It is believed that age (young), sex (feminine), psychological profile, severity, and duration of gastroenteritis are all risk factors in contracting IBS.

The 2007 Leirisalo-Repo definition of reactive arthritis (ReA) is "joint inflammation that develops soon after or during infection elsewhere in the body but in which the microorganism cannot be recovered from the joint." It usually occurs in the first 4 weeks after infection, is self-limiting, and affects a single joint. Incidence varies according to the germ and its serotype, as well as the patient characteristics and case definition in each different study. Although the frequency of bacterial musculoskeletal symptoms after food-borne infection can reach up to 50% of affected patients, the incidences of ReA are positioned between 0% and 29%. Microorganisms related to ReA are enteric *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* O157:H7, and *C. difficile*. Perhaps there may be more. Apparently women, adults (above 18 years), and those who have suffered more serious illnesses are at greater risk. The genetic marker HLA B27 would be associated more with severity than incidence. The effect of taking antibiotics during the acute phase of intestinal infection is an object of discussion relating to the appearance of ReA.

Guillain-Barré syndrome (GBS) is an acute neuropathy of immune origin, which is associated with infections from *Campylobacter* and cytomegalovirus. Studies from the United Kingdom give an incidence of GBS, which takes place 1–3 weeks after infection,

in 2 out of every 100 000 inhabitants, especially for some serotypes of *Campylobacter* such as O19 and O41. Males are at greater risk of suffering from GBS.

After 4 years of monitoring, a greater risk of hypertension and problematic kidney function after exposure to *C. jejuni* and *E. coli* O157:H7 has been observed in hydric outbreaks of gastroenteritis. Autoimmune diseases (Graves' disease, autoimmune thyroiditis, Kawasaki disease, Sjogren syndrome, and psoriasis) have been related to previous intestinal infections by *Staphylococcus* and *Yersinia*.

### Long-Term Effects of Viral Gastroenteritis

The aftereffects of viral intestinal processes are less well known due to limitations of diagnosis in conventional laboratories. Some of them are fibromyalgia or chronic fatigue syndrome (CFS), and chronic inflammatory muscle disease (CIMD). Studies of stomach biopsies and the presence of enterovirus in skeletal muscles suggest the persistence of infection with viral replication in these patients.

Some cohort studies carried out in the United States suggest that children between 6 and 36 months of age infected by norovirus, sapovirus, or rotavirus are at greater risk of displaying persistent diarrhea in the 6 months following viral infection.

Cross-sectional epidemiological studies and prospective studies in children have suggested the importance of enteric viral infections in the development of autoimmune celiac disease (ACD).

According to a cohort study carried out in Finland in 2006, enteric viruses (rotavirus, adenovirus, and others) could increase the risk of type 1 diabetes in children with a genetic predisposition to that disorder.

It will be necessary to incorporate knowledge of medium and long-term effects to what is already known about the acute effects of intestinal infections. Epidemiological investigation has a prominence in this investigation. Possibly intestinal infections will gain even greater importance in public health.

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