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Health Risks of Enteric Viral Infections in Children

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Contents

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I. Introduction

A growing body of scientific knowledge demonstrates that children (persons less than 18 yr of age) may suffer disproportionately from some environmental risks. These risks may arise because children's neurological, immunological, and digestive systems are still developing. In addition, children are more exposed to pathogens in the environment because of poor or lack of sanitary habits. Because all enteric microorganisms have a potential to be transmitted by the fecal–oral route, waterborne exposure is a major concern.

Children are potentially at a greater risk of infections from serious enteric viral illness for a number of reasons (Table 1). Most important is the immune system, which is needed to control the infection processes; this can lead to more serious infections than in adults, who have fully developed immune systems.

It has been shown that the immune system in the infant is immature. B-lymphocyte function is immature in neonates and impaired in children less than 2 yr of age, which is partially caused by immature T-cell helper function (Cummins et al. 1994). The spleen in children <2 yr of age is characterized by an immature marginal zone compartment, which indicates that B cells are not as well developed and do not react to antigenic stimuli as effectively (Timens et al. 1989).

Immunoglobulin A (IgA) is essential in combating microbial infections in the gastrointestinal tract. Levels increase with age, with adults having 70–300 times that of newborns (Roy 1995). Even at 10 yr of age, IgA levels are half those found in an adult. It has been demonstrated that there is an increase in macrophage production, and the percentage of these cells expressing immunoreactive interferon-alpha in infant lungs is lower when compared with fetal lungs (Khan et al. 1990).

Heinberg et al. (1964) proposed that infection with coxsackievirus B1 in young mice is fatal because of an inadequate production of interferon, whereas older animals that produce interferon can usually survive these infections. It is thought that foreign nucleic acids must enter the cell for interferon to be produced, but it has also been proposed that viral infec-

Table 1. Why Children are at Greater Risk of Gastrointestinal Infections.

Immature immune system
Intestinal mucosa more permeable to water
Proportionately less extracellular fluid than adults
Physiological deficiency in IgA[a]
Reduced stomach acid and pepsin secretion
Absent or poor sanitation habits

[a]Immunoglobulin A, a group of antibodies in bodily secretions.

tion can occur so quickly that cells are destroyed before they can produce interferon (Kunin 1964).

In a study evaluating the increased susceptibility of newborns to infections by group B streptococci, it was proposed that phagocytic defenses *in utero* and at birth may be lacking. The newborn is unable to produce enough phagocytes in adequate numbers to deliver them to the site of infection (Wilson 1986); this may also play a role in enteroviral infections. Lung macrophages from monkeys and rabbits less than 7 d old have less microbiocidal activity than lung macrophages from adults (Bellanti et al. 1979; Jacobs et al. 1983).

The digestive system of children is also not fully developed, resulting in greater susceptibility to enteric viral disease. Enteric pathogens need to pass through the harsh acidic environment of the stomach before they can initiate infection and disease. Infants and undernourished children may have a reduced acid and pepsin secretion by the gastric mucosa; as a result, these agents may better survive the transit from the stomach to the intestine.

The intestinal tract of the newborn mouse has been shown to be an ineffective barrier against orally acquired group B coxsackieviruses, whereas the adult mouse is very resistant to infection by this agent (Loria et al. 1976). The intestinal tract of the adult mouse offers two modes of protection against oral infection. First, it acts as a barrier that prevents the virus from passing through the mucosal side of the gut and, second, provides a clearance mechanism that eliminates the virus from the enteric tract after infection (Loria et al. 1976).

Infants and children are more susceptible to dehydration because secreted liquids, as a proportion of extracellular fluid, may be twice as much as that of adults. Infants are at higher risk of dehydration, as their intestinal mucosa tends to be more permeable to water. Therefore, the same pathologic process in infants may result in greater loss of water and electrolytes than in older children whose intestinal mucosa is less permeable to water (Roy 1995).

The neurological system of children may also be less likely to defend against a viral infection. Enterovirus infections are generally more severe in infant humans and mice. It has been shown that the brains of mice less than 48 hr old are more prone to infection by coxsackievirus B and typically die of encephalitis, whereas the brains of adult mice are resistant to infection (Khatib et al. 1980).

The heart and endocrine system are also more likely to be affected in children than in adults during enterovirus infection. Myocarditis is typical among mice less than 48 hr old infected with coxackievirus B1 and B4, but infected mice less than 14 d old experience myocarditis less frequently. Adult mice infected with coxsackievirus B1 or B4 do not develop myocarditis (Khatib et al. 1980). Pancreatitis is a more common condition in mice less than 14 d old than in adult mice.

Exposure to fecal–oral agents is also more likely in children. Infants are not yet developmentally capable of habits that would reduce their exposure; these include toilet use and handwashing. The frequency of hand-to-mouth or fomite (inanimate object)-to-mouth contact is also greater in children. Small children may bring their hands to their mouths once every 3 min (Springthorpe and Sattar 1990).

II. Viral Diseases in Infancy and Childhood

A. Diarrheal Diseases

Diarrheal diseases are the leading cause of childhood morbidity and mortality in developing countries (Kosek et al. 2003). It has been estimated (LeBaron et al. 1990) that infectious gastroenteritis in the United States alone causes more than 210,000 children of 5 yr of age or younger to be hospitalized, at a yearly cost of nearly $1 billion. Throughout the world, 3–5 billion cases of diarrhea occur (LeBaron et al. 1990). In the U.S., 250–350 million cases of diarrhea occur every year, with more than 4,000 deaths in all age groups (Glass 2000).

Worldwide, more than 500 million episodes of diarrhea occur each year in children under 5 yr of age (Fimberg et al. 1993), with an associated 2.5 million deaths, representing the leading cause of infant mortality. Approximately half of those deaths are among children under 1 yr of age (Kosek et al. 2003). Case fatality rates average from 1.8% in children under 1 yr of age to 0.15% in children aged under 5 yr (Kosek et al. 2003). Although developing countries account for the majority of all diarrheal disease deaths, the diarrheal syndrome is one of the 10 leading causes of death in infants in the U.S. An estimated 21–37 million episodes of diarrhea occur annually in children under 5 yr of age; 10% of the affected children are seen by a physician, more than 200,000 are hospitalized, and 300–400 die of the illness (Wyllie 1999).

From 1968 to 1991, a total of 14,137 deaths associated with diarrhea were reported in the U.S. Infants (1–11 mon) accounted for 78% of these deaths. Although the median age at the time of death, from 1961 to 1985, was reduced from 5 to 1.5 mon and the disease mortality decreased by 75%, no further reduction in mortality has been recorded since then, with a yearly average of 300 gastroenteritis-associated deaths (Kilgore et al. 1995).

No etiological agent is identified in the majority (79.5%) of hospital admissions of children associated with gastroenteritis in the U.S. However, viral gastroenteritis is the leading cause of identified causes of diarrhea-associated hospitalization in children, accounting for 25.3% of such admissions, followed by bacteria (5.4%) and parasites (<0.3%) (Parashar et al. 1999). Rotavirus, adenovirus, Norwalk virus, astrovirus, and calicivirus are the most common viral pathogens, rotavirus being the most common, with 16.5% of all diarrhea-associated hospital admissions (Newman et al. 1999). In Connecticut, the annual incidence of diarrhea-associated hospitalizations

from 1987 through 1996 was 49.4 per 10,000, whereas the cumulative incidence over the first 5 yr of life was 247 per 10,000. A breakdown by ethnicity and race indicates that the incidence of diarrhea-associated hospitalizations is greater in Hispanics and African-Americans than in Anglo-whites (Parashar et al. 1999).

Greater Susceptibility of Children. Age plays a significant role in the pathogenesis of diarrhea. It was shown in the Philippines that age was inversely related to the duration of diarrhea in children (San Pedro and Waltz 1991). Many of the host defense mechanisms of the enteric mucosa are immature or inefficient in the newborn. Secretory immunoglobulin A (sIgA) provides a major line of defense against enteric pathogens. However, in infants and children there is a physiological deficiency of this type of antibody. This deficiency is partially compensated by breastfeeding (Roy 1995).

There is indirect evidence that some, still unidentified, components of maternal milk may enhance the ability of the infant to mount a more vigorous immune response (Haffejee et al. 1990). Breast-fed infants had significantly higher antibody titers (i.e., concentration) to the oral polio vaccine (OPV) than infants fed formulas (Pickering et al. 1998). A study conducted in Sri Lanka showed that infants breast-fed for 3 mon or less developed respiratory and gastroentric infections earlier than infants who were breast-fed for longer periods, whereas those who were never breast-fed suffered earlier and more severe infections (Perera et al. 1999). In addition, in the first year of life, the incidence of diarrheal illnesses among breast-fed infants is half that of formula-fed infants (Dewey et al. 1995).

Infants and children are more susceptible to dehydration because the absorbed and secreted liquids, as a proportion of extracellular fluid, may be as much as twice that of adults. Infants are at highest risk of dehydration because their intestinal mucosa tends to be more permeable to water. Therefore, the same pathological process in infants may result in a greater loss of water and electrolytes than in older children whose intestinal mucosa is less permeable to water (Roy 1995).

Enteric pathogens need to pass through the harsh acidic environment of the stomach before they can initiate infection and disease. Infants and undernourished children may have reduced acid and pepsin secretion by the gastric mucosa; as a result, these agents may survive better the transit from the stomach to the intestine. Furthermore, undernourished infants have a reduced ability to replace lost epithelial cells of the intestinal mucosa (Sherman and Litchman 1995). Ironically, it has been postulated that the relatively uncommon occurrence of rotavirus gastroenteritis in neonates may be related, in part, to their immature proteolytic enzyme inability to cleave viral protein 4 (VP4) of virulent strains, rendering them noninfectious (Haffejee 1995).

Low birth weight has been identified as a significant risk factor for infant hospitalization with viral gastroenteritis. Infants weighing less than 1.5 kg were at highest hospitalization risk, whereas those weighing more than 4.0 kg had a decreased risk (Newman et al. 1999).

In addition to physiological differences between children and adults, young children seldom follow proper sanitary practices unless closely supervised. Therefore, children are more prone to acquire infections transmitted through the fecal–oral route (Sherman and Litchman 1995).

Rotavirus. Rotaviruses are the most important agents of infantile gastroenteritis around the world. The antigenic characteristics of rotaviruses are defined by group, subgroup, and serotype. There are seven rotavirus groups (A through G), whose specificity is given by the viral protein VP6. All seven groups are found in animals, but only A, B, and C are found in humans (Kapikian 1996).

Group A rotavirus is endemic worldwide. It is the leading cause of severe diarrhea among infants and children, and accounts for about half of the cases requiring hospitalization. In temperate areas, it occurs primarily in the winter (Kapikian and Chanock 1996), but in the tropics it may occur throughout the year (San Pedro and Waltz 1991; Stewien et al. 1991; Kapikian 1996). Worldwide rotavirus infections in children cause 2 million hospitalizations, and 352,000–592,000 deaths in children less than 5 yr of age (Parasher et al. 2003). In the U.S. alone, as many as 18,000 hospitalizations occur each year from rotavirus (Fischer et al. 2004).

Group B rotavirus, also called adult diarrhea rotavirus, has caused major epidemics of severe diarrhea affecting thousands of persons of all ages in China (Ramachandran et al. 1998). Group C rotavirus has been associated with rare and sporadic cases of diarrhea in children in many countries (Kapikian and Chanock 1996). Rotavirus infections are very common in both developed and underdeveloped countries, as evidenced by the prevalence of serum antibodies, which are found in the majority of children by 3 yr of age.

In adults, rotaviral infection is usually subclinical. However, rotavirus gastroenteritis outbreaks have occurred in army recruits, geriatric patients, and hospital staff (Kapikian and Chanock 1996). Over 3 million cases of rotavirus gastroenteritis occur annually in the U.S. It has been estimated that rotaviruses, in the U.S. alone, cause more than 1 million cases of severe diarrhea and up to 150 deaths per year. Worldwide, close to 1 million infants and young children die of rotavirus infection each year. Rotavirus infection does not result in an efficient or long-lasting immunity. Therefore, rotavirus infection in the same child often occurs up to six times during childhood (Kapikian and Chanock 1996).

Most reports agree that the highest incidence of rotavirus gastroenteritis occurs in children 6–24 mon old; however, some studies have found the highest incidence at 6–12, and 9–14 mon. In general, infants in developing

countries tend to become infected by rotavirus much earlier than children in the developed world (Haffejee 1995).

Apparently, rotavirus infection occurs at a very early age. A study conducted in South Africa showed that 15 of 19 rotavirus-infected asymptomatic neonates shed rotavirus during the first 5 d of age; among those, 2 excreted the virus during the first 24 hr of life (Haffejee et al. 1990). Nevertheless, rotavirus gastroenteritis in neonates is relatively uncommon and when present is usually mild. It has been established that approximately 80%–90% of rotavirus-infected babies remain asymptomatic, probably because of the presence of maternal antibodies (Haffejee 1995).

The highest prevalence of rotavirus gastroenteritis occurs in children between 6 and 24 mon of age, with the next highest prevalence in infants 1–6 mon of age, with neonates experiencing a low rate of rotavirus gastroenteritis (Kapikian 1996; Bartlett et al. 1988). Nevertheless, outbreaks of neonatal gastroenteritis caused by rotaviruses have been documented (Steele and Sears 1996).

During 1993–1995, 13.5% of hospitalizations among U.S. children aged 1 mon through 4 yr were associated with diarrhea (162,478/year). Rotavirus was the most common pathogen identified (16.5%), with an average of 26,798 cases per year (Parashar et al. 1998) (Fig. 1). Most hospitalizations caused by rotavirus occur in the 12- to 23-mon-old age group (Ferson 1996) (Fig. 2).

In a Connecticut study from 1987 through 1996, diarrhea-associated hospitalizations peaked from February through April, especially in children 4 mon to 3 yr of age. The apparent lower incidence peak was not observed among infants 1–3 mon of age (Parashar et al. 1999). This difference has been associated with the presence of protective maternal antibodies in children born from October through December (Newman et al. 1999).

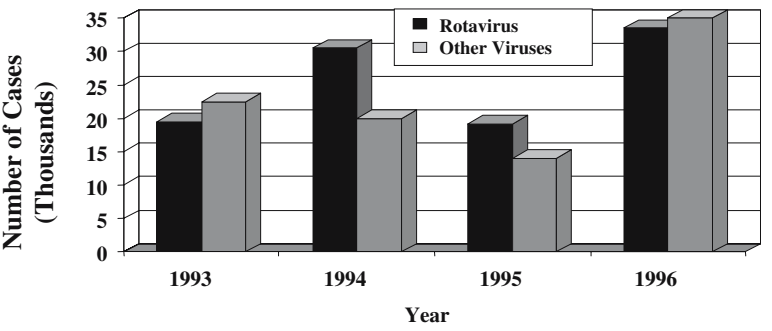

Fig. 1. Hospital admissions for enteric viruses in the U.S. (1993–1996) for those less than 15 years of age. Data from U.S. Department of Health and Human Services Vital and Health Statistics (National Hospital Discharge Survey) (Parashar et al. 1998).

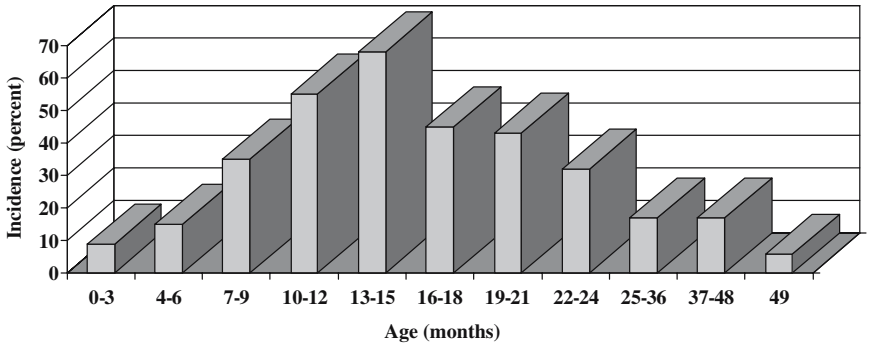

Fig. 2. Hospitalization of rotavirus gastroenteritis in the U.S. Data from Brandt et al. (1979).

Table 2. Rotavirus Prevalence in Selected Countries.

Country	Prevalence (%)	Reference
Australia	39.6	Ferson et al. 1996
England and Wales	43.0	Ryan et al. 1996
United States	39.0	Brandt et al. 1979
Hong Kong	28.5	Tam et al. 1986
Philippines	33.9	San Pedro et al. 1991
Mexico	49.0	Velazquez et al. 1993
Brazil	25.0	Stewien et al. 1991

In the U.S. from 1993 to 1996, rotavirus was identified as the cause of 10.4% of gastroenteritis-associated hospital admissions, increasing from 8.6% in 1993 to 14.7% in 1996. The annual incidence of rotavirus-associated hospitalizations was 4.4 per 10,000. The unadjusted median cost of a diarrhea-associated hospitalization during 1993–1996 was estimated to be $2,428 (Parashar et al. 1999). Each year in the U.S., rotavirus gastroenteritis results in $264 million in direct medical cost and more than $1 billion in total cost to society (CDC 1999c). The prevalence of rotavirus infection in children around the world varies from country to country, but most studies report a prevalence of 25%–50% (Table 2).

Enteric Adenoviruses. Enteric adenoviruses (Ead) are double-stranded DNA icosahedric viruses approximately 70 nm in diameter (Joki-Korpela and Hyypia 1998). At least 49 human adenoviruses have been identified (Calisher and Fauquet 1992). Adenoviruses may cause acute respiratory disease, pneumonia, epidemic conjunctivitis (Straus 1984), and acute gastroenteritis in children (Uhnoo et al. 1986). Documented waterborne out-

breaks of conjunctivitis, by adenovirus type 3 (Martone et al. 1980; McMillan et al. 1992) and type 4 (D'Angelo et al. 1979), have been reported. Two outbreaks of gastroenteritis associated with drinking water have been reported (Kukkula et al. 1997; Divizia et al. 2004).

Ead 40 and 41 have been recognized as important etiological agents of gastroenteritis in children throughout the world (Uhnoo et al. 1986; Brandt et al. 1985; Leite et al. 1985; Albert 1986; Cruz et al. 1990; San Pedro and Waltz 1991), second in importance only to rotavirus. Where extensive studies have been conducted, it appears that Eads may be more important than rotavirus as a cause of diarrhea in developing countries (Herrmann and Blacklow 1995; Cruz et al. 1990).

Ead types 40 and 41 have been associated with outbreaks of gastroenteritis in day-care centers for children in the U.S. (Van et al. 1992). A large outbreak of keratoconjunctivitis within two day-care centers in Australia was caused by Ead type 8 (McMinn et al. 1991). An investigation in Guatemala (Cruz et al. 1990), showed that Ead40 (Reina et al. 1994; Parashar et al. 1999) and Ead41 were associated with diarrheal episodes in ambulatory children three times more often than rotaviruses. The incidence of adenovirus gastroenteritis in the world has ranged from 1.5% to 12.0%. Other types of adenoviruses have also been isolated from feces, but only Eads 40 and 41 have been consistently associated with gastroenteritis (Herrmann and Blacklow 1995).

In a 13-yr survey conducted in Australia in hospitalized children (0–14 yr of age), the Eads 40 and 41 were identified as the second most common cause of acute viral gastroenteritis, with an overall incidence of 6%; however, Ead infection was more common among infants (9.4%) (Barnes et al. 1998). In the Philippines, Eads have been associated with 5.4% of infant gastroenteritis, mainly during the rainy season (San Pedro and Waltz 1991).

Intussusception has been associated in some patients with adenovirus (types 1, 2, 5, and 6) infection. Mesenteric adenitis has been suggested as the probable cause; however, hyperirritability of the small intestine as a result of adenovirus infection has also been proposed as a possible cause of intussusception (Horwitz 1996). Eads may cause serious life-threatening illness in the immunocompromised (Gerba et al. 1996). For example, in cancer patients who are immunosuppressed the fatality rate for adenovirus infection is 53% (Hierholzer 1992). Similar fatality rates have been noted in bone marrow transplant patients.

There have been only two suspected drinking water outbreaks where an adenovirus may have been involved (Kukkula et al. 1997; Divizia et al. 2004). The lack of epidemiological evidence, the small number of studies, and limitations of methods of detection make this difficult to demonstrate. However, waterborne outbreaks of conjunctivitis and nose and throat infection by adenovirus types 3 and 4 are well documented (Martone et al. 1980; D'Angelo et al. 1979; McMillan et al. 1992). The Eads, in contrast to other adenoviruses, are not shed in respiratory secretions (Petric et al. 1982;

Blacklow and Greenberg 1991); thus, their transmission must be limited to the oral–fecal routes as with important waterborne pathogens (Beneson 1990).

Williams and Hurst (1988) reported that the number of indigenous adenoviruses detected in primary sewage sludge was 10 times greater than that of the enteroviruses. In addition, a greater number of adenoviruses than enteroviruses has been consistently found in raw sewage around the world (Irving and Smith 1981; Hurst et al. 1988; Krikelis et al. 1985a,b; Girones et al. 1993; Puig et al. 1994). Adenoviruses may survive longer in water than other enteric viruses (Enriquez et al. 1995).

The enteric nature of the adenoviruses 40 and 41, their presence only in the gastroenteric tract, and their extensive distribution suggest that water may play a role in the transmission of these agents. Furthermore, adenovirus type 31 has been increasingly detected during the last few years as an important cause of infant gastroenteritis (Thorner et al. 1993). Results of a comparative study of cytopathogenicity using immunofluorescence and *in situ* DNA hybridization as methods for the detection of adenoviruses from water, suggested that 80% of infectious adenoviruses in raw sewage may be Eads (Hurst et al. 1988).

As with other viral gastroenteritis, treatment of Ead diarrhea is directed at prevention of severe dehydration and electrolyte imbalance. Depending on the severity of dehydration, oral or intravenous rehydration may be needed (Hermann and Blacklow 1995).

Astrovirus. Astroviruses were first observed by electron micrographs of diarrheal stools by Madeley and Cosgrove (1975). These are icosahedral viruses with a starlike appearance and a diameter of approximately 28 nm. The human astrovirus group includes seven serotypes (Willcocks et al. 1994). Astrovirus type 1 seems to be the most prevalent strain in children. Type 4 has been associated with severe gastroenteritis in young adults. Astrovirus-like particles have been found in feces of a number of animals suffering from a mild self-limiting diarrheal infection, but no antigenic cross-reactivity has been found between these agents and human astroviruses.

Astrovirus infections occur throughout the year, with a peak during the winter/spring seasons in temperate zones in warm climates, but the highest incidence of astrovirus infection has been registered in May. Astroviruses cause a mild gastroenteritis after an incubation period of 3–4 d. Overt disease is common in 1- to 3-yr-old children. However, adults and young children are also affected. Astrovirus infection has been observed also in immunocompromised individuals and the elderly. Astroviruses are transmitted by the fecal–oral route. Outbreaks of astrovirus infection have been associated with oysters and drinking water (Kurtz and Lee 1987). An epidemiologic study in Guatemala showed that the astrovirus infection rate was 38% among children less than 3 yr of age, followed by Eads (22.3%),

and rotaviruses (10.3%). Although astroviruses are common in developing countries, they have been identified also as a significant cause of infantile gastroenteritis in developed countries. A 10-yr study of astrovirus prevalence in Japan reported that 6%–10% of viral gastroenteritis cases in that country are caused by astroviruses. In England, these agents have been found in 7% of diarrheal samples examined by electron microscopy (Cubitt 1987). Astroviruses have also been associated with outbreaks in day-care centers for children (Mitchell et al. 1999).

A study in Glasgow reported that 80% of infants shedding astroviruses were suffering from gastroenteritis whereas 12% remained asymptomatic (Caul 1996b). Seroprevalence studies have indicated that by the age of 4 yr, 64% of all children have antibodies to astrovirus, with this number increasing to 87% in 5- to 10-yr-old children (Caul 1996b).

Caliciviruses. Caliciviruses are transmitted by the fecal–oral route. These viruses are important etiological agents of acute epidemic gastroenteritis that affect adults, school-age children, and family contacts (Kapikian 1996; Roper et al. 1990). Until recently, they were thought to only rarely infect children; however, recent studies (Koopmans et al. 2000; Inouye et al. 2000; Pang et al. 1992) suggest that they are a common cause of diarrhea in children <5 yr of age. In one study, the prevalence of diarrhea in children <5 yr exceeded that of rotavirus (Koopmans et al. 2000). It is now believed that the majority of previously undiagnosed cases of nonbacterial gastroenteritis is associated with caliciviruses (Glass et al. 2000). In a large study of outbreaks of infectious intestinal disease involving 40,000 cases in England and Wales, SRSVs (caliciviruses) were the most commonly identified agents (43% of cases), being more numerous than the cases of gastroenterititis caused by *Salmonella* and *Campylobacter* (Evans et al. 1998).

The family Caliciviridae is currently divided into four genera (Green et al. 2000). *Vesivirus* and *Lagovirus* contain only animal caliciviruses, which do not infect man. The human caliciviruses are divided into two genera, noroviruses and sapporoviruses. The noroviruses are divided into two subgroups based on genotyping (Table 3).

Immunity to caliciviruses is poorly understood. Infectivity studies with volunteers have shown that immunity correlates inversely with serum or intestinal antibodies (Kapikian and Chanock 1996). Individual resistance to norovirus gastroenteritis is more important than acquired immunity (Blacklow et al. 1987). It has been suggested that genetically determined factors are the primary determinants of resistance to norovirus infection, perhaps at the level of cellular receptor sites (Blacklow et al. 1987). In developing countries, antibodies to norovirus are acquired early in life, and peak incidence of illness may also occur among younger age groups than that in developed nations (Roper et al. 1990). It has been proposed that noroviruses may circulate in low numbers in a population until an infected individual contaminates a common source of food or water, resulting in

Table 3. Human Calicivirus Genera and Representative Strains.

Genus and genogroup	Virus common name
Noroviruses	
Genogroup I	Norwalk virus
	Southhampton virus
	Desert Shield virus
	Cruise ship virus
Genogroup II	Snow Mountain agent
	Hawaii virus
	Toronto virus
	Lordsdale virus
	Grimsby virus
	Gwyneld virus
	White River virus
Sapporoviruses	Sapporo virus
	Manchester virus
	Parkville virus
	London virus
	Houston virus

explosive outbreaks (Roper et al. 1990). Noroviruses and related viruses usually produce a mild and brief illness, lasting 1–2 d, characterized by nausea and abdominal cramps, followed commonly by vomiting in children and diarrhea in adults (Gouvea et al. 1994). The involvement of norovirus as a pathogen of adults was further suggested by Numata et al. (1994), who reported a very low prevalence of antibodies to recombinant norovirus capsid protein in children <7 yr of age, but an increasing prevalence in individuals from 12 to 50 yr of age in Japan. Recent studies suggest that they may be the most common cause of foodborne outbreaks (Inouye et al. 2000; Deneen et al. 2000).

Oral rehydration is generally sufficient to treat Norwalk virus and calicivirus gastroenteritis. In rare cases, intraveneous administration of liquids and electrolytes may be necessary (Estes and Hardy 1995).

B. Hepatitis Viruses

Hepatitis A Virus (HAV). HAV is a picornavirus that is morphologically indistinguishable from other members of the same family (Hollinger and Ticehurst 1996). Relatively resistant to heat, it is partially inactivated after 12 hr at 60°C. Infectivity at room temperature is maintained for 1 mon after drying, and the virus can survive for days to months in different types of water (Hollinger and Ticehurst 1996). Each year, approximately 140,000

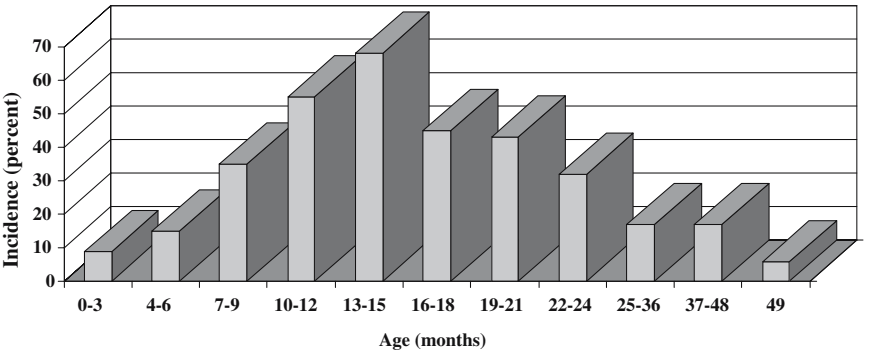

Fig. 3. Incidence of hepatitis A by age in the U.S. (1997). Data from Brandt et al. (1979).

Table 4. Sources of Hepatitis A Virus (HAV).

Source	Percent
Personal contact	25–30
Day-care centers	10–15
Contaminated food and water	3–8
Travel to endemic areas	9
Unknown	50

persons in the U.S. are infected with HAV with an approximate annual cost of $200 million (Fishman et al. 1996). A more recent study placed the costs for adolescents (>15 yr of age) and adults between $332 and $580 million a year (Berge et al. 2000). The highest rates of disease are among persons 5–14 yr old (CDC 1999b) (Fig. 3).

The incubation period for HAV is approximately 28 d. The infected individual sheds HAV actively during the initial stage of the infection period, 1–2 wk before overt disease (Fishman et al. 1996). Propagation of HAV is mainly fecal–oral because hepatitis A is often associated with unsanitary and crowded conditions; however, bloodborne transmission may be possible during the viremic phase that occurs in the initial stage of the disease (Fishman et al. 1996). Personal contact accounts for 25%–30% of HAV cases in the U.S., followed by day-care centers (10%–15%), contaminated food or water (3%–8%), and travel to endemic areas (9%) (Fishman et al. 1996) (Table 4). In almost half the cases, no source of exposure can be documented.

Hepatitis A is usually a mild illness, which almost always results in complete recovery. Severity and disease manifestation are age related. An esti-

mated 80%–95% of infected children younger than 5 yr of age do not develop overt disease, whereas clinical manifestations are observed in approximately 75%–90% of infected adults (Harrison 1999). Neither chronic hepatitis nor a carrier state results from HAV (Fishman et al. 1996).

The mortality rate in children of 14 yr or younger is 0.1%; this rate rises to 0.3% in individuals between the ages of 15 to 39 yr, reaching 2.1% in those older than 40 yr (Hollinger and Ticehurst 1996). Although hepatitis A is usually benign in children, studies in India have shown that 10% of cases of acute liver failure are associated with HAV infection. Furthermore, HAV coinfection with hepatitis E virus (HEV) accounts for 22.5% of acute liver failure in children, with the 5- to 10-yr-old group being the most affected. The mortality rate observed in these patients was 63.6% (Arora et al. 1996).

In developing countries, the incidence of symptomatic hepatitis A in adults is relatively low because of exposure to the virus in childhood. Most individuals 18 yr and older possess an immunity that provides lifelong protection against reinfection (Hollinger and Ticehurst 1996). In the U.S., the percentage of adults with immunity increases with age (10% for those 18–19 yr of age to 65% for those >50) (Margolis et al. 1997).

In areas with poor sanitation, nearly all children up to 9 yr of age have been infected by HAV. In these areas, outbreaks rarely occur, and clinical disease related to HAV infection is uncommon. Under better sanitation, HAV infection shifts to older individuals, and the incidence of overt disease increases.

Hepatitis A is one of the few viral diseases that has been clearly proved to be transmitted by the water route. In a retrospective study of waterborne disease outbreaks, occurring in the U.S. from 1946 to 1980, Lippy and Waltrip (1984) reported that viral hepatitis was frequent, with 68 outbreaks and 2,262 cases. Many outbreaks have been traced to the consumption of raw shellfish (Rao and Melnick 1986).

Treatment of hepatitis A is usually supportive, although passive immunization with pooled human immunoglobulin (Ig) containing high titers of anti-HAV has been the only means to provide preexposure or postexposure immunoprophylaxis against hepatitis A. Although a hepatitis A vaccine was first licenced in 1995, hepatitis A continues as one of the most frequently reported vaccine-preventable diseases in the U.S. (CDC 1999b). Initially, immunization against HAV was mainly of children living in communities with the highest rates of HAV infection (CDC 1996). To reduce HAV incidence, widespread vaccination of appropriate susceptible populations needs to be implemented. The Advisory Committee on Immunization Practices (ACIP) recently recommended the routine vaccination of children from communities with rates that are twice the 1987–1997 national average (10–19 cases per 100,000 population) and the consideration of routine vaccination of children from communities with rates higher than the 1987–1997 national average (CDC 1999b).

Two inactivated HAV vaccines have been licensed in the U.S. (CDC 1999b). HAV exists as a single serotype and exposure to it induces a lifelong immunity. In HAV-endemic areas, children of 10–15 yr of age are likely to be HAV seropositive. Due to the high HAV antibody prevalence in adults in the U.S., pooled sera contain titers of anti-HAV immunoglobulins that are protective (Fishman et al. 1996).

Hepatitis E Virus (HEV). The hepatitis E virus (HEV), formerly known as enterically transmitted non-A, non-B hepatitis virus, is the leading etiology of acute viral hepatitis in developing countries (Bradley et al. 1992; White and Fenner 1994). HEV accounts for more than 50% of acute hepatitis cases in Asia and Africa and is the most common cause of hepatitis in children (Fishman et al. 1996). In the U.S. and in Europe, most hepatitis E cases have been confirmed only in people returning from endemic areas (Fishman et al. 1996).

HEV was originally placed in the Calicivirdae family but has now been removed (Berke and Matson 2000). Its taxonomic position is now uncertain. Isolates of this agent can be broadly grouped into two serotypes, Mexico-HEV and Burma-HEV, the latter being more prevalent. In experimental trials, primates infected with the Burma isolate were protected from infection by the Mexico-HEV. This finding indicates that these two serotypes share neutralizing antigens (Bradley et al. 1992). Balayan (1993) has suggested that the higher prevalence of HEV in adults may result from a silent infection early in life, with subsequent waning of immunity after 10–20 yr, becoming again susceptible to infection by HEV at a later age. An important epidemiological feature of HEV infection is the frequent occurrence of outbreaks associated with consumption of sewage-polluted water (Balayan 1993).

In contrast to hepatitis A, hepatitis E occurs in young and middle-aged adults. In addition, most cases originate from a primary source, with infrequent cases among secondary contacts, compared to hepatits A in which close contact is a common risk factor (Harrison 1999). Transmission of HEV is fecal–oral, often through contaminated water and food (Tan et al. 2003). Outbreaks often occur during the rainy season, monsoons, or flooding, with sporadic cases resulting from person-to-person transmission (Fishman et al. 1996). Current evidence suggests that HEV is zoonotic and can be transmitted by undercooked deer, pork, and boar meat (Tei et al. 2004).

The incubation of HEV is 2–8 wk with an average of 5–6 wk, which is slightly longer than HAV (White and Fenner 1994). The most evident pathologic feature of hepatitis E, in contrast to hepatitis A, is cholestasis. Hepatitis E is a self-limiting, acute disease. Similar to hepatitis A, its severity increases with age; this may explain why the disease is mostly reported among young adults, whereas children are usually unaffected. However, simultaneous infection of young children with HEV and HAV has resulted in severe disease, sometimes with acute liver failure (Arora et al. 1996). The

disease is most often seen in older children to middle-aged adults (15–40 yr old). The disease is often mild and resolves in 2 wk, leaving no sequela; however, the fatality rate may be high (2%–3%) (Haas et al. 1999). Furthermore, pregnant women appear to be exceptionally susceptible to severe disease, and the fatality rate may reach 17%–33% (Haas et al. 1999). There is no evidence of immunity against HEV in the population that has been exposed to this virus (Margolis et al. 1997).

HEV has been isolated from pigs in the U.S., and this isolate has been shown to be infectious to primates. In addition, the pig isolate is highly homologous, at the nucleotide level, to HEV strains isolated from humans (Harrison 1999).

Unlike hepatitis A, specific antibodies do not prevent or mitigate the clinical manifestation of hepatitis E; therefore, only the implementation of appropriate sanitary practices and the consumption of uncontaminated drinking water and food may diminish the risk of HEV infection (Fishman et al. 1996). Treatment is only supportive of the clinical symptoms.

C. Enteroviruses

Enteroviruses (polioviruses, coxsackieviruses, echoviruses, and enteroviruses) are among the most common and significant causes of infectious illness in infants and children. Non-polio enteroviruses are estimated to cause 10–15 million symptomatic infections in the U.S. annually (Zaoutis and Klein 1998). They are associated with a broad spectrum of clinical syndromes, including aseptic meningitis, herpangina, hand-foot-mouth disease, conjunctivitis, pleurodynia, myocarditis, poliomyelitis, various exanthems (rashes), and nonspecific febrile illness. While all age groups can become affected, the most serious outcomes are in the newborns, young children, and adults. Poliomyelitis, once a common crippling disease, largely in older children in the U.S., has largely been eliminated around the world due to the development of poliovirus vaccines in the 1950s. Because enteroviruses were the first human viruses grown in cell culture, a great deal has been learned about their epidemiology. Infections are most common in childhood. Isolation of echovirus and coxsackievirus from stools of children may be as high as 8%–10% during the summer months (Fox and Hall 1980). The fecal–oral route is believed to be the main route of transmission, although respiratory transmission may also be significant for some types (Morens et al. 1991). It is believed that almost all enteroviruses (except possibly enterovirus type 70, which causes eye infections) can be transmitted by the fecal–oral route.

Incubation periods vary greatly with the type of virus and may be as short as 12 hr for coxsackievirus type A24 (eye infections) to as long as 35 d for poliovirus. The presentation of symptomatic illness is also highly type- and strain dependent. Some enterovirus infections may pass through a community with no illness observed (Fox and Hall 1980). Echoviruses

usually cause milder illnesses than those of coxsackievirus. The overall case fatality ratio in recognized cases of enterovirus illness has been reported to range from 0.01% to 0.94% (Assad and Borecka 1977). The incidence of serious neonatal coxsackievirus infections is about 1 in 2,000 live births, 10% of which are usually fatal (Kaplan et al. 1983). Such infections are usually acquired by the mother and transmitted to the child after birth. Because of the large variety of symptomatic to asymptomatic cases among enterovirus types, long incubation periods, a wide variety of symptoms, and costly isolation methods, it has been difficult to document common-source outbreaks.

Newer technologies, such as polymerase chain reaction (PCR), are rapid and sensitive testing methods for diagnosis of enteroviral infections, which may expand the list of diseases attributable to this group of pathogens. Although treatment of enteroviral infections remains unsatisfactory, immunization against poliovirus has been remarkably successful.

Properties of the Enteroviruses. The enteroviruses are a subgroup of single-stranded RNA, nonenveloped viruses belonging to the Picornaviridae family (pico = small, RNA = ribonucleic acid). They include the polioviruses, coxsackieviruses, echoviruses (echo = enteric cytopathogenic human orphan), and unclassified enteroviruses. Early classification of enteroviruses involved groupings based on cytopathological effect in tissue culture. Newly discovered enteroviruses are now simply assigned enterovirus type numbers. The enteroviruses currently recognized to infect humans are outlined in Table 5.

The virion consists of an icosahedron-shaped protein capsid and an RNA core. Although the capsid proteins determine antigenicity, there are no significant antigens common to all members of this group of viruses. The virus can withstand the acidic pH of the human gastrointestinal tract and can survive at room temperature for several days. These features enable the fecal–oral mode of transmission. Most enteroviruses can grow in primate (human or nonhuman) cell cultures, exhibiting cytopathic effects. Enteroviruses are commonly referred to as "summer viruses" because resulting infections occur primarily during the warmer, summer months

Table 5. Human Enteroviruses.

Group	Serotypes
Poliovirus	1–3
Coxsackievirus group A	1–22, 24
Coxsackievirus group B	1–6
Echovirus	1–9, 11–27, 29–33
Enterovirus	68–91

(May through October) in temperate northern hemisphere climates such as in the U.S. In tropical climates, enteroviral infection is seen all year without seasonal variation. Humans are the only known natural hosts for enteroviruses.

The fecal–oral route is the most common mode of transmission, but oral–oral and respiratory spread are also possible. Risk factors for infection include poor sanitation, crowded living conditions, and low socioeconomic class. Children <5 yr of age are the most susceptible to infection, partly because of a lack of prior immunity and the poor hygienic habits associated with this age group.

Enterovirus Illness. The incubation period for most enteroviral infections ranges from 3 to 10 d. The virus enters the host via the oral and/or respiratory tract, then invades and replicates in the upper respiratory tract and small intestine, with a predilection for lymphoid tissue in these regions (Peyer patches, mesenteric nodes, tonsils, and cervical nodes). Virus then enters the bloodstream, resulting in a minor viremia and dissemination to a variety of target organs, including the central nervous system (CNS), heart, liver, pancreas, adrenal glands, skin, and mucous membranes.

The infections cause a wide spectrum of disease that can involve almost any organ system (Table 6). Disease severity can range from life threatening with significant morbidity to mild or subclinical. It is believed that approximately 50% of non-polio enterovirus infections are asymptomatic. The more common syndromes include nonspecific febrile illness, aseptic meningitis, herpangina, hand-foot-mouth syndrome, and exanthems. The clinical manifestations of infection in the neonate can be distinct and are discussed separately. Currently, there are no vaccines (except poliovirus) or treatment of enterovirus infections, except those supportive of clinical symptoms.

Paralysis. Before the advent of vaccination, poliovirus was a major cause of permanent paralysis in the U.S. Vaccination has largely eliminated poliomyelitis in the U.S., and no indigenous wild viruses have been detected in the U.S. since 1979 (Morens et al. 1991). Most infections are asymptomatic (90%–95%), with only 0.1%–2% resulting in paralytic poliomyelitis. Most poliovirus infections occur in children <4–5 yr of age, but the older the age of infection, the greater the severity of the outcome. Mortality in children averages 2.5% for symptomatic infections and 30% in adults (Morens et al. 1991).

Non-polio enteroviruses have been associated with paralysis, but this is uncommon compared to poliovirus (Gauntt et al. 1985; Grist and Bell 1984). Coxsackievirus A7 has been associated with outbreaks of paralytic disease (Grist and Bell 1970), and outbreaks of enterovirus 71 have been involved in several outbreaks of CNS involvement, with fatal cases mostly in children (Melnick 1984).

Table 6. Common Clinical Syndromes Associated with Enterovirus Infections in Children.

Syndrome	Predominant Virus	Clinical Features
Nonspecific febrile illness	All types	Febrile illness (fever), with nonspecific upper respiratory and gastrointestinal tract symptoms
Aseptic meningitis	Echovirus, group B coxsackieviruses, and polioviruses	Fever, meningeal signs with mild cerebrospinal fluid (CSF) pleocytosis, usually normal CSF glucose and protein, and absence of bacteria
Herpangina	Group A coxsackieviruses	Fever, painful oral vesicles on tonsils and posterior pharynx
Hand-foot-mouth disease	Coxsackievirus A16	Fever, vesicles on buccal mucosa and tongue and on interdigital surfaces of hands and feet
Nonspecific exanthem	Echoviruses	Variable rash (usually rubelliform but may be petechial or vesicular), with or without fever
Pleurodynia	Coxsackievirus B3, B5	Uncommon, epidemic, fever, and severe muscle pain of chest and abdomen
Myocarditis	Group B coxsackieviruses	Uncommon, myocarditis/ pericarditis, which can present with heart failure or dysrhythmia
Acute hemorrhagic conjunctivitis	Enterovirus 70	Epidemic cause of conjunctivitis with lid swelling, subconjunctival hemorrhage, and eye pain without systemic symptoms
Paralytic disease	Poliovirus, enterovirus 71, echoviruses, and coxsackieviruses	Paralysis

Perinatal and Neonatal Infections. Neonates represent a population at great risk from severe enteroviral disease. Adverse effects also occur from enteroviral infection during pregnancy with adverse effects to the fetus. In the prevaccine era, paralytic poliomyelitis occurred during pregnancy in apparent excess of age-adjusted expected rates, suggesting predisposition among pregnant women (Abzug et al. 1995). Infections of pregnant women by the non-poliovirus enteroviruses occur frequently. In a seroepidemiologic study, Brown and Karunas (1971) found a 42% rate of infection during pregnancy in a population evaluated prospectively over a 10-yr period. In a review of coxsackie B infections, Modlin and Rotbart (1997) suggested

that greater viral replication and prolonged maternal enterovirus excretion occurring in late pregnancy may well enhance the risk of infection of the newborn infant in the perinatal period.

Neonatal non-polio enteroviral infections are common. Estimated attack rates indicate that disease in newborns and young infants is comparable or exceeds symptomatic neonatal infections caused by herpes simplex virus and cytomegalovirus (Jenista et al. 1984; Kaplan et al. 1983; Modlin 1986). Enteroviruses were responsible for the majority (65%) of >3 mon-old infant admissions to one hospital in one community for suspected sepsis (Dagan et al. 1989; Kaplan et al. 1983; Modlin 1986). In another study, enteroviruses were the most frequently identified pathogen between days 8 and 29 of life, accounting for at least one-third of all cases of neonatal meningitis (Dagan et al. 1989; Kaplan et al. 1983; Modlin 1986; Shattuck and Chonmaitree 1992).

Age is one of the most important determinants of outcome of enterovirus infections. Different age groups have different susceptibilities to infection, different clinical manifestations and degrees of severity, and different prognoses following enteroviral infection. Young children have higher attack rates. In one study, echovirus 9 disease attack rates in children were found to be 50%–70% compared with 17%–33% in adults (Lerner et al. 1963). Age-specific attack rates of echovirus 30 per 1,000 persons in an outbreak in the United Kingdom ranged from 19.7 (children age 0–9 yr) to 7.11, 4.82, 4.73, 1.5, and 0 for the succeeding 10-yr age cohorts, respectively (Irvine et al. 1967).

Severity of illness may also be age dependent. With poliovirus infection, adults are more likely to be severely affected, tending to acquire paralytic poliomyelitis rather than nonparalytic poliomyelitis (i.e., aseptic meningitis) or asymptomatic infections. On the other hand, coxsackie B virus infection is clearly more severe in newborns than in older children and adults, often causing myocarditis, encephalitis, hepatitis, and death (Eichenwald et al. 1967; Gear and Measroch 1973; Woodruff 1980). Coxsackievirus and echovirus encephalitis and aseptic meningitis are most frequent among those 5–14 yr old (Ball 1975; Forbes 1963; Karzon et al. 1961), while myocarditis is most common in adults and neonates. In another study (Dery et al. 1974), the mean age among patients with coxsackievirus B meningitis was 7.7 yr, pericarditis was 9.9 yr, and gastroenteritis was 1.3 yr.

Herpangina. Herpangina is characterized by a painful vesicular eruption of the oral mucosa associated with fever, sore throat, and pain on swallowing. It is seen most commonly in children ages 3–10 yr (Morens et al. 1991). Group A coxsackieviruses are the most common etiological agents, but group B coxsackieviruses and echoviruses also have been isolated from patients. Fever, usually mild, develops suddenly, but higher temperatures up to 41°C (105.8°F) can be seen, particularly in younger patients. Nonspecific early symptoms may include headache, vomiting, and myalgia. Sore throat

and pain with swallowing are the most prominent symptoms and precede the characteristic exanthem (eruption of mucous membranes) by approximately 1 d. Herpangina is self-limiting, and symptoms resolve within 1 wk. Young children are at risk for dehydration because of refusal to eat or drink.

Aseptic Meningitis. Non-polio enteroviruses are the leading causes of aseptic meningitis, accounting for 70%–90% of all cases from which an etiological agent is identified (McGee and Barmger 1990; Zaoutis and Klein 1998). The most common enterovirus types associated with aseptic meningitis are coxsackievirus B5 and echovirus 4, 6, 9, and 11. These have occurred in epidemic outbreaks as well as sporadic cases, being most common in the 5- to 15-yr age group (Morens et al. 1991). Outbreaks have been associated with child-care centers (Helfand et al. 1994; Mohle-Boetani et al. 1999).

The initial presentation of enteroviral meningitis is similar to that of nonspecific febrile illness. Commonly, a biphasic pattern of symptoms is seen, with signs of CNS involvement in addition to recurrence of fever. Evidence for meningeal irritation commonly includes headache and photophobia, with 50% of children >1–2 yr of age also developing a stiff neck.

The course of enteroviral meningitis usually is self-limiting and benign, but there has been an ongoing debate about the occurrence of long-term sequelae (Modlin and Rotbart 1997). Recent studies have shown that there are no long-term neurological, cognitive, or developmental abnormalities from this infection in older children (Rorabaugh et al. 1993). However, several investigations have documented that 10% of children <3 mon of age who have aseptic meningitis may suffer long-term sequelae, especially speech and language delay (Etter et al. 1991).

Nonspecific Febrile Illness. The most common clinical presentation of non-polio enterovirus infection is a nonspecific febrile illness (fever). Typically, fever develops suddenly, and temperatures range from 38.5°C to 40°C (101°F to 104°F) and last an average of 3 d. Occasionally, a biphasic pattern of symptoms can be seen, with an initial fever for 1 d, followed by 2–3 d of normal temperatures and recurrence of fever for an additional 2–4 d.

Studies have found that enteroviruses are the major cause of hospitalization for young infants (<2–3 mon of age) for suspected fever caused by septicemia during the summer and fall (Dagan 1996). A recent study of infants <90 d of age found that non-polio enteroviruses were the most common cause of fevers in infants requiring hospitalization (Byington et al. 1999). More than 25% of the infants were infected; the average stay was 3 d with average medical costs of $4,500.

Exanthems (Eruption of the Skin). Non-polio enteroviruses are the leading cause of exanthems in children during the summer and fall months. The most common serotype causing exanthem is echovirus 9. The classic

enteroviral exanthem consists of a pink, macular, rubelliform rash. The rash may be the sole manifestation of infection or may be present in association with febrile illness or aseptic meningitis. Enteroviral exanthems are seen most commonly in children <5 yr of age and decrease in prevalence with age. The rash is self-limiting and disappears in 3–5 d (Zaoutis and Klein 1998). Most infections occur in infants and young children 3–10 yr of age (median, 4 yr) (Morens et al. 1991). An outbreak has been reported in a day-care center (Moreira et al. 1995).

The best known enteroviral exanthem is hand-foot-mouth (HFM) disease. It is commonly associated with coxsackievirus A16, but may also be caused by coxsackievirus A5 and several other enteroviruses including enterovirus 71 (Hagiwara et al. 1978). Children usually have a fever, with multiple discrete red macular lesions of about 4 mm appearing on the palms, soles, fingers, and toes. The infection is usually self-limiting, lasting 1–2 wk.

Complications associated with HFM disease caused by enterovirus type 71 include encephalitis, meningitis, hemorrhage, acute flaccid paralysis, and myocarditis. During a large outbreak of HFM disease in Taiwan in 1990 of enterovirus type 71, 129,000 cases were estimated, resulting in 405 hospitalizations and 78 deaths (Ho et al. 1999). Almost all the severe cases and deaths were in children <5 yr of age.

Respiratory Illness. Worldwide enteroviruses appear to account for 2%–15% of all viruses that cause upper and lower respiratory tract diseases (Chonmaitree and Mann 1995). The illness is most commonly associated with coxsackie A10, A21, A24, and B2 (Moren et al. 1991). Both children and adults are affected, with infections lasting only a few days. Pneumonia associated with enteroviral infection has been reported in both outbreaks and individuals (Chonmaitree and Mann 1995). Fatal pneumonia has been associated with coxsackievirus and echovirus infections in infants and children (Boyd et al. 1987; Cheeseman et al. 1977; Craver and Gohd 1990).

Acute Hemorrhagic Conjunctivitis (AHC). This explosive epidemic conjunctivitis, first described in 1969 in Africa and Asia, is now found worldwide. It is common in tropical and densely populated regions. The majority of outbreaks have been caused by enterovirus serotype 70, but recently coxsackievirus A24 has been isolated during outbreaks (Morens et al. 1991). AHC is characterized by sudden onset of severe eye pain, photophobia, and blurred vision. Subconjunctival hemorrhages, erythema, edema of the lids, and eye discharge are characteristic of infections. Recovery occurs within 7–10 d. Spread is by the eye-hand-fomite route, in contrast to the fecal–oral route seen with most enteroviral infections. Overall, it is more common in adults, but it also does affect school-age children. Some enterovirus outbreaks have been associated with poliomyelitis-like paralysis.

Diabetes. Insulin-dependent diabetes mellitus (IDDM) is the most common severe chronic childhood illness, affecting an estimated 123,000 children in the U.S. (Libman et al. 1993). More than 11,000 new cases are diagnosed annually. The disease is the leading cause of renal failure, blindness, and amputation and a major cause of cardiovascular disease and premature death in developed countries (Rewers and Atkinson 1995). IDDM occurs most frequently at the ages of 2, 4–6, and 10–14 yr, perhaps because of physiological increases in sex hormone levels and insulin resistance or because of alterations in the pattern of childhood infections. Season and latitude affect incidence, suggesting an infectious etiology (Rewers and Atkinson 1995). The infectious agents most commonly linked to IDDM have been the enteroviruses.

To date, epidemiological studies have failed to prove or disprove the association of enteroviruses with IDMM (Green et al. 2004), perhaps because the nature of the disease may involve both genetic factors of the host and environmental exposure, with clinical symptoms taking years to develop. Autoimmunity, potentially induced by a preceding enterovirus infection, could play a role in human IDDM (Rewers and Atkinson 1995). Recent studies continued to support some association with enterovirus infections and IDDM (Nairn et al. 1999; Pallansch 1997; Smith et al. 1998; Knip and Akerblom l998, 1999; Hoyoty et al. 1998, Honeyman et al. 2000; Lonnrot et al. 2000).

Pleurodynia (Bornholm Disease). Pleurodynia or epidemic myalgia is characterized by an acute onset of severe muscular pain in the chest and abdomen accompanied by fever. Coxsackieviruses B3 and B5 are the major causes of epidemic disease; rare sporadic cases have been described with other non-polio enteroviruses.

The muscular pain is sharp and spasmodic, with episodes typically lasting 15–30 min, although they can last up to several hours. During spasms, patients may develop signs of respiratory distress or appear shocklike with diffuse sweating and pallor. Pain localized to the abdomen in young children may falsely suggest intussusception or appendicitis. The illness usually lasts 1–2 d, but frequent recurrences are possible several weeks after the initial episode. Associated signs and symptoms include anorexia, headache, nausea, and vomiting. In contrast to many other enteroviral syndromes, pleurodynia is more common in older children and adolescents.

Cases are recognized mostly in school-age children and adults, with the peak age being children 2–9 yr old (Morens et al. 1991). However, older boys have also been reported to develop orchitis or inflammation of the testes (Morens et al. 1991). It has not been established whether involvement of the ovaries occurs.

Myocarditis. Coxsackievirus B infections are increasingly being recognized as a cause of primary myocardial disease in adults as well as children

(Melnick 1997). In some studies, up to 39% of persons infected with coxsackievirus B5 developed cardiac abnormalities. Coxsackieviruses of group A and echoviruses have also been implicated, but to a lesser degree. The illness is common in neonates and adults. Older adults represent the vast majority of cases, with patients aged 40 and older composing 69% of the cases (Martino et al. 1995). Although the incidence is less in neonates, the outcome is potentially more severe, with mortality among infants reported to be 30%–50% (Modlin and Rotbart 1997). Symptoms usually begin within the 10th day of birth with fatigue, poor feeding, or mild respiratory distress.

Most children and adults recover; however, one or more recrudescences several weeks to more than a year later have been reported in approximately 20% of the cases after the initial illness (Modlin 1990). Persistent electrocardiographic abnormalities (10%–20%), cardiomegaly (5%–10%), and chronic congestive heart failure indicate that permanent heart damage occurs as a result of this illness.

Diseases Associated with Immunocompromised Children. Enteroviruses are not prominent among the microorganisms that cause serious morbidity and mortality among the immunocompromised. In childhood, serious enterovirus infection does not appear to be particularly common in the T-cell immunodeficiency syndromes (Morens et al. 1991). However, enteroviral infections pose significant risk to children who have defects in B-lymphocyte function, the most common of which is X-linked agammaglobulinemia (Gewurz et al. 1985; McKinney et al. 1987; Hertal et al. 1989). Unlike other viruses that are combated by cellular immune mechanisms, enteroviruses are eliminated from the host by humoral immune mechanisms. An intact B-cell response is believed to be necessary to block viral entry into the CNS. Children who have agammaglobulinemia may develop chronic enteroviral infection, most commonly meningoencephalitis. Patients experience headache, lethargy, seizures, motor dysfunction, and altered sensorium. Symptoms may wax and wane for years, but there is an overall progressive deterioration in CNS function. Infections are fatal in most children who are immunodeficient. Echovirus 11 has been the most common cause of chronic infection, but cases caused by other echoviruses and coxsackieviruses have been reported (Morens et al. 1991).

Enterovirus infections in infants who have received organ transplants can result in serious complications (Chuang et al. 1993; Aquino et al. 1996). Serious life-threatening infections of both echovirus and coxsackievirus have been documented in infants receiving both bone marrow and liver transplants. Children cancer patients receiving chemotherapy may also suffer from severe illness when infected with a coxsackievirus (Geller and Condie 1995).

Other Illnesses. Enteroviruses have been associated with a number of other illnesses that affect children (Kennedy et al. 1986), including juvenile

Table 7. Less Common Illnesses Associated with Enterovirus Infections in Children.

Syndrome	Reference
Rheumatoid arthritis	Blotzer and Myers 1978 Heaton and Moller 1985 Zaher et al. 1993
Pancreatitis	Kennedy et al. 1986
Hemorrhagic syndrome	el-Sageyer et al. 1998
Gastroenteritis	Birenbaum et al. 1997
Hepatitis	Jeffery et al. 1993
Mental Disorders	Hirayama et al. 1998
Alice in Wonderland syndrome	Wang et al. 1996
Schizophrenia	Rantakallio et al. 1997
Vertigo	Simonsen et al. 1996
Hydrancephaly (absence of cerebral hemisphere in the newborn)	Marlin et al. 1985

rheumatoid arthritis (Blotzer and Myers 1978) and gastroenteritis (Joki-Korpela and Hyypia 1998). Case reports have also linked enteroviruses to short-term mental impairment in children and other illnesses or symptoms in children (Table 7). Other studies have suggested relationships between enterovirus infections and sudden infant death syndrome (SIDS) (Rambaed et al. 1999), risk of schizophrenia from infections early in childhood (Rantakallio et al. 1997), amyotrophic lateral sclerosis (Lou Gehrig's disease) (Berger et al. 2000), vertigo (Simonsen et al. 1996), and chronic fatigue syndrome (Galbraith et al. 1997; Lane et al. 2003). These studies have been limited in scope or speculative.

III. Incidence of Enteric Virus Infection by Age

A. Rotavirus

Rotavirus is the major cause of childhood gastroenteritis, although all age groups are affected. The highest incidence of the disease is in the fall and winter in the U.S. In one study rotavirus was detected in 29% of the stools of children <2 yr of age, with 48% of the cases being asymptomatic (Champsaur et al. 1984a,b). In another study the incidence of rotavirus gastroenteritis was found to be 40% in the 1–2 yr age group, 12% in the 2–3 yr age group, and 5% in adults (Rodriguez et al. 1987). Crowley et al. (1997) found that almost 65% of the diagnosed cases in England and Wales occurred in the 6-mon to 1-yr age group (Table 8).

Table 8. Distribution (Percent) by Age of Gastroenteritis Infections in Small Children in England and Wales, 1990–1994.

Virus	<1 mon	1–2 mon	3–5 mon	6–11 mon	1 yr	2 yr	3 yr	4 yr	Total number of cases
Rotavirus	1.6	4.9	10.8	29.3	35.3	12.2	4.2	1.7	6,591
Adenovirus	1.6	8.3	15.7	27.2	27.5	11.5	5.4	2.8	10,362
SRSV	1.5	5.0	12.7	27.5	29.8	12.9	6.9	3.6	1,756
Astrovirus	0.5	4.6	12.5	25.0	31.1	16.5	6.3	3.5	1,760

Source: Crowley et al. (1997).

B. Adenovirus

The incidence of adenovirus gastroenteritis in the world has ranged from 1.5% to 12.0% (Herrmann and Blacklow 1995). In England, a survey of stool samples from patients suffering from viral gastroenteritis showed that enteric adenoviruses were present in 14% of the examined specimens. Recent studies in England and Wales (Caul 1996b) have indicated that enteric adenoviruses account for 8.2% of all viral gastroenteritis. Although most reports indicate that the enteric adenoviruses are only second in importance to rotavirus as a cause of viral gastroenteritis, an epidemiological study in Guatemala showed that the adenoviruses 40 and 41 were associated with diarrheal episodes in ambulatory children three times more often than rotaviruses (Cruz et al. 1990).

C. Caliciviruses

Recent research suggests that calicivirus diarrhea may be common among infants and young children (Koopmans et al. 2000; Inouye et al. 2000; Pang et al. 1992). Koopmans et al. (2000) reported that it was a more common cause of gastroenteritis in children <5 yr than rotavirus. Norwalk virus antibodies are acquired gradually, beginning slowly in children, and increasing in adulthood. By age 50, approximately half the population has developed antibodies to Norwalk virus (Estes and Hardy 1995).

D. Hepatitis A Virus (HAV)

Infection of HAV in children is usually asymptomatic; however, the risk of symptomatic cases increases to 75% in adults in whom the most severe cases are seen. The incidence of reported hepatitis A in the U.S. is 9.7 cases per 100,000 (CDC 1996). However, the actual incidence may be much higher because many persons do not seek treatment and because physicians are believed to report fewer than 15% of hospital diagnosed cases (Hollinger and Ticehurst 1996). Thus, the true incidence is at least 6.6 times

Table 9. Percentage of Stool Samples Positive for Enteric Viruses.

Virus	<1 yr	1–4 yr	5–14 yr	15–74 yr	>74 yr
Rotavirus group A	10.3	8.8	4.5	2.0	0.0
Adenovirus types 40 and 41	7.1	6.1	1.8	0.0	0.0
Astrovirus	7.1	4.0	0.9	1.2	0.0
SRSV[a] and Calicivirus	17.8	13.5	9.9	5.2	4.5

[a]Small round structured viruses (Tompkins et al. 1999).

that reported (i.e., 0.1%). Also, this incidence does not take into consideration the number of asymptomatic cases, which occur commonly among young children. In an endemic area of Italy, De Filippis et al. (1987) found that 8.2% of stool samples from healthy individuals contained HAV, with the highest prevalence found in children. The greatest incidence is among children 5–14 yr of age. It has been estimated that 95,000–180,000 infections occur yearly in children <10 yr of age in the U.S. (Armstrong and Bell 2002).

E. Hepatitis E Virus (HEV)

In a survey in Mexico, where HEV is endemic, it was found that 10.5% of 3,549 individuals had antibodies to HEV. Seroprevalence increased with age, from 1.1% in children <5 yr old to 14.2% in the group of 26- to 29-yr-olds (Alvarez-Munoz et al. 1999). Similar seroprevalence was observed in Ghana, where 1% of children 6–7 yr of age were HEV seropositive. This number increased to 8.1% among children 16–18 yr of age (Martinson et al. 1999).

F. Enterovirus

In two studies on virus occurrence in solid waste, Peterson (1974) isolated enteroviruses in 10% of the fecally soiled diapers that she examined (Table 9). The excretion rate of enteroviruses has been found to vary with month, with the greatest percentage from May to October in the U.S. The incidence in children over the entire year ranges from 2.4% to 13.3%, with the higher excretion rate in the lower socioeconomic group (Melnick 1997). The most extensive work done on virus excretion was during the "Virus Watch" studies in which the incidence of virus illness and excretion was conducted in families for many years in several locations across the U.S. (Fox and Hall 1980). In Seattle and New York, stool samples were collected from family members regularly, usually at monthly intervals, whether illness was present or not. Over a 3-yr period, the incidence of excretion of any enteric virus in children (<15 yr of age) was found to range from about 10% in the winter to almost 40% during the summer. During summer and autumn months (June through October), more than one-third of healthy children were

Table 10. Incidence of Enteric Virus Infections in the United States.

Pathogen	Incidence (%)	Remarks	Reference
Enterovirus	10	Occurrence in fecally soiled diapers	Peterson 1974
	30–40	During the summer months (June–Oct.): all enteric viruses[a]	Fox and Hall 1980
	2.4–13.3	12 mon average	Melnick 1997
Hepatitis A	0.0097	Reported cases of clinical illness	CDC 1996
	8.2	Occurrence of virus in stools of healthy persons	DeFilippes et al. 1987
Rotavirus	10.4	Annual rate of clinical infection	Ho et al. 1999
	29	All age groups	Champsaur et al. 1984a,b

[a]Any virus isolated from stool samples causing destruction of cell culture.

excreting some virus in the feces, as detected by cell culture. Overall, the frequency of illness associated with echovirus infections was 44%. However, symptomatic infections were greater for children <4 yr of age; 78% for 0- to 4-yr-olds, and 12% for children >5 yr of age and older. The rate of symptomatic infections among adults was 28% for both coxsackievirus and echovirus versus 42% for children <4 y of age (Table 10).

IV. Economic Impact of Enteric Viral Infections in Children

A. Rotavirus

Rotaviruses are the most common cause of severe vomiting and diarrhea in children, with an estimated 3.1 million cases annually in the U.S. (Smith et al. 1995). A study of hospitalizations in children involving diarrhea from 1993–1995 indicated that rotavirus was the most common identified agent (Parashar et al. 1998). In total, viruses accounted for 32.9% of hospitalizations involving diarrhea, followed by bacteria (4.1%), and parasites (0.3%). Overall, rotavirus accounted for 16.5% of hospitalizations for diarrhea among children aged <5 yr. A study by Parashar et al. (1999) on hospital discharge data in Connecticut found that the median cost of diarrhea-associated hospitalization during 1987–1996 and 1993–1996 was $1,941 and $2,428, respectively (Table 11). Because only about half the children admitted to hospitals may be tested, the actual data based on hospital discharges may be underestimated. Hospitalization due to rotavirus gastroenteritis has been estimated at 65,000 to 70,000 annually in the U.S., with 125 deaths (Smith et al. 1995). Ryan et al. (1996) estimated that in England and Wales

Table 11. Indirect and Direct Costs (in Dollars) of Enteric Viral Infections in Children.

Virus	Duration of illness (ds)	Medical costs		Indirect and direct costs		Year[a]	Reference
		Hospitalization	No hospitalization	Hospitalization	No hospitalization		
Rota	3.5	3,615	94	ND	325	1993	Smith et al. 1995
	2	2,428	ND	ND	ND	1993–1996	Parashar et al. 1999
Norwalk	1	887	160–320	1,151	88–480	1993	Crabtree 1996
Hepatitis A	ND	7,138	ND	ND	ND	1999	O'Conner et al. 1999
Enteroviruses							
HFMD	7	ND	69	ND	132	1994	Pichichero et al. 1998
Meningitis	6.5	ND	771	ND	1,193	1994	Pichichero et al. 1998
Echovirus 30 meningitis	ND	1,757	450	ND	ND	1991	Rice et al. 1995
Febrile illness in infants	3	ND	ND	4,500	ND	1997	Byington et al. 199

HFMD, hand-foot-and-mouth disease; ND, no data.
[a]Year for which cost was estimated.

the hospitalization rate for rotavirus-related illness for children <5 yr old was 5/1000.

Smith et al. (1995) estimated, in 1993 dollars, outpatient visits at $94 per visit, hospitalization at $3,615, and loss of productivity at $66/d. For a non-hospitalized child with mild diarrhea (3.5 d of illness), total direct and indirect costs would be $325 per case. Crabtree (1996) estimated total direct and indirect costs of $176/case for those not needing medical attention, $512–$672 for those needing outpatient medical attention, and $4,340 for those needing hospitalization. Yearly costs of childhood rotavirus in the childhood rotavirus in the U.S. were in 1993 determined to be approximately $1.8 billion.

B. Calicivirus

Crabtree (1996) attempted to estimate the cost to individuals due to Norwalk virus illness that might be attributable to drinking water. From a review of outbreaks of Norwalk virus, it was determined that an average of 28% of all cases visited a physician and 2.5% were hospitalized. No deaths were reported in any of the outbreaks; however, to assess costs that may incur from death, a 0.0001% case-fatality rate was applied (Bennett et al. 1987). Direct and indirect costs (1993 dollars) for those who did not see a physician were estimated at $88/case, those seeing a physician at $336–$480/case, and those hospitalized at $1,151/case. It was estimated that more than $1 billion/yr may be associated with Norwalk virus illnesses in the U.S., with nearly $0.5 billion attributable to waterborne transmission (Payment et al. 1991).

C. Hepatitis A Virus

Two studies have examined the cost benefits of hepatitis A immunization in developed countries. O'Connor et al. (1999) evaluated the economic benefits of vaccinated adults and estimated the per case nonhospitalized medical cost at $142, hospitalized at $7,138, and fatal cases at $19,603. Das (1999) estimated average direct medical costs of $1,070–$2,460 per case. Although estimates of indirect costs are available, Lucioni et al. (1998) studied the economic cost of hepatitis A caused specifically by the contamination of food. The direct and indirect cost per patient was $662; costs of hospitalized patients were as great as $86,899.

D. Enterovirus

Studies on the economic cost of non-polio enterovirus infections have only recently been attempted. Pichichero et al. (1998) conducted a study on children >4 yr to assess the economic impact of enterovirus infection. Some 380 children in two clinics, over a period of 4 mon in different regions of the U.S., were involved in the study. The children were followed for 2 wk to document absenteeism and follow-up medical care. The majority of the illnesses were mild, and no hospitalizations were required. Most of the ill-

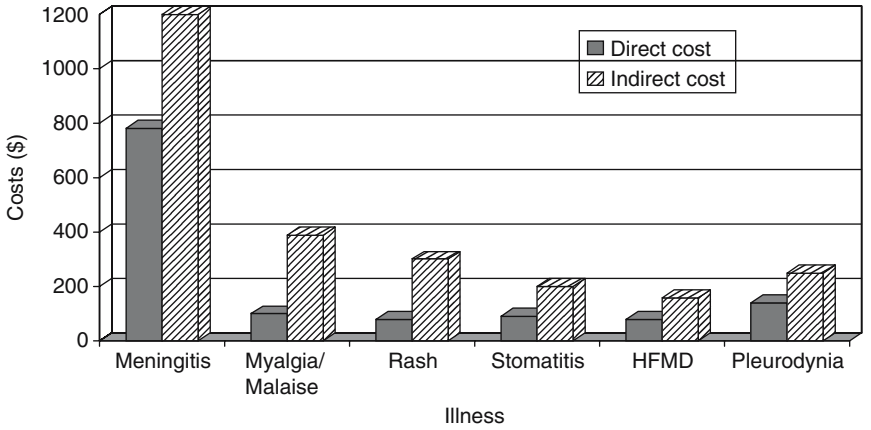

Fig. 4. Comparison of direct and indirect costs of nonpolio enterovirus illness in children. HFMD, hand-foot-and-mouth disease. *Source*: Pichichero et al. (1998).

nesses occurred in children 4–12 yr of age. The duration of illness in most children was prolonged, 9.5 d on average. The total of direct medical care costs and indirect costs per case ranged from $132 for hand-foot-and-mouth disease to $1,193 for meningitis (Fig. 4).

In 1991, a large outbreak of echovirus 30 meningitis occurred in New England, affecting more than 1,500 individuals (Rice et al. 1995). A cost analysis of the hospital billing for the inpatient and outpatient care of 103 patients involved in the outbreak was performed at a hospital serving the region. The average inpatient management cost of a patient with enterovirus meningitis, in this outbreak, was $1,757 ± $198 and the outpatient management cost was $477 ± $63. Indirect costs were not determined. Crabtree (1996) estimated the direct and indirect costs of enterovirus aseptic meningitis to range from $512 to $702 for nonhospitalized cases and $5,403 for hospitalized cases. The indirect costs of cases that did not see a physician were estimated at $176 per case. Bennet et al. (1987) estimated the numbers of aseptic meningitis cases in the U.S. by multiplying the number of estimated enterovirus cases by 6.34%, which is the percent of enterovirus illnesses related to a specific meningitis and reported to the Centers for Disease Control (CDC 1981). From these analyses, the total medical and productivity costs were estimated to range from $1.8 billion to $7 billion annually, with potentially $2.4 billion attributable to water (assuming 35% are waterborne) (Payment et al. 1991).

V. Exposure

A. Drinking Water

Infants and young children have a greater environmental exposure to enteric organisms than adults. They have not yet developed proper sanitary habits (e.g., use of toilet facilities, hand-washing, frequent hand-to-mouth

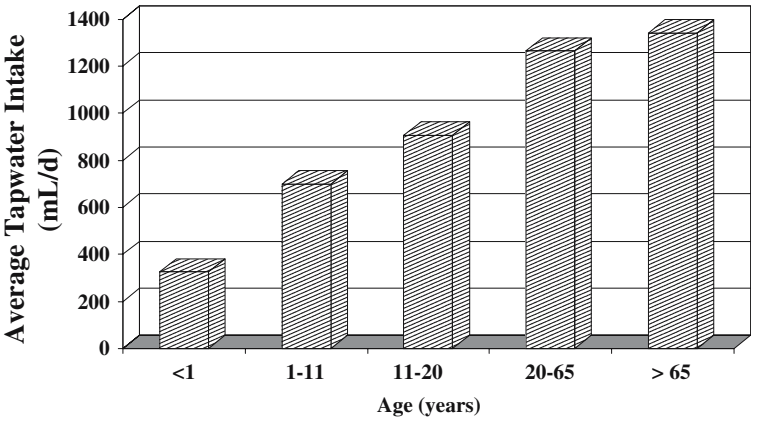

Fig. 5. Average tapwater intake by age. Data from Roseberry and Burmaster (1992).

or fomite-to-mouth contact) (Springthorpe and Sattar 1990). Object-to-mouth and mouth-to-mouth contact is much greater among children than adults. Viruses are readily transferred from contaminated objects (fomites) directly to the mouth or contamination of the hand. The median number of such contacts by age, per day, are as follows: 1–12 mon, 64; 13–24 mon, 34; 25–30 mon, 27; 31–36 mon, 5; and 37–48 mon, 10 (Hutto et al. 1986). During recreational activities, they may ingest greater quantities of dirt and water (Sedman and Mahmood 1994). However, they do consume less tapwater than adults do (Roseberry and Burmaster 1992), although children <10 yr of age consume more per body weight than any other age group (EPA 2000). Children <11 yr of age consume almost half the amount of tapwater consumed by adults (Fig. 5). However, pregnant and lactating women ingest more tapwater than other women (Burmaster 1998). Because it is believed that many of the serious fetal and neonatal enteric viral infections are contracted from the mother (see enteroviruses in Section C), a greater exposure via tapwater to pregnant and lactating women would imply greater exposure to the fetus and the neonate.

B. Social Economic Factors (Environmental Justice)

Numerous studies have documented the greater incidence of enteric viral infections in lower social economics groups (see II. 3) Behnke et al. 1988. During community-wide outbreaks of hepatitis A in the U.S., neighborhoods of lower socioeconomic status have been identified as a risk factor (Shaw et al. 1986). Households that lack piped water and access to safe water supplies also suffer higher attack rates (Cama et al. 1999; Gurwith et al. 1983; Hyams et al. 1992).

VI. Infectivity (Infectious Dose)

No studies could be found in which an attempt had been made to determine if the infectious dose or infectivity of enteric viruses was different for adults compared to children. Dose–response models have been developed from studies involved in the oral exposure of poliovirus types 1 and 3 (Regli et al. 1991) in which infants and premature babies were used as subjects. The dose response of those viruses is similar to that observed for echovirus 12 and rotavirus in adults; however, infectivity is not directly comparable because this is likely dependent both on the type and strain of virus. Factors that could predispose children to have a greater probability of becoming infected from a given dose than adults are reduced stomach acid and pepsin secretion (Haffejee 1995) (see Section I). Although the severity of illness is usually greater for children than adults, it is currently not known if severity is related to dose for enteric viruses (see II.C. Properties of Enteroviruses).

VII. Risk Assessment

Microbial risk assessment is the application of the principles of risk assessment to estimate the consequences from an exposure to infectious microorganisms. This approach can be used to estimate the magnitude of the risk and the probability of adverse effect (Haas et al. 1999). There is epidemiological evidence that members of all the enteric viruses are transmitted by water (EPA 1999a,b; Haas et al. 1999). Quantitative microbial risk assessments have been conducted for adenovirus (Crabtree et al. 1997), coxsackievirus (Crabtree 1996), and rotavirus (Gerba et al. 1996) in drinking water.

These assessments are patterned after the widely accepted paradigm on chemical risk assessment developed by the National Academy of Sciences in 1983 (NAS 1983). This approach follows the processes of first identifying the pathogen of concern, then developing a dose–response relationship between ingestion of the pathogen and a susceptible host, determining the risk of infection from a given exposure and, finally, characterizing the overall risk.

A. Dose–Response Models

The probability density functions are relatively simple models, with several inherent assumptions (e.g., infection has occurred, the chance of contracting disease is independent of ingested dose). Generally, the first step in the probability analysis is the determination of the probability of infection based on the application of the exponential model or the beta-Poisson model (Haas et al. 1999). The second step is to determine the relationship between infection and developing clinical disease.

In assessing exposure to waterborne adenovirus (Crabtree et al. 1997), an exponential model was used. The probability of becoming infected (P_i) was calculated as:

$$P_i = 1 - \exp(-rN)$$

where

P_i = probability of being infected
N = number of organisms ingested or inhaled
r = 0.4172 for adenovirus (Rose et al. 1996), the probability after ingestion or inhalation that the organism survives to initiate an infectious focus

The "r" value is derived from human exposure studies. For both viruses, the probabilities of developing clinical illness ($P_{illness}$) and of dying as a result of this illness (P_m) were also determined. The probability of becoming ill from exposure was calculated by multiplying the probability of infection (P_i) by the morbidity rate of 0.5 for adenovirus (Haas et al. 1993).

Crabtree et al. (1997) calculated the probability of death by multiplying the probability of infection (P_i) by the mortality rate of 0.0001 for adenovirus.

Gerba et al. (1996) assessed the risks associated with exposure to waterborne rotavirus in tap water using the beta Poisson probability model to calculate probabilities of infection, of illness, and of mortality. The probability of infection was calculated as:

$$P_i = 1 - (1 + N/\beta)^{-\alpha}$$

where

P_i = probability of being infected
$\beta = 0.42$ and $\alpha = 0.26$ (Haas et al. 1993), parameters that describe host-virus interaction after ingestion or inhalation
N = number of organisms ingested

The probability of clinical infection ($P_{illness}$) and the probability of dying as a result of illness (P_m) were also determined. The probability of becoming ill was calculated by multiplying the probability of infection (P_i) by the morbidity rate of 0.5 (Haas et al. 1993). The probability of death (mortality) from infection was calculated by multiplying the probability of infection (P_i) by the morbidity rate and a case/fatality of 0.0001.

The beta Poisson model has been identified as the model that best fits most of the dose–response data for viruses and which provides a conservative method for low-dose extrapolation (Haas et al. 1993; Regli et al. 1991). However, several assumptions are made that limit the use of probability models from estimating risks from exposure to pathogens in drinking water. The Poisson model assumes random distribution of microorganisms in drinking water. The risk estimates for low-level exposures are based on extrapolation to low doses and, at very low pathogen concentration, the

relationship between risk of infection and dose is approximately linear (Haas et al. 1993). The models assume that the exposed population is equally susceptible to a single exposure and ingests 2 L of water per day. The relationship between infection and the development of clinical illness is regarded as a conditional probability that, once having been infected, a certain number of individuals will develop disease (Haas et al. 1993). The chance of developing a symptomatic illness once infected by a virus is assumed to be independent of dose. Each exposure is regarded as statistically independent [i.e., the chance of developing an infection (illness or death) from one exposure is not related to prior exposures and effects]. The calculated risk is for the nonimmune person; therefore, immunity plays no role in the risk assessment for a nonimmune person.

B. Epidemiological Evidence for Transmission of Viral Diseases to Children by Water

Because of the need to consume fluids, drinking water-associated outbreaks inadvertently affect all age groups. Two epidemiological studies, designed to study the impact of conventionally treated drinking water meeting all standards, found that children were the most affected group (Payment et al. 1991). Figure 6 shows the relative incidence of gastroenteritis by age in those individuals drinking tapwater and those drinking tapwater after filtration by a reverse-osmosis filter, designed to remove pathogens (Payment et al. 1991). A greater impact of highly credible gastrointestinal illness was

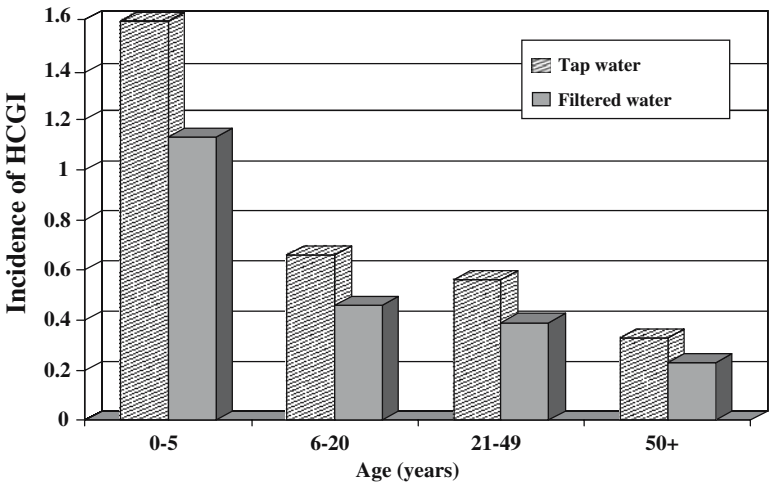

Fig. 6. Incidence of highly credible gastrointestinal symptoms (HCGI) episodes for period 2 by selected population subgroups. Data from Payment et al. (1991).

seen among children who drank the nonfiltered tapwater. In the other study, families were provided with purified bottled water, or with tapwater delivered from the water treatment plant after treatment (bottled tapwater), or drank only tapwater after it had been delivered through the distribution system (Payment et al. 1997). Using the purified water as the baseline, the excess of gastrointestinal illness associated with tapwater was 14% in the bottled tapwater group and 19% in those who consumed water from the tap in the home. Children 2–5 yr old were the most affected, with an excess of 17% in the bottle tapwater group and 40% in those drinking water from the tap. In either study, the agent causing the illness was not identified. The system was served by a poor-quality surface water.

Rotavirus. Rotavirus has been responsible for several drinking waterborne outbreaks worldwide (Gerba et al. 1996). In a 1981 outbreak of rotavirus in Colorado, an estimated 1,500 individuals were infected, including both adults and children (Hopkins et al. 1984). In a waterborne outbreak in a school in Brazil, higher attack rates of gastroenteritis were seen in nursery-age and kindergarten-age children (Sutmoller et al. 1982). A study in Lima, Peru, found that attack rates were higher in children who were not exclusively breast-fed in early infancy and who also lacked piped water in their homes (Cama et al. 1999).

Caliciviruses. Numerous drinking waterborne outbreaks of caliciviruses have been documented. Several outbreaks have occurred at elementary schools and summer camps (Kaplan et al. 1982; Taylor et al. 1981), while others were community outbreaks in which individuals of all ages were affected (Goodman et al. 1982). Although attack rates were similar for both adults and children, secondary transmission rates were greater among children. In one swimming-associated outbreak, the secondary attack rate was highest among children <10 yr of age (Baron et al. 1982). Also, attack rates were significantly higher during common source outbreaks, such as drinking water (median, 60% vs. 39% for person-to-person) (Kaplan et al. 1982). A study of viral diarrhea in three native Indian villages in Canada noted that infections of Norwalk virus were greatest in infants in the one community with an untreated water supply (Gurwith et al. 1983).

Adenovirus. Although there has only been two suspected drinking water outbreak involving an adenovirus (Papapetropoulou and Vantarakis 1998), there have been numerous outbreaks of swimming-associated adenovirus infections, many involving children (Foy et al. 1968; McMillian et al. 1992; Martone et al. 1980). Outbreaks have been associated with adenovirus 3, 4, and 7 causing conjunctivitis or pharyngoconjunctival fever affecting children 1–18 yr of age. Attack rates have been as high as 67% in children, with secondary attack rates of 19% for adults and 63% for children (Foy et al. 1968) (Fig. 7).

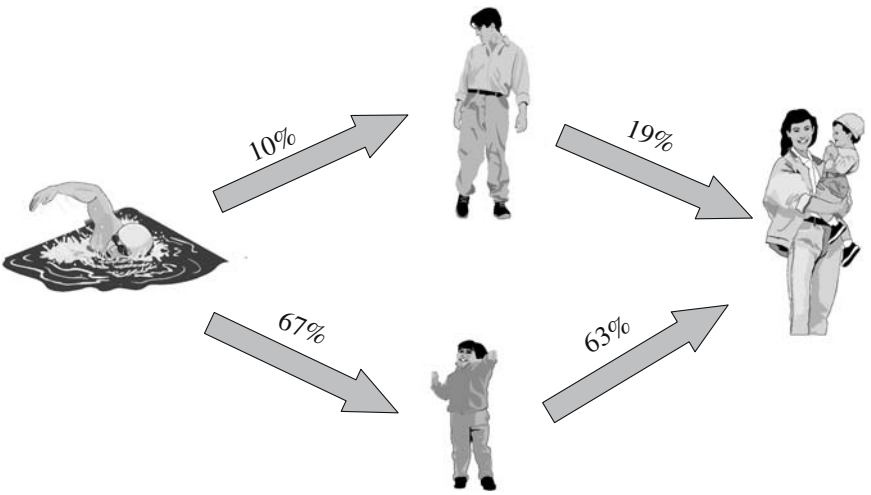

Fig. 7. Impact of a waterborne disease outbreak of adenovirus on attack rates and person-to-person transmission.

Hepatitis A Virus (HAV). Waterborne outbreaks of HAV are well documented in the U.S. (Gerba et al. 1985). Although asymptomatic infections are more common among children than adults (see earlier section), higher attack rates have been observed during waterborne outbreaks in older children. In an outbreak in Maryland traced to a heavily contaminated spring used as drinking water, the highest attack rates were in the 10–14-yr age group (Whatley et al. 1968). In an outbreak associated with a water fountain, the 16–20-yr age group (Bowen and McCarthy 1983) was affected the most.

Hepatitis E Virus (HEV). During the past decade, at least 30 outbreaks of HEV have been associated with waterborne outbreaks involving drinking water in 17 countries (Craske 1992). Although outbreaks of hepatitis E have not been reported in the U.S., it has recently been found to occur in pigs, which may serve as a reservoir of human infection (Meng et al. 1998, 1999). Although children become infected with HEV during waterborne outbreaks, the most serious resulting illness occurs in adults. In two drinking water-associated outbreaks in Mexico, the attack rate for persons <15 yr of age was 1%–2% vs. 10% for those >15 yr of age. However, mortality among pregnant women generally ranges from 20% to 30% and can be as high as 40% (Craske 1992). Thus, the fetus is at serious risk of mortality during waterborne outbreaks. Hepatitis E infection in children has also been associated with the lack of indoor plumbing in the developing world (Hyams et al. 1992).

Enteroviruses. Although there have been no clearly documented drinking water outbreaks associated with enteroviruses, several recreational outbreaks have been documented among children. An outbreak of coxsackievirus B4 or B5 meningitis linked to swimming in a lake occurred at a boys' summer camp (Hawley et al. 1973). Another outbreak of meningitis, this time caused by coxsackievirus A16, occurred due to exposure to lake water (Denis 1974). An epidemiological study among bathers swimming in non-disinfected lake waters demonstrated an association with increased risk of enterovirus infection. D'Alessio et al. (1981) surveyed children 1–15 yr of age at a pediatric clinic to determine where they had been swimming and the location and frequency of the swimming during the prior 2 wk. Children swimming at a beach versus in a pool with a chlorine residual had a statistically significant increase in the relative risk of having an enterovirus illness. Of the 134 viruses isolated from the patients, 119 (90%) were non-polio enteroviruses and 33.6% were coxsackievirus type A.

Echovirus 30 transmission to children has also been associated with a community swimming pool (Kee et al. 1994). The risk of echovirus 30 was greatest among those who swallowed pool water.

C. Endpoints

An assessment endpoint for microbial risk assessment has usually been risk of infection (Regli et al. 1991). Greater uncertainty exists in assessing the probability of illness and mortality, because this is dependent not only on the type of virus but on also a particular strain. Other factors include the immune state of the host, age, and other preexisting conditions. In the case of HAV, very young children are more likely to develop clinical symptoms than older children and adults, and the disease is generally more severe in adults. However, in the case of rotavirus, the resulting diarrhea is more severe in children than adults, which is reflected by the large number of hospitalizations for rotavirus infections in the U.S. Adenoviruses and astroviruses appear to be largely involved in infections of children. In contrast, Norwalk viruses appear to affect all age groups almost equally. Enteroviruses cause a wide range of illnesses, being most severe in neonates and children. Although most children recover, infections in neonates, especially of coxsackieviruses, are frequently fatal. With the possible exceptions of hepatitis A and E, a greater severity of illness and risk of mortality exists for children than adults. Thus, in assessing the risks of enteric viral infections in children, it is important to assess the endpoints of severity of illness and mortality because they can be significantly greater than in adults.

D. Risk Characterization of Enteric Viruses in Water and Children

The only dose–response data available for children are those obtained from studies conducted with vaccine strains of poliovirus. Lepow et al. (1962) conducted studies on newborn infants less than 5 d old with poliovirus Sabin

Table 12. Probability of Infection from Different Types of Poliovirus by the Oral Route in Children.

Virus type and Strain	Probability of infection	ID_{50}[a]	Reference
1 LSc-2	7.14×10^{-4}	6.93×10^{4}	Lepow et al. 1962
1	9.10×10^{-3}	76.2	Minor et al. 1981
3 Fox	1.90×10^{-1}	5.5	Plotkin et al. 1959
3 Fox	2.66×10^{-1}	5.0	Katz and Plotkin 1967

[a]The number of viruses required to cause infection in 50% of the individuals exposed.
Source: Teunis et al. (1996).

Table 13. Probability of Infection by Poliovirus Type 1 by Age-Adjusted Exposures for Tapwater Ingestion.[a]

Age (yr)	Exposure (L)	Daily risks of infection	Yearly risks of infection
<1	0.323	2.94×10^{-4}	1.04×10^{-1}
1–11	0.701	6.38×10^{-4}	2.08×10^{-1}
11–20	0.907	8.25×10^{-4}	2.60×10^{-1}
21–65	1.265	1.15×10^{-3}	3.43×10^{-1}

[a]Assuming ingestion of one infectious virus in 10 L of drinking water.
Exponential model of Teunis et al. (1996); $r = 0.009102$.

type 1 (LSc-2). Minor et al. (1980) exposed 2-mon-old infants via the oral route with a syringe with a vaccine strain of polio type 1. Plotkin et al. (1959) and Katz and Plotkin (1967) orally exposed premature infants to an attenuated strain of poliovirus type 3 (Fox strain). The probability of being infected by ingesting one virus in these studies was assessed by Teunis et al. (1996). They found that the probability ranged from 7.14×10^{-4} to 1.90×10^{-1} (Table 12). The range probably reflects the type of virus and method of administration. Using the data of Roseberry and Burnmaster (1992) on average ingestion of tapwater by age, an assessment was made of the probability of infection in different age groups for poliovirus type 1 (Table 13).

The risk of infection, illness, and death associated with coxsackievirus levels in conventionally treated water are shown in Table 14 for children. The data suggest that significant risks of illness for children could exist from these exposure levels; however, outcome would always be dependent on the virulence of the individual virus.

VIII. Conclusions

This review suggests that children and immunocompromised individuals bear the greatest burden of illness associated with drinking water-transmitted enteric viral diseases. They suffer the highest attack rates and

Table 14. Risk of Infection, Illness, and Death Associated with Coxsackievirus Levels in Tapwater.

Age	Exposure (L)	Daily risk Infection	Illness	Mortality	Yearly risk Infection	Illness	Mortality
<1	0.323	1.2×10^{-5}	9.34×10^{-6}	5.6×10^{-8}	4.5×10^{-3}	3.4×10^{-3}	1.99×10^{-5}
1–11	0.701	2.7×10^{-5}	2.0×10^{-5}	1.2×10^{-7}	9.8×10^{-3}	7.3×10^{-3}	4.3×10^{-5}

[a]Concentration of 0.005 MPNCU (most probable number of cytopathic units)/L of virus in the tapwater (Payment et al. 1985): surface water supply.

Risk of infection and mortality from Crabtree (1996).

A cytopathic unit is defined as destruction of cells in culture by a virus.

the most severe illness. To better quantify the impact on children, the literature should be further reviewed for case studies of waterborne outbreaks where data are available on the resulting illness by age group. The EPA and/or Centers for Disease Control should attempt to collect these data as future outbreaks are documented.

Given the differences in the physiology between children and adults, it may be that children have a greater probability of infection with a given dose than adults. Studies in animals or vaccine strains of viruses with children should be conducted to determine if a significant difference exists. Because the major route of infection of neonates by enteroviruses appears to be transmission from the mother to the child, at or shortly after birth, greater development of dose–response data in animals may be useful to assess if a greater susceptibility of the mother to enteroviruses occurs during pregnancy. Better documentation of long-term sequelae, particularly for enterovirus infections, is needed.

Summary

Children are at a greater risk of infections from serious enteric viral illness than adults for a number of reasons. Most important is the immune system, which is needed to control the infection processes. This difference can lead to more serious infections than in adults, who have fully developed immune systems. There are a number of significant physiological and behavioral differences between adults and children that place children at a greater risk of exposure and a greater risk of serious infection from enteric viruses.

Although most enteric viruses cause mild or asymptomatic infections, they can cause a wide range of serious and life-threatening illnesses in children. The peak incidence of most enteric viral illnesses is in children <2 yr of age, although all age groups of children are affected. Most of these infections are more serious and result in higher mortality in children than adults. The fetus is also affected by enterovirus and infectious hepatitis

resulting in significant risk of fetal death or serious illness. In addition to the poliovirus vaccine, the only vaccine available is for hepatitis A virus (HAV). A vaccine for rotavirus has currently been withdrawn, pending review because of potential adverse effects in infants. No specific treatment is available for the other enteric viruses.

Enteric viral infections are very common in childhood. Most children are infected with rotavirus during the first 2 yr of life. The incidence of enteroviruses and the viral enteric viruses ranges from 10% to 40% in children and is largely dependent on age. On average, half or more of the infections are asymptomatic. The incidence of hepatitis A virus is much lower than the enteric diarrheal viruses. There is no current evidence for hepatitis E virus (HEV) acquisition in children in the U.S.

Enteric viral diseases have a major impact on direct and indirect health care costs (i.e., lost wages) and amount to several billion dollars a year in the U.S. Total direct and indirect costs for nonhospitalized cases may run from $88/case for Norwalk virus to $1,193/case for enterovirus aseptic meningitis. Direct costs of hospitalization ran from $887/case for Norwalk virus to $86,899/case for hepatitis A. These costs are based on 1997–1999 data.

Generally, attack rates during drinking water outbreaks are greater for children than adults. The exception appears to be hepatitis E virus where young adults are more affected. However, pregnant women suffer a high mortality, resulting in concurrent fetal death. Also, secondary attack rates are much higher among children, probably because of fewer sanitary habits among this age group. Overall, waterborne outbreaks of viral disease have a greater impact among children than adults.

To better quantify the impact on children, the literature hould be further reviewed for case studies of waterborne outbreaks where data are available on the resulting illness by age group. The EPA and/or Centers for Disease Control should attempt to collect these data as future outbreaks are documented.

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