Noroviruses, Sapoviruses, and Astroviruses

20

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1 Introduction

Acute gastroenteritis (AGE) is among the most common diseases of humankind affecting people of all ages and particularly those at the extremes of life: children and the elderly. In developing countries, AGE remains one of the most important causes of death in children [1] and has been associated with a cycle of malnutrition and problems of impaired neurocognitive development [2]. In developed countries, the disease is an important cause of doctor visits and hospitalization of children, and a less frequent but persistent problem for adults and the elderly, all at appreciable medical cost [3, 4]. Prior to 1970, an etiology could be specified for fewer than 15 % of episodes of AGE, but since that time, more than 50 different infectious agents and toxins have been identified to cause the disease. This wealth of new information has challenged investigators and public health professionals to understand the relative importance of each agent, assess its contribution to human health, and consider prospects for prevention and control. Control has focused on understanding routes of transmission of each pathogen and determining whether public health interventions could interrupt their spread or investigating whether natural immunity to repeat infection might provide an opportunity to consider prevention with vaccines. Many of the infectious agents of AGE have been discovered in epidemics where a common illness has led to the identification of a single point source of infection. However, patients with these infections also present individually as "sporadic cases" in clinics and hospitals, where despite careful questioning, their illnesses cannot be linked to an outbreak or to other common cases or exposures.

Noroviruses and sapoviruses belong to two separate genera of the family *Caliciviridae* [5]. These single-stranded RNA nonenveloped viruses are highly infectious agents transmitted through a variety of routes including person-to-person; contact with fecally contaminated food, water, or environmental surfaces; or possibly via airborne droplets. In the United States, noroviruses are now recognized to be the most common cause of outbreaks of AGE, the most common cause of sporadic AGE across all ages, and the most common cause of foodborne disease [6]. They are also an important cause of healthcare-associated infections in both long-term and acute care settings. In addition to accounting for the high burden of AGE, noroviruses are often detected in people without the occurrence of symptoms, particularly among people in resource-poor settings [7]. Immunity is complex and incompletely understood but generally regarded to be short-lived [8]. The sapoviruses, which initially were thought to cause AGE in children, are now recognized to cause outbreaks in people of all age groups including the elderly [9]. Astroviruses are non-enveloped, single-stranded RNA viruses in the family *Astroviridae*. Although astroviruses have been detected in all age groups, most infections are in children <2 years of age and tend to be relatively mild, rarely requiring hospitalization [10].

Over the past two decades, this new appreciation of the major burden of norovirus and sapovirus AGE has been brought about by laboratory advances in the molecular detection of these viruses and their genetic characterization. In the 1990s, the prototype Norwalk virus and its close relative, Southampton virus, were cloned and sequenced [11, 12],

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paving the way for the development of new molecular diagnostic tests based upon RT-PCR detection and sequencing of virus directly from fecal specimens [13–15]. Furthermore, expression of the capsid proteins meant that serologic assays could be performed with antigens that could be replenished in the laboratory [16] rather than relying on immunoassays that required fecal specimens for antigen and paired sera collected from human volunteers. Genetic factors associated with resistance to infections and acquired immunity both play a role in susceptibility to infection and disease. With this in mind, and because of the great difficulty in controlling most outbreaks through routine public health interventions, vaccines for norovirus are currently a priority for development.

Unfortunately, there are currently few specific interventions to prevent the spread of these viruses. Management of outbreaks is based on identifying, where possible, the means of spread, be it from person to person or from fecally contaminated food and water, and then intervening with control measures to interrupt that spread. Treatment is supportive and based on oral rehydration solution (ORS) or intravenous fluid replacement in cases of severe dehydration. Recent advances have led not only to major changes in our recognition of the importance of these viruses in human health but also novel approaches to their control through public health measures and the potential future use of vaccines.

2 Historical Background

The history of noroviruses and our understanding of the viruses that cause AGE track directly with the development of modern diagnostic methods to detect and characterize these viruses. Each advance in diagnostics has furthered our understanding of the epidemiology of the virus and expanded our appreciation of the role that these viruses play in human health. Consequently, over the past 40 years, noroviruses have emerged from being an obscure and rarely detected viral cause of outbreaks of AGE to become the most common cause of these outbreaks and of sporadic episodes of AGE in developed countries and a common pathogen in developing countries. In the 1940s, investigators suspected viruses to be possible causes of AGE because volunteers administered bacteria-free stool filtrates from patients suffering from AGE developed the disease [17]. Unfortunately, they were unable to isolate a pathogen. Most episodes and outbreaks of AGE, one of the most common illnesses of humans, went without an etiologic diagnosis and were defined with descriptive terms – diarrhea of weaning, travelers' diarrhea, winter vomiting disease, or idiopathic diarrhea. The first major breakthrough occurred in 1972 when Kapikian discovered a virus-like particle by immune electron microscopy (IEM) in the fecal specimen of victims linked to an outbreak of AGE at a school in Norwalk, Ohio, which had been investigated by CDC epidemiologists 4 years earlier [18]. The discovery of the Norwalk virus opened a golden era for electron microscopists to discover new viral pathogens in fecal specimens and use IEM to characterize the patient's immune response in acute and convalescent sera. A stream of other enteric viruses were then discovered – rotaviruses, astroviruses, "classic caliciviruses," as well as antigenically distinct variants of Norwalk virus, named according to the location where first identified (e.g., the Hawaii agent, the Snow Mountain agent, the Sapporo virus, the Taunton agent) [19–21]. Other viruses were seen in fecal specimens in the absence of a corresponding serologic response, a *sine qua non* of a true infection – parvoviruses, reoviruses, enteroviruses, and picobirnaviruses. Thus began the journey to discover the relevance of each of these viruses to cause disease and to public health. Viruses found in stool were first classified by their morphologic appearance by EM. Noroviruses were first classified simply as "small round-structured viruses" (SRSVs) to distinguish them from small round viruses (SRVs) without a distinct surface structure such as parvovirus and enterovirus. Differentiating between variant SRSVs required IEM using human paired sera specimens, but few research groups had the human reagents or skills needed to distinguish one SRSV from another.

Following their discovery, the Norwalk-like viruses began to be linked to the majority of outbreaks of AGE where another bacterial or parasitic pathogen could not be found [22]. The frequency of detection depended initially upon the skill of the microscopist. Because no animal model for norovirus infection was available, a long series of human volunteer challenge studies was conducted to assess immunity to infection [23, 24] and cross-protection between strains [25] and to develop novel immunoassays using fecal specimens and paired acute and convalescent sera from human volunteers. Virus was often not seen in fecal specimens from patients directly implicated in outbreaks. Therefore, serologic assays, both radioimmunoassay (RIA) and an enzyme immunoassay (EIA), were developed using human reagents (stool for antigen and paired sera) to monitor the immune responses of those involved in outbreaks [26, 27]. At CDC, for more than a decade, these assays became the diagnostic tests of choice [28]. The application of serology greatly increased the number of outbreaks of AGE that were attributed to the Norwalk virus. Of note, however, was that some people with documented exposure to the contaminated food or water did not become ill or seroconvert, suggesting a role for innate or acquired immunity. Also, some people involved in outbreaks of norovirus did not seroconvert to stool filtrates from Norwalk volunteers; however, they did respond to human reagents developed from volunteers challenged with an inoculum from patients infected with antigenically distinct Norwalk-like viruses such as the Snow Mountain agent

or the Hawaii agent suggesting serotype differences in susceptibility and immunity to disease [25]. A laboratory diagnosis of norovirus was rarely sought in patients routinely hospitalized for diarrhea because no simple diagnostic test was commercially available, and few had a history of exposure in an outbreak. Noroviruses remained almost exclusively agents of outbreaks of AGE and were not associated with sporadic illness leading to hospitalization [28].

All this changed in the early 1990s when the Norwalk and Southampton viruses were cloned and sequenced [11, 12, 29], an advance that revolutionized the field. These discoveries led immediately to the development of molecular assays that were more sensitive, specific, and reproducible than electron microscopy and that used chemical reagents that could be produced or purchased rather than biological reagents obtained from human volunteers. Molecular characterization immediately placed the Norwalk virus and the Norwalk "family of viruses," i.e., the other SRSVs, into a separate genus, *Norovirus*, in the family *Caliciviridae*. The Sapporo virus and related viruses with typical calicivirus morphology were grouped in their own genus *Sapovirus* [5]. Knowledge of the sequence meant that individual strains could be identified and traced within and between outbreaks allowing for the identification of common source exposures [30, 31]. Furthermore, strains previously characterized simply by the location where they had been found, or studied for antigenic differences by IEM, could now be sequenced and classified into genogroups and genotypic clusters [32]. When reverse transcription polymerase chain reaction (RT-PCR) was applied to examine fecal specimens from a large collection of outbreaks of AGE in the United States, Europe, Australia, and Japan, which had gone without an etiologic diagnosis, more than 80 % could be attributed to a norovirus, making it the most common cause of outbreaks of AGE [28, 33, 34]. Knowledge of sequence allowed new studies of the molecular epidemiology of the virus and facilitated tracing transmission of a single strain to a common source, such as fecally contaminated shellfish or foods prepared by a single sick food handler [30, 35, 36]. Similarly, outbreaks caused by foods irrigated with sewage (e.g., raspberries transported in a worldwide distribution chain) had a mixture of viruses representing multiple sources of contamination [37, 38].

The cloning of a number of HuCVs cleared the way for their single capsid protein to be expressed in different vectors [11, 12, 29]. When the Norwalk virus capsid gene was introduced into a baculovirus expression system, it formed viruslike particles (VLPs) that were indistinguishable by EM from natural virus [11]. VLPs could be used as antigens in immunoassays to monitor the immune response to specific infections, to differentiate between strains of virus, and to consider as potential vaccines [39]. They also provided targets to study the structure of related viruses and consider novel targets for drugs. Noroviruses can genetically be grouped into at least six different genogroups of which viruses from GI and GII viruses being the most common [6, 40]. GII viruses have caused the majority of all norovirus outbreaks over the past decade worldwide [41].

Traditionally, public health laboratories studied noroviruses almost exclusively in the context of outbreaks reported to them. However, AGE is responsible for both mild disease leading to doctor and clinic visits and severe disease leading to hospitalizations and some deaths [3, 42, 43]. That few of these patients are directly linked to an outbreak suggested a role for noroviruses as a cause of sporadic AGE. A national cohort study in England was the first to widely apply RT-PCR for noroviruses to study patients with AGE in the community [44–46]. Norovirus was identified as the most common cause of disease among adults and second only to rotavirus as the causative agent among children. A study of the etiology of AGE in adults hospitalized or treated in the emergency room in three sites in the United States yielded similar results: noroviruses were the most common cause of diarrhea in US adults [47]. With the advent and widespread use of rotavirus vaccine in the United States, norovirus has become the most common cause of medically attended gastroenteritis [48]. Application of molecular diagnostics have now demonstrated noroviruses and sapoviruses to be common in children and adults as well and a major cause of AGE in low- and middle-income countries [49].

In a parallel trajectory, astroviruses were first discovered in 1975 through electron microscopic examination of stools from an outbreak of pediatric diarrhea [50, 51]. The modern standard for laboratory diagnosis is real-time RT-PCR [52, 53]. In the pediatric population, astroviruses are consistently associated with acute diarrhea, though at substantially lower levels than the noroviruses [54].

3 Epidemiology

Noroviruses are now recognized to be one of the most common pathogens causing AGE in a wide range of settings, ages, and risk groups. In the United States, they are the most common cause of AGE in the community, the most common cause of outbreaks of AGE, and the most common cause of foodborne disease outbreaks [3, 55, 56]. Following the introduction of routine rotavirus immunization in the U.S., noroviruses are now the most common cause of pediatric gastroenteritis requiring medical care [48]. They also cause the great majority of outbreaks of AGE in institutional settings such as nursing homes, hospitals, and chronic care facilities in industrialized countries [57]. Sapoviruses are a less common cause of AGE in all age groups and in a wide variety of settings as well. For norovirus, sapovirus, and astrovirus, our more complete appreciation of the burden of disease has developed over the last decade, largely due to the availability of more sensitive and specific diagnostic tests.

3.1 Methods for Epidemiological Analysis

3.1.1 Epidemics and Outbreak Investigation

Data from the United States and Europe have demonstrated that norovirus is responsible for approximately 50 % of all reported AGE outbreaks (range 36–59 %) [58]. These generally occur throughout the year, although there is a seasonal pattern of increased activity during the winter months (Fig. 20.1) [58]. Outbreaks occur in various settings; they are propagated by nosocomial transmission in hospitals and nursing homes, foodborne spread in restaurants and aboard cruise ships, and waterborne outbreaks, all affecting people of all ages. Although initial reviews of norovirus outbreaks in the United States implicated contaminated food as the main vehicle of infection [59], newer reports suggest that the majority involve person-to-person transmission [55, 60–62]. Moreover, given the high infectivity and environmental stability of noroviruses, transmission during outbreaks may involve multiple routes [63], and contaminated fomites, surfaces, and droplets may also act to perpetuate outbreaks [64–66].

HuCV infections often come to the attention of public health authorities in the form of outbreaks, and these events present an opportunity to learn about transmission of the virus. In the United States, thousands of outbreaks have been identified and investigated over the past four decades, and a few have provided critical clues to understand transmission. The original Norwalk virus outbreak occurred in an elementary school and provided important initial observations. It was clear that the virus was highly infectious with primary and secondary attack rates of 50 and 30 %, respectively [18, 67]. The incubation period was determined to be short at <48 h, and occurrence in both students and teachers implied a lack of protective immunity with age. Other outbreak investigations from the 1980s demonstrated that norovirus could be transmitted by drinking water [10], as well as recreational water use [68]. Transmission by contaminated oysters was demonstrated to be an important route of transmission, as were a range of other foodborne exposures (e.g., to leafy greens, raspberries, and foods prepared by ill food handlers) [69–72]. The role of norovirus in healthcare facilities, including nursing homes, also becomes apparent from these early investigations [73]. Outbreak investigation led to the observation that norovirus can also be transmitted directly by apparent airborne or droplet spread [74–77], not only directly from person to person. More recent investigations have provided compelling evidence of environmentally mediated transmission [78, 79] and even by unusual fomites such as reusable shopping bags [80, 81]. An other outbreak started from a contaminated food product, subsequently spread by person to person among players on opposing football teams, and went on to attack the roommates of the players several days later; it demonstrated the potential for multiple transmission routes in a single outbreak [82]. While astroviruses primarily cause sporadic disease, outbreaks have been reported in a range of settings and may be a fairly common cause of nosocomial gastroenteritis in children's hospitals [83].

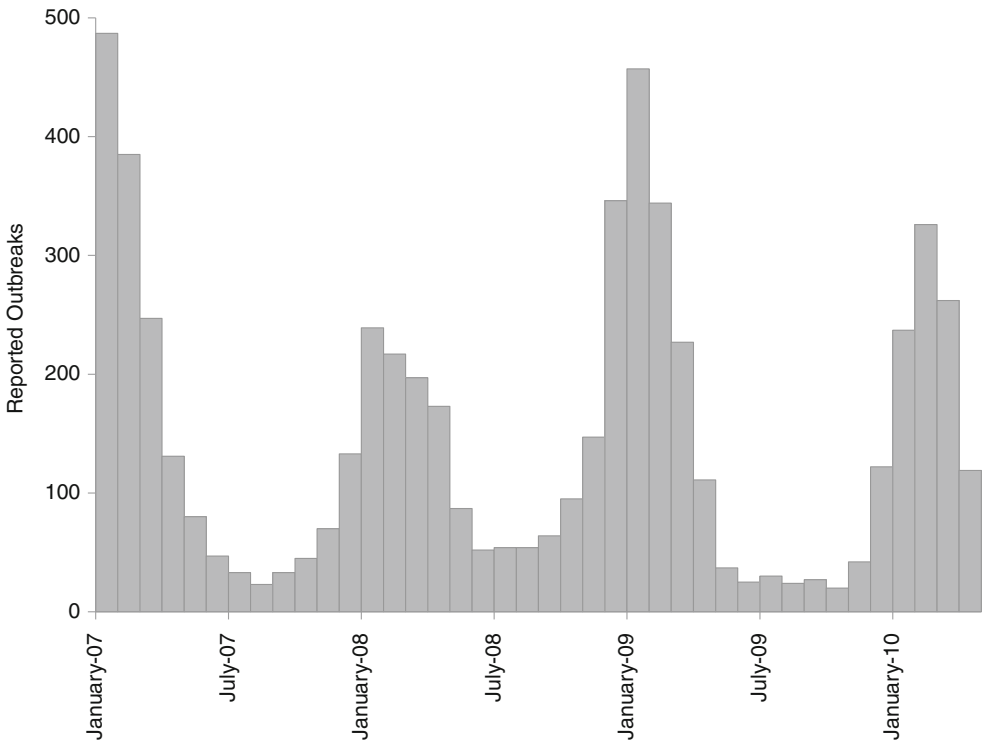

Fig. 20.1 Suspected and confirmed norovirus outbreaks reported by 30 US states, January 2007–April 2010 (Adapted from Yen et al. [55])

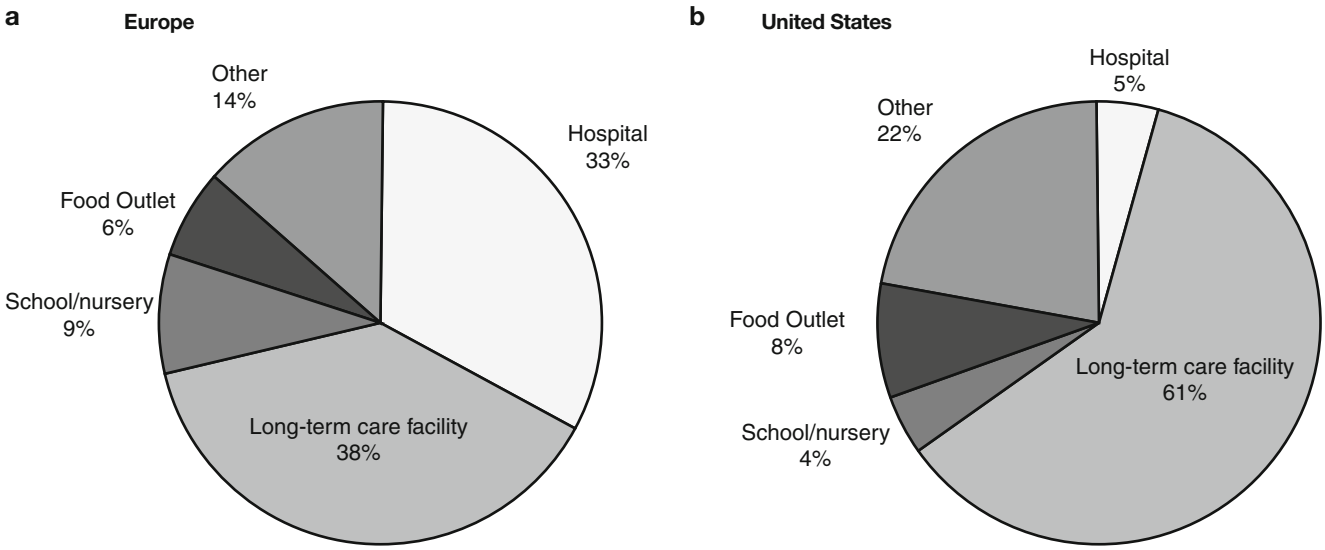

Fig. 20.2 Setting of reported outbreaks of norovirus AGE in (**a**) Europe, 2004 [33], and the (**b**) United States, 2006–2008 [89]. In both settings, the majority of outbreaks occur in healthcare settings; in Europe many more outbreaks are reported from acute care hospitals

Periodically, the number of norovirus outbreaks has increased at the same time that new genogroup II genotype 4 (GII.4) strains have emerged, likely because these new variants escape immunity in the population [84, 85]. These emergent GII.4 strains rapidly replace circulating strains and can sometimes cause unusually severe seasons, as occurred in 2002/2003 and 2006/2007 [41, 86, 87]. GII.4 variants predominate across all settings, though the role of GI and other GII genotypes appears to be greater in settings that involve foodborne or waterborne transmission compared to the GII.4 viruses [88].

A major difference in the reported epidemiology of norovirus between the United States and most other high-income countries lies in the frequency of outbreaks in acute care (hospital) settings. In Europe approximately one-third of reported outbreaks occur in hospitals compared with 4 % in the United States (Fig. 20.2) [90]. It is not known whether this difference in reported outbreaks represents a real difference in the epidemiology of outbreaks, an underreporting of hospital outbreaks in the United States, or differences in infection control practices in hospitals.

Recently, more sophisticated statistical and modeling studies have used data from traditional outbreak investigations to examine issues of virus transmission. Transmission models have been fit to demonstrate the important role that vomiting plays in the spread of norovirus [91]. By using methods that reconstruct the most likely transmission trees [92], Sukhrie and colleagues found that in healthcare settings, people with symptoms are far more likely to transmit infection than those who remain asymptomatic, and patients are more important to virus transmission than staff [93, 94].

Outbreaks of sapovirus-associated AGE have been reported in settings similar to those of noroviruses – schools [95], child care facilities, [96] hospitals [97], long-term care facilities, and occasional foodborne outbreaks [98, 99]. The broad age range of individuals affected in these outbreaks demonstrates that sapovirus infection is not restricted to young children as was previously thought. Although the molecular epidemiology of sapovirus is less well studied than norovirus, strains belonging to four different sapovirus genogroups (GI, GII, GIV, GV) have been observed to infect humans. Two of these viruses, GI.2 and GIV, have been most commonly associated with outbreaks in Europe, Asia, and North America primarily affecting older adults [9, 100, 101].

Similar to the norovirus and sapovirus, astrovirus outbreaks may occur in a range of settings including long-term and acute care facilities, schools, and child care centers [102]. However, such outbreaks appear to be much less common than those caused by norovirus.

Few studies have quantified the direct healthcare or societal costs due to the noroviruses, but given how common these infections are, the direct healthcare costs and the indirect costs to society are likely to be substantial. Most studies to date have only quantified the cost of outbreaks, as opposed to endemic disease, for which the cost must be much greater. For example, an outbreak in a single 946-bed US hospital cost an estimated $650,000 [103]. During the 2002–2003 season, the cost to the English National Health Service of nosocomial AGE outbreaks was estimated at $184 million [57]. Norovirus foodborne disease in the United States costs an estimated $2 billion annually [4].

3.2 Surveillance

There are some major limitations to what can be learned from individual outbreak investigations since published reports likely represent a biased sample of events in terms of disease severity [104, 105] and provide limited insight into the efficacy of control measures and the full burden of disease [106]. In most countries, AGE from norovirus is not a notifiable cause of disease; surveillance has focused on the recognition of outbreaks, many of which would not be reported in the peer-reviewed literature. What constitutes an outbreak can be hard to define; as a result, the data collected by any given surveillance system may in part reflect the definitions used, the size of the outbreaks reported, and the focus of the surveillance effort. For example, in the United States, outbreaks linked to food historically were prioritized for reporting, whereas in England and Wales, surveillance targeted outbreaks occurring in National Health Service hospitals, thereby emphasizing nosocomial spread [107]. When more broad-based assessments have been conducted, the profile of outbreaks in the United States has been consistent with those from other industrialized countries where a majority occur in healthcare settings and are spread by person-to-person transmission [55]. In response to this surveillance gap, CDC has recently developed the National Outbreak Reporting System (NORS) as an integrated national surveillance system for all enteric disease outbreaks [108]. Launched in February 2009, NORS now provides the framework through which all outbreaks of enteric disease, regardless of transmission mode, may be reported from state and local health departments to the CDC. CDC also coordinates a norovirus outbreak surveillance network known as CaliciNet, also launched in 2009 [109]. State and local public health and food regulatory agency laboratories upload sequences of norovirus outbreaks to allow rapid comparison to potentially link outbreaks with a common (e.g., food) source as well as to identify emerging norovirus strains (e.g., GII.4 Sydney in late 2012).

Large reviews of surveillance datasets have been published from a number of countries including England and Wales, [61, 110] some European countries (as part of the Foodborne Viruses in Europe group) [33, 90], Australia, and New Zealand [111, 112]. These broad-based surveillance systems have consistently demonstrated that the majority of reported outbreaks occur in healthcare settings (including nursing homes or hospitals) and are predominantly spread from person to person while at the same time identifying an important role for food in disease transmission. Systems dedicated to the surveillance of outbreaks in healthcare settings have shown a large burden of disease, in both acute and long-term care settings, as well as a high degree of severe disease and economic burden [112, 113]. Regional or state-wide surveillance reports have also been useful for understanding patterns of disease when national surveillance systems are incomplete or do not exist [114, 115].

3.2.1 Etiologic Studies and Endemic Disease

Globally, norovirus is estimated to account for 12 % (95 % CI 9–15 %) of community- or clinic-based AGE cases and 11 % (95 % CI 8–14 %) of emergency department- or hospital-based cases [49]. These proportions are similar in developing and developed country populations [49]. In the United States, norovirus causes an estimated 21 million cases of AGE [3], 1.7 million outpatient visits [116], 400,000 emergency care visits, 70,000 hospitalizations [42], and 800 deaths annually across all age groups (Fig. 20.3) [43]. The burden of hospitalizations and death surges by approximately 50 % in those years when novel GII.4 variant strains emerge [86, 87, 117]. Although symptomatic norovirus infections are usually mild and self-limiting in otherwise healthy adults, they may be fatal among the elderly [118] and immunocompromised persons [119]. Excess mortality associated with norovirus has been documented in a number of countries as well [120, 121].

Etiologic studies of norovirus can be grouped into two categories: (1) community-based cohort/case–control studies or (2) healthcare facility-based studies, with the former being much less common. Community-based cohort studies are expensive and logistically complicated to conduct, but when conducted, have established norovirus to be the most common cause of AGE in the community [46, 54, 122]. In England and the Netherlands, these studies have estimated the incidence of norovirus in the general population to be 4.1 and 4.6 cases per 100 person-years [46, 54, 122], with regional studies providing generally consistent results [116, 123]. This means that with a life expectancy of ~80 years, a person will experience an average of three to five episodes in their lifetime. Incidence is approximately five times higher in children under the age of 5 years [46]. The incidence of norovirus at the general practitioner (primary care) level has been estimated at 0.49 per 100 person-years in England and 0.62 in northwest Germany, suggesting about one in ten who are ill with AGE seeks medical care [46, 54, 123].

Community-based studies of the incidence of sapoviruses have been less common. In England and Wales, the incidence of sapovirus-associated illness in the community was estimated at 2.6 cases per 100 person-years [54]. Estimates from a study of a Healthcare Management Organization population in the state of Georgia yielded similar results, 9 and 1 cases per 1,000 population, respectively [116]. A prospective study of Finnish children <2 years of age reported sapoviruses in 9 % of sporadic gastrointestinal illness compared with rotavirus in 29 % and norovirus in 20 % [124].

As noted earlier, astroviruses are also comparatively less common than norovirus. In the England and Wales study, incidence across the age range (at 0.5 per 100 person-years)

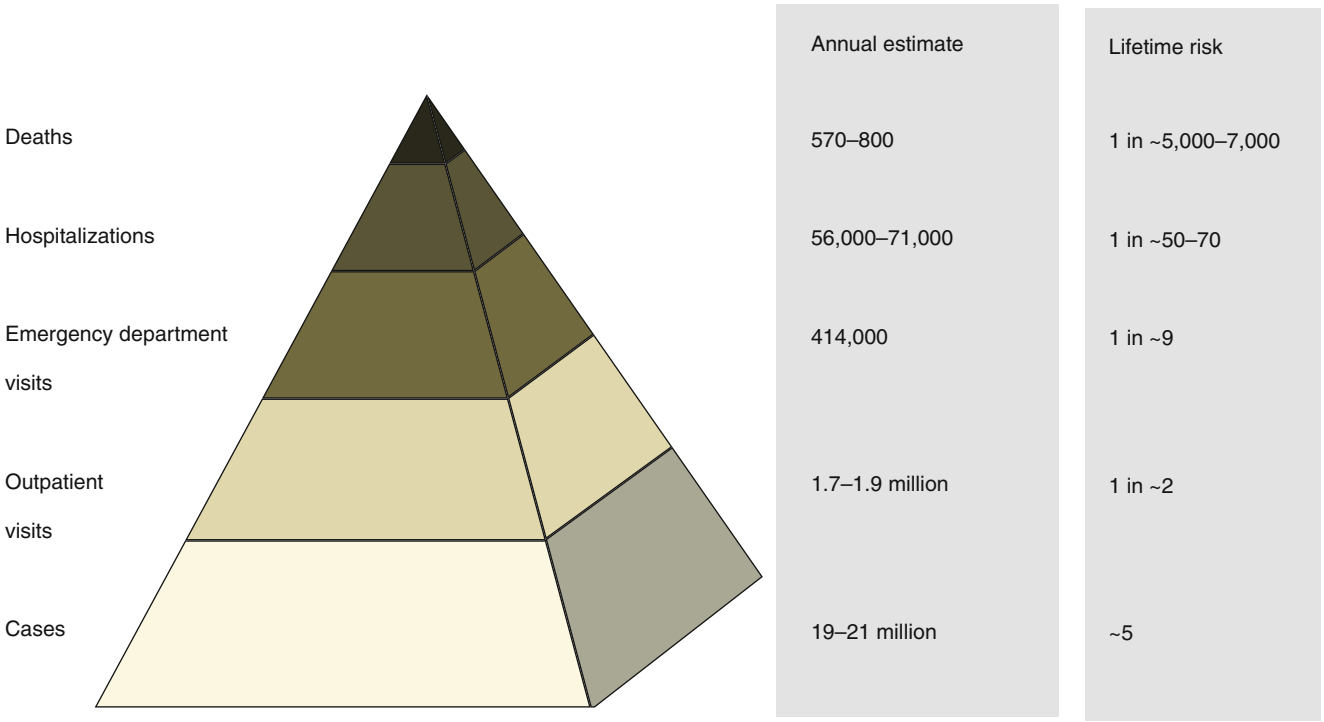

Fig. 20.3 Annual cases, outpatient visits, emergency room consultations, hospitalizations, and deaths from norovirus annually in the United States. Lifetime risk estimate based on a life expectancy of 80 years and US population of 300 million [125]

was about one-tenth and one-fifth of the incidence of norovirus and sapovirus, respectively, in 2008/2009, while in a recent study in the United States, the classical human astroviruses caused about one-fourth of the norovirus cases [54, 126]. Astroviruses are usually detected in <10 % of young children treated for gastroenteritis in outpatient clinics or in hospitals [127, 128].

The only nationally comprehensive estimate of the burden of disease due to human caliciviruses and the associated disability-adjusted life years (DALYs) exists for the Netherlands. This assessment included the incidence of cases in the community that did not seek healthcare, those visiting a general practitioner, hospitalizations and deaths that were derived from cohort studies, and surveillance data and literature. In total, these yielded an estimate of 1,622/100,000 (95 % CI 966–2,650) disability-adjusted life years in a population of 16.5 million [129]. This burden is similar to that of disease due to *Salmonella spp*. in the same population. While endemic disease-related costs have not been comprehensively assessed, norovirus-associated hospitalizations specifically have been estimated at nearly $500 million annually in the United States [42].

3.2.2 Severe Disease Outcomes

Although norovirus AGE is typically a mild self-resolving illness in healthy adults, it can lead to severe dehydration, hospitalization, and, in rare cases, death. These severe outcomes are more common in vulnerable populations such as young children and the elderly residing in long-term care facilities (LTCFs) or hospitals [105, 107]. In nearly all instances of norovirus-associated death reported in the literature, the decedents had other serious underlying heath conditions, such as immunosuppression [130–133]. Data from passive surveillance systems and outbreak investigations provide estimates of norovirus case hospitalization in the range of 0.1–5 hospitalizations per 1,000 cases [61, 107, 110, 112, 134]. A large systematic review of published outbreak reports estimated norovirus-associated hospitalization and mortality rates at 7 and 0.7 per 1,000 cases, respectively [105]. However, severity may be overestimated when based on published outbreak reports since the larger and more severe outbreaks are more likely to be investigated and reported.

It has been challenging to isolate the risk factors leading to hospitalization and death because the mode of transmission, population affected, and genotype causing the outbreaks are highly correlated. Specifically, GII.4 outbreaks are predominant in healthcare facility outbreaks, which affect vulnerable individuals (i.e., the elderly) and are typically spread from person to person [135, 136]. A review of over 800 outbreaks has highlighted that hospitalizations and deaths were much more likely to occur in healthcare outbreaks and, somewhat surprisingly, in GII.4 virus-associated outbreaks, independent of those factors that could be analyzed. This suggests that in addition to increased vulnerability of certain population groups, there is increased severity

associated with GII.4 viruses. GII strains are shed at higher levels [137], may be more likely to induce vomiting [138], and cause more severe disease in children; [139] this genogroup thus appears to demonstrate a consistent pattern of higher virulence. The relatively high hospitalization rates in long-term care facilities and mortality in all healthcare settings underscore the vulnerability of populations affected by outbreaks in these settings.

3.2.3 Risk Factors

Consistently, the strongest risk factors for community disease are proxies for contact with an infectious person. For both young children and older children/adults, reporting a symptomatic household member, especially a child, is a strong predictor of disease [122, 123, 140, 141]. It appears that young children frequently bring infection into the household, and older children/adults acquire many of their infections within the household [141, 142]. Foreign travel is also a risk factor; [141, 143] the increased risk may be attributable to changes in behavior while traveling or exposure to a different spectrum of norovirus strains. Although outbreak investigations frequently attribute norovirus AGE to contamination of food during preparation by a range of mechanisms and in a range of settings, food-related risk factors have not shown consistent associations with disease in community-based studies [122, 141]. In fact, consumption of raw fruits and vegetables, often considered potential vehicles for transmission, is generally associated with a protective effect [141]. Other potential factors such as recreational water exposure and animal contact have also been associated with reduced risk [122, 123, 141]. Taken together, the unexpected relationships observed in these studies suggest that these putative risk factors are correlated with other lifestyle factors that may actually be protective against norovirus or that frequent exposure results in immunity. The foods consistently associated with disease are oyster and other shellfish harvested from areas where the seabeds are contaminated with sewage [141, 144]. However, in most populations, consumption of these products is not common, and this exposure likely accounts for only a small fraction of disease.

4 Mechanisms and Routes of Transmission

Norovirus is extremely contagious, with an estimated infectious dose as low as 18 viral particles [145]. In contrast, approximately five billion infectious doses are contained in each gram of feces during peak shedding. Humans are the only known reservoir for human norovirus infections. Transmission occurs via fecal-oral and vomit-oral pathways by four general routes: direct person-to-person, foodborne, waterborne, or through environmental fomites (Fig. 20.4). Because humans are the only known reservoir for human norovirus, sapoviruses, or astroviruses, in a sense, all transmission is ultimately person to person. From that perspective, foodborne, waterborne, and environmental transmission are "special cases" of person-to-person spread.

4.1 Direct Person-to-Person Spread

Direct person-to-person transmission is believed to be the primary mode of spread in most outbreaks [55, 61] and in sporadic disease [141, 146]. The proportion of outbreak spread primarily by person-to-person transmission is highest in settings with close contacts. Direct person-to-person transmission is reported as the primary route in >90 % of norovirus outbreaks in hospitals, long-term care facilities, and schools [61]. GII and, specifically, GII.4 viruses are more commonly associated with person-to-person transmission [62] or found in settings where person-to-person transmission is common [135, 136]. Furthermore, there is a strong wintertime seasonality of person-to-person outbreaks [55, 147–149], a pattern not clearly seen for norovirus spread by other routes of transmission [61]. However, when new strains of GII.4 emerge by escaping population immunity, aberrant seasonal patterns may occur, [41, 87, 150, 151] highlighting the importance of host factors (i.e., population immunity) in transmission [152]. The most consistently identified risk factors for transmission are all related to the exposure of a symptomatic contact (see Sect. 3.2.3). Although infection in asymptomatic individuals is common, the importance of these shedders in person-to-person spread is unclear. However, based on current evidence, it appears that disease symptoms, especially vomiting, are fundamental to disease transmission [91, 93, 94, 153].

4.2 Foodborne Disease

Norovirus is the most common cause of foodborne disease outbreaks in the United States [154, 155], accounting for >50 % of foodborne disease outbreaks with known causes reported to CDC during 2006–2008 [154, 155]. Foodborne transmission most frequently occurs by contamination from infected food handlers during preparation and service. Only a small dose of virus is needed to cause infection, and thus infected food handlers can contaminate large quantities of product, especially when they put their hands into large-volume liquids (e.g., salad dressing), which allow for mixing. In one example, an estimated 3,000 cases of AGE were traced to icing prepared by an ill baker and put on a variety of bakery products [71]. Unlike with direct person-to-person transmission, the role of both pre- and post-symptomatic shedding has been clearly linked with onward transmission

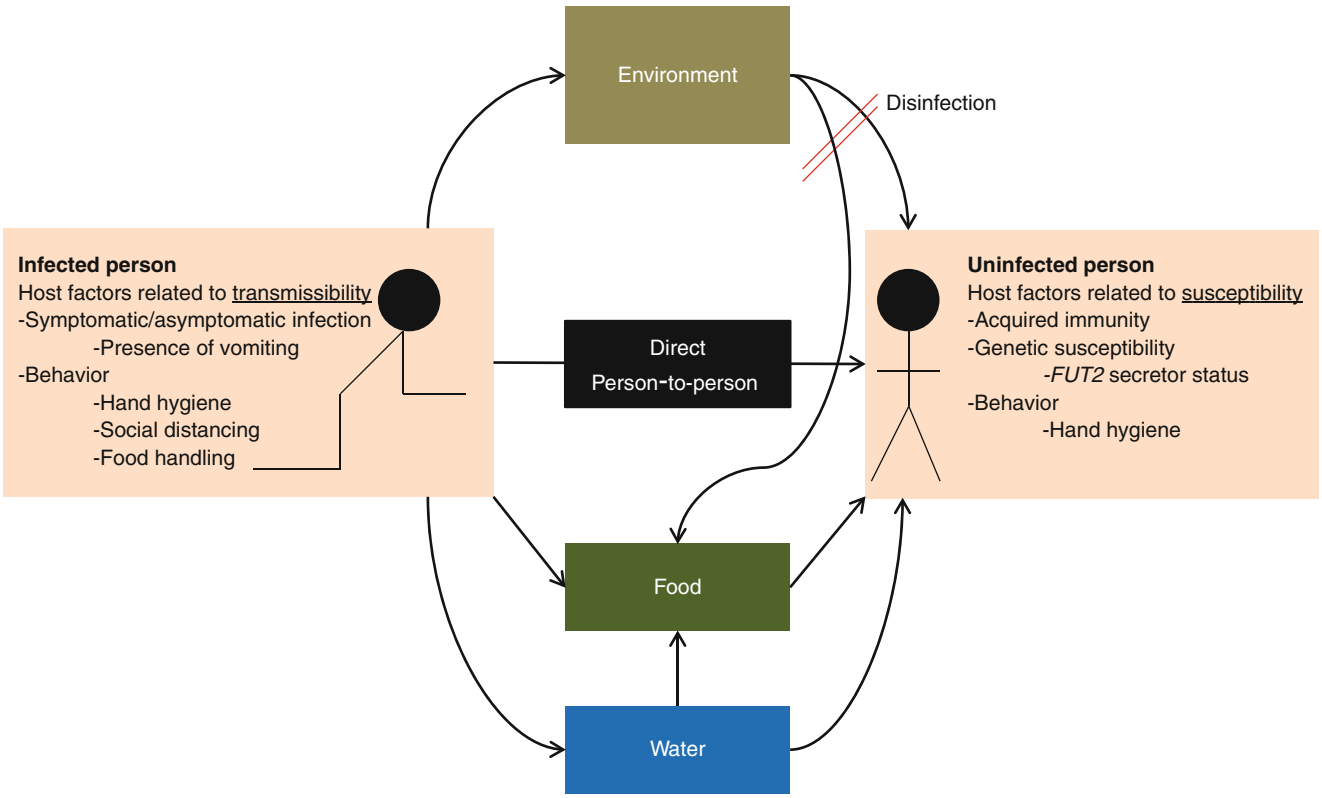

Fig. 20.4 Routes of transmission of norovirus from infected to uninfected people (Reproduced with permission from Current Opinion in Virology [7]). Norovirus transmission can occur via a range of transmission routes. Characteristics and behaviors of the infected host and potential susceptible individuals may mitigate the risk of transmission. This simple schematic is not meant to depict all the intricacies of each pathway but rather to highlight the interaction of the various routes and to illustrate that all pathways require shedding of virus from infectious hosts. Different control measures may be targeted at each *arrow*; here, the role of environmental disinfection is highlighted. Certain practices (such as hand hygiene) may reduce transmission through all pathways, while targeted interventions (such as exclusion of ill food handlers from work) may reduce transmission through specific pathways

[156–158]. Foodborne astrovirus outbreaks have been reported, [159] though this route of transmission, relative to person-to-person spread, is not well defined.

Food can become contaminated with norovirus at any point along the farm-to-fork continuum, including production, processing, and preparation. Thus, a variety of products have been implicated in outbreak investigations, especially those foods irrigated with or grown in fecally contaminated water and eaten raw, such as leafy vegetables, fruits, raspberries, and shellfish [31, 108, 154, 160–163]. Because gross sewage contamination will contain a collection of viruses circulating in the community, multiple norovirus genotypes are often detected in such outbreaks.

4.3 Environmental Transmission

Many factors may facilitate environmental transmission of norovirus. They include a large human reservoir, [3, 46, 116, 122] high levels of shedding [164, 165] (which can be asymptomatic and prolonged [164, 166, 167]), small infectious dose, [145] and widespread contamination by vomitus [65, 77, 91, 164, 165, 167–169]. The viruses are relatively stable in the environment, [149, 167, 170] resistant to disinfection, [171, 172] and can contaminate a range of fomites [65, 165, 168, 173, 174]. The most convincing evidence of environmental transmission comes from outbreaks where groups in a common setting with no known direct contact have been sequentially affected [175]. Such transmission has occurred aboard airplanes and cruise ships, [78] [63] in a concert hall, [176] and from the use of a reusable grocery bag [80]. In all these examples, the environment or fomites likely became contaminated by airborne transmission following an episode of vomiting. Widespread contamination of environments during outbreaks has been documented, particularly in hospital settings where virus has been detected on surfaces of many different objects – switches, televisions, cellular phones, public phones, water taps, toilet light switches, microwave ovens, keyboards, bed frames, and chairs [165, 168]. The role of this contamination is nevertheless

unclear because noroviruses are hardy: outbreak strains have been detected on environmental surfaces during non-outbreak periods, and the converse has also been observed [173, 177]. Although the highest levels of contamination probably occur on surfaces directly contaminated by vomitus or feces, virus has been detected on mantle pieces and light fittings, located above 1.5 m in a hotel affected by an outbreak [65].

4.4 Waterborne Transmission

Sewage-contaminated water is also a recognized route of transmission [178–180]. Norwalk virus can remain infectious in groundwater for at least 2 months and can be detected for over 3 years [170, 181]. Drinking water or ice may become contaminated with norovirus and result in outbreaks in food service settings. The same contaminated water can cause disease directly through drinking and when used in food preparation [182]. Recreational and drinking water can become contaminated from septic tank leakage and sewage or from breakdowns in municipal treatment plants, resulting in large community outbreaks [183–185] [186]. However, outbreaks have even been reported from wells built in compliance with regulations when groundwater becomes contaminated by septic systems or percolation of sewage through unusual geologic formations [187]. For reasons that are not clear, most waterborne outbreaks are associated with GI noroviruses [88, 188]. However, in contrast to these epidemiological observations, some laboratory data suggest that GII viruses are more stable in water as well as on surfaces [181, 189]. Waterborne transmission of astrovirus has also been documented [190]. Because they often result from gross contamination, waterborne outbreaks are also more commonly associated with mixed infections with multiple noroviruses or even multiple pathogens [88].

5 Biological Characteristics

Noroviruses are a group of nonenveloped, single-stranded RNA viruses with an icosahedral symmetry classified into the genus *Norovirus* of the family *Caliciviridae*. Other genera within this virus family include *Sapovirus*, which also causes AGE (AGE) in humans, as well as *Lagovirus*, *Vesivirus*, and *Nebovirus*, which are not pathogenic for humans [5]. Upon approval by the calicivirus study group of International Committee on the Taxonomy of Viruses (ICTV), novel caliciviruses detected in rhesus monkeys and swine may be accepted as additional genera [191, 192]. By structural analysis, the Norwalk VLP capsid is formed with 180 capsid molecules organized into 90 dimers with a T =3 icosahedral symmetry (where T is triangulation number), [193] using two distinct dimer types to form the higher-order structure [194]. Noroviruses cannot be classified by serotypes, since it cannot be grown in cell culture and neutralized with antisera, but can be divided into at least five genogroups (G), designated GI–GV, based on amino acid identity in the major structural protein (VP1) [195]. Viruses from at least one additional genogroup have been recognized in dogs [40, 196]. The strains that infect humans are found in genogroups GI, GII, and GIV, whereas the strains infecting cows and mice are found in GIII and GV, respectively (Fig. 20.5a). Although interspecies transmission of noroviruses has not been documented, strains that infect pigs are found in GII [197], and a GIV norovirus was discovered recently as a cause of diarrhea in dogs [196], suggesting the potential for zoonotic transmission. On the basis of phylogenetic analysis of the complete VP1, noroviruses can be further classified into genotypes, with at least nine genotypes belonging to GI and 21 genotypes belonging to GII (Fig. 20.5a). At least since 2001, GII.4 viruses have caused the majority of viral AGE outbreaks worldwide [41, 198]. Recent studies have demonstrated that these viruses evolve over time through serial changes in the VP1 sequence, which allow evasion of immunity in the human population [117]. Sapoviruses are divided into at least seven different phylogenetic clusters, four (GI, GII, GIV, and GV) of which include viruses that infect humans, while GIII, GVI, and GVII have only been found in swine [199]. Detection of additional sapovirus genogroups in mink and recently in bats illustrates the enormous genetic variability and host range of viruses within the *Sapovirus* genus (Fig. 20.5b).

Astroviruses, first discovered in 1975 [200, 201], are nonenveloped, single-stranded RNA viruses in the family Astroviridae. Astroviruses are 28 nm in diameter with a smooth edge and may have a characteristic 5- or 6-pointed starlike appearance in the center (Greek, *astron* = star). Since then eight serotypes of human astrovirus (classical human astroviruses) have been identified and characterized. Serotype 1 is the most common, though multiple serotypes can co-circulate during the same season. Greater serotype diversity may be found in developing countries [202, 203]. In addition, viruses belonging to two other phylogenetic clades (MLB and VA) have been detected in human stools, some of which has been directly linked to AGE in children [204, 205].

6 Pathogenesis

The primary replication site for noro- and sapoviruses has not been established. It is likely that these viruses replicate in the upper intestinal tract because volunteers who develop

gastrointestinal illness following oral administration of virus have histopathologic lesions on biopsies from the jejunum [19, 206]. Pigs infected with porcine sapovirus demonstrate blunting and shortening of the villi of the proximal small intestine [207]. Interestingly, the same characteristic jejunal lesion has also been observed in volunteers who were fed Norwalk or Hawaii virus but did not become ill [208–210]. Increased mononuclear infiltrates in the lamina propria and villous blunting in intestinal biopsies of pediatric patients compared with uninfected controls have been reported [211]. Levels of small intestinal brush border enzymes (trehalase and alkaline phosphatase) are significantly decreased compared with baseline and convalescent-phase values [206]. It has been proposed that abnormal gastric motor function is responsible for the nausea and vomiting associated with noroviruses [208], but the precise mechanism responsible for illness is not known. Astrovirus infection appears to be restricted to villous enterocytes and the exposed epithelium. Histological damage and inflammation is generally mild [212], and the specific mechanism by which astrovirus causes diarrhea is not known [102, 213].

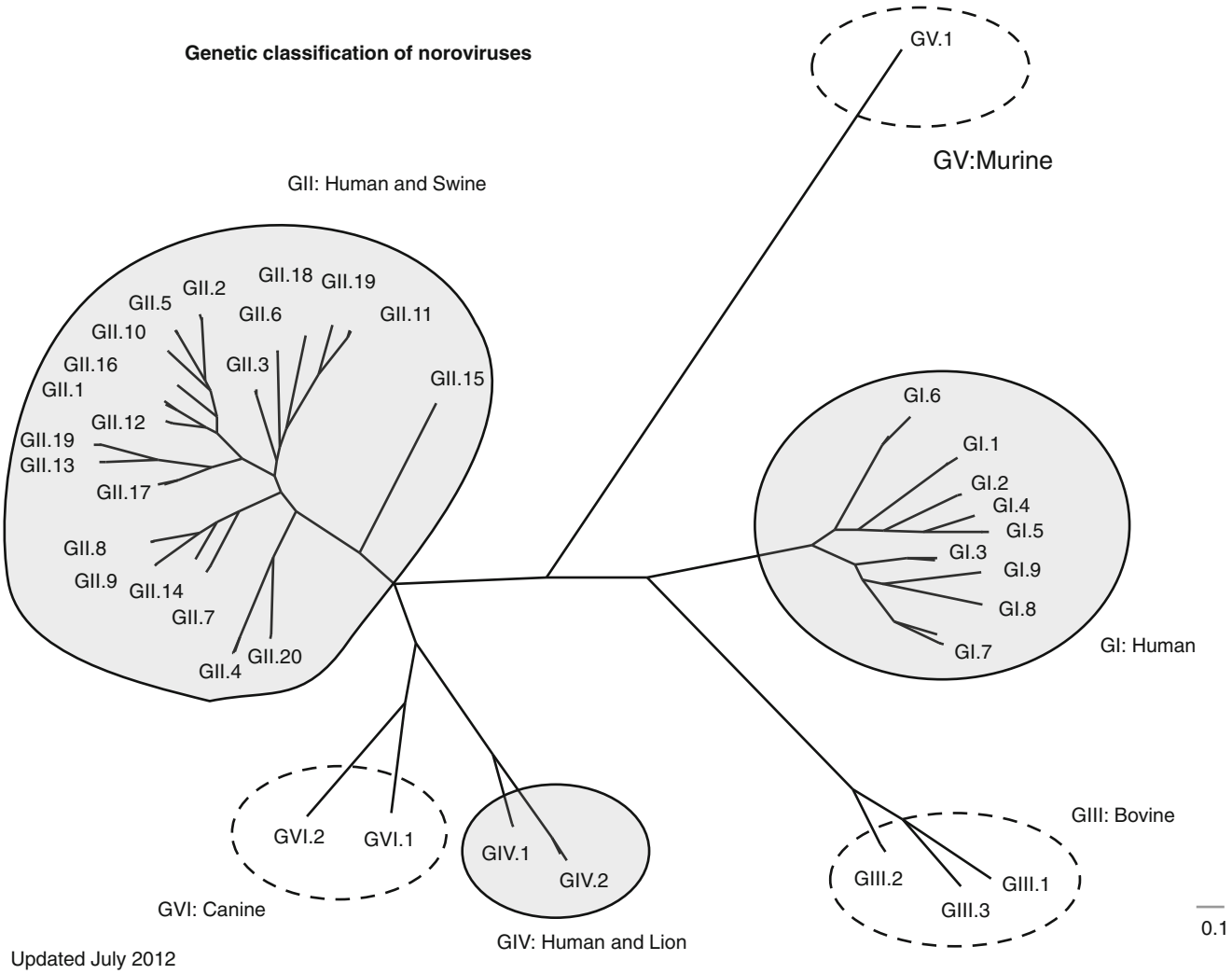

Fig. 20.5 Genetic classification of (**a**) noroviruses and (**b**) sapoviruses based on phylogenetic analysis of sequences of the major capsid protein VP1. Noroviruses can be grouped into six different genogroups (GI–VI) of which *GI* (9 genotypes), *GII* (18 of the 21 genotypes), and *GIV* (1 of the 2 genotypes) can infect humans. Strains belonging to *GIII*, *GV*, and *GVI* infect bovine, murine, and canine species. (**b**) Sapoviruses can be grouped into at least seven different genogroups (GI–VII) with several additional viruses (mink sapovirus and bat sapovirus) that are tentative new genogroups. Sapoviruses in *GI* (5 genotypes and 1 unassigned), *GII* (3 genotypes and 2 unassigned), *GIV* (1 genotype), and *GV* (1 genotype) can infect humans. The scale bar of 0.1 reflects the number of amino substitutions per site (Data analysis and graphs were developed by Everardo Vega, CDC)

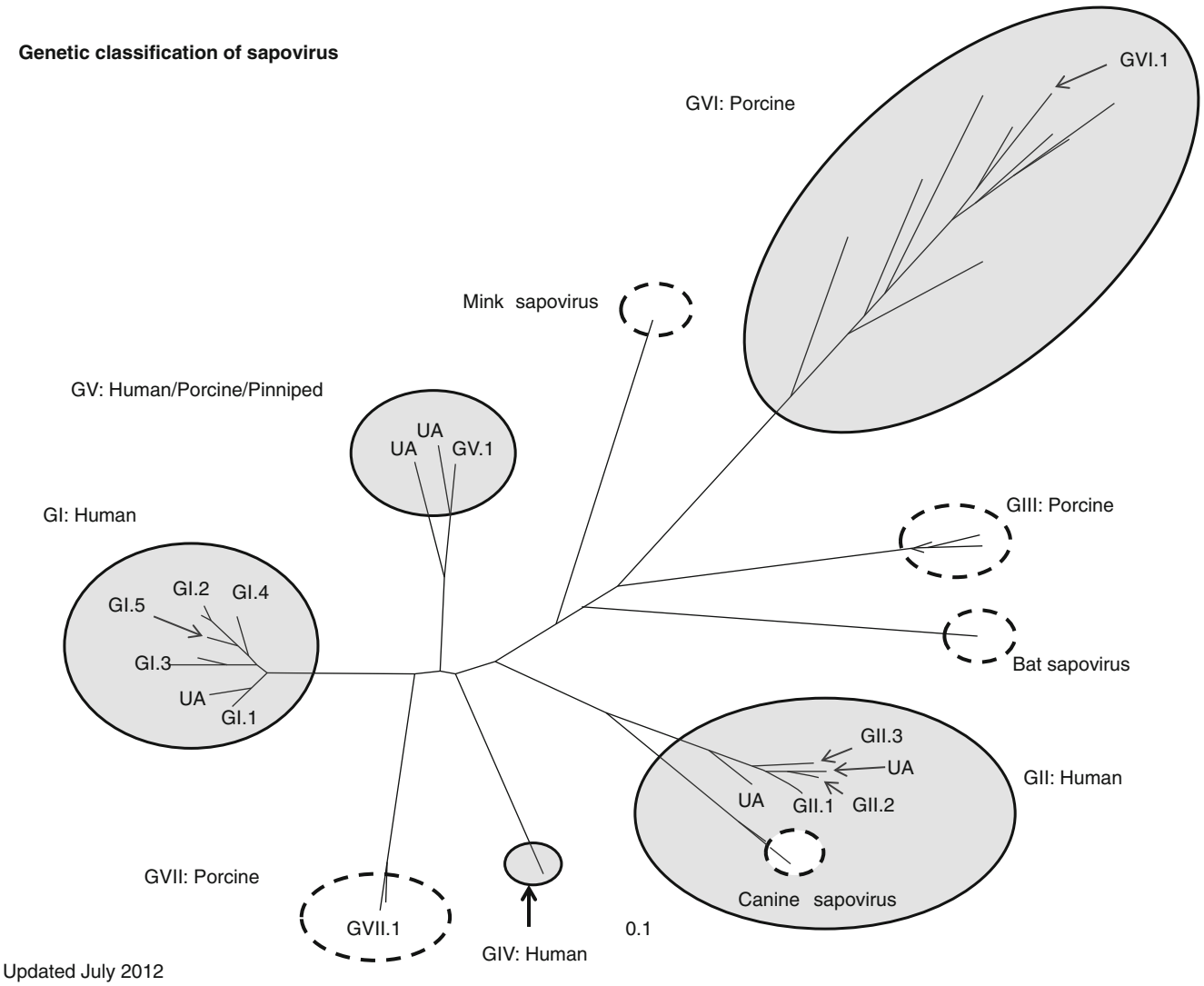

Fig. 20.5 (continued)

7 Patterns of Host Response

Protective immunity to norovirus appears to be different from other enteric viral pathogens and is incompletely understood. Although seroepidemiological studies have shown an antibody prevalence to norovirus of >80 % by age 20, adults consistently demonstrate a high degree of susceptibility to both naturally occurring and experimentally administered noroviruses. In a classic study from the 1970s, 50 % of adult volunteers infected with Norwalk virus consistently developed illness following challenge [25, 214]. In human challenge studies, infected volunteers were susceptible to reinfection with the same strain as well as to infection with heterologous strains [23, 25, 215, 216]. In addition, individuals with preexisting antibodies were not protected from infection unless repeated exposure to the same strain occurred within a short period. Two of these studies demonstrated that homologous antibody protection might last anywhere from 8 weeks to 6 months [23, 216]. Because preexisting antibodies among challenged volunteers did not confer immunity in all individuals and because some persons remained uninfected despite significant exposure, both innate host factors and acquired immunity have been hypothesized to contribute to the susceptibility to infection [23]. However, the infectious dose of virus given to volunteers in these challenge studies was several thousand-fold greater than the small dose of virus capable of causing human illness, and thus immunity to a lower, more natural challenge dose might be greater and more cross-protective. A mathematical modeling study suggests the duration of protective immunity may be on the order of 4 to 8 years [217].

Histo-blood group antigens (HBGAs), including H type, ABO blood group, and Lewis antigens, are a diverse family of carbohydrates expressed on mucosal surfaces. Several

studies indicate that they act as putative receptors or co-receptors for noroviruses. Although there is no evidence that binding to HBGA is mediating viral entry, there is a strong correlation between polymorphic expression of HBGA and human susceptibility to norovirus infection [8]. Genetic resistance to norovirus infections has been associated with mutations in the *FUT2* (or "secretor") gene, which encodes an α1,2-fucosyltransferase; in the homozygous state, null mutant alleles (FUT2–/–) lead to the absence of the α1,2-linked fucose residue on the H-type carbohydrate structures, which characterize the so-called non-secretor phenotype [218]. The most frequent null allele (se428) is characterized by the 428G > A nonsense mutation, and homozygous non-secretors (FUT2–/–) represent up to 20 % of the European population [219]. Results from two landmark studies of human volunteers who were challenged with Norwalk virus demonstrated that non-secretors were not infected by the virus and none of the volunteers showed an increase in anti-Norwalk virus antibodies or had detectable RNA in feces, while secretors (FUT2+/+ or FUT2+/–) excreted the virus and developed a strong antibody response [8, 220]. In addition, both volunteer studies demonstrated that FUT2-positive individuals of the B blood group type were less likely to be infected than A or O individuals but, if infected, more likely to remain asymptomatic. Thus, alleles at the *FUT2* locus determine sensitivity or resistance to the Norwalk virus strain, and the polymorphism at the ABO locus modulates sensitivity within the secretor-positive group. HBGAs are differentially expressed in humans, and several conserved amino acids of the P2 domain of VP1 are important for HBGA binding [221]. The expression of HBGAs has been shown to be associated with strain-specific susceptibility to norovirus infection [8, 222–224]. However, specific binding profiles are not genotype or genogroup exclusive [225] suggesting a host-pathogen coevolution driven by carbohydrate-protein interactions. For GII.4 viruses, single amino acid replacements seem to drastically alter the binding capacity of the VLP [226]. Overall no single norovirus strain seems to be able to cover the whole spectrum of human HBGAs diversity, although collectively, they are likely to be able to infect nearly everyone. The only notable exception is the subgroup of individuals who have a rare genotype, either FUT2–/– or FUT3–/– [218], who may be completely resistant.

Recent studies have reported that innate immunity plays an important role in the control of murine norovirus infection, but little is known about cell-mediated immune responses against noroviruses [227, 228]. A study using oral immunization of human volunteers with Norwalk viruslike particles showed an increase in interferon-γ (IFN) in the absence of IL-4 production, suggesting a dominant Th1 pattern of cytokine production [229]. This dominant Th1 response was confirmed in a study of 15 volunteers infected with Snow Mountain virus, who experienced significant increases in serum IFN-γ and IL-2, but not IL-6 or IL-10, on day two after challenge [224]. Interestingly, in an in vitro study using a Norwalk virus replicon-bearing cells, IFN-α efficiently cleared the NV replicon in a dose-dependent manner at comparable levels to hepatitis C virus, indicating a potential therapeutic application of IFN to norovirus infection [230].

Because diarrheal disease caused by astrovirus is largely restricted to children, immunity is believed to be long lasting; however, little is known regarding the specific immune responses that result in immunity to astroviruses. $CD4^+$ T cells may be involved in the anti-astrovirus response [231] and animal models point to a possible role for the innate immune system [232].

8 Control and Prevention

Efforts to prevent norovirus and sapovirus disease are directed at interrupting the person-to-person transmission cycle, even in the case where contaminated food or water can be identified. Most gastroenteritis viruses are transmitted via the ingestion of infectious fecal (or, less commonly, vomitus) material. Therefore, standard sanitation and hygienic precautions are key. These include frequent hand hygiene, environmental disinfection, proper disposal of fecal or vomit-soiled materials, and limited contact with ill persons. Even when these precautions are put firmly in place, our ability to control outbreaks remains limited [233].

8.1 Hand Hygiene

The single most important method to prevent norovirus infection and control transmission is appropriate hand hygiene [234, 235]. Washing with soap and water is the preferred method to prevent norovirus transmission, with alcohol-based hand sanitizers useful only as an adjunct when hands are not visibly soiled [236]. Plain soap and water reduces the number of microbes on hands via mechanical removal of loosely adherent microorganism [234]. In finger pad studies, soap and water used for 20 s have been shown to reduce norovirus by 0.67–1.20 $\log_{10}$ by RT-PCR assay [235]. The use of alcohol-based hand sanitizers remains controversial, due to both inconclusive in vitro finger pad studies [171, 235, 237] and epidemiological studies where higher rates of infection have been detected during outbreaks in long-term care facilities that use alcohol-based hand sanitizers [238], though the reasons for association in this one study are debated [239].

Surrogate viruses such as murine norovirus (MNV) or feline calicivirus (FCV) and porcine sapovirus are typically used since norovirus cannot be cultured, so its infectivity cannot be directly assessed. Additionally, detection and quantification of viral RNA is not necessarily a reliable

means of estimating the effectiveness of hand sanitizers against human norovirus [171]. Studies on disinfectant and hand sanitizers using MNV and FCV have given contradictory results [237, 240]. The sensitivity of FCV to low pH and the relatively high susceptibility of MNV to alcohols suggest that disinfectants that are effective against both surrogate viruses may be more likely to be effective against human norovirus [171].

8.2 Exclusion and Isolation

Considering the highly infectious nature of norovirus, exclusion and isolation of infected individuals are often the most practical means of interrupting transmission of virus and limiting contamination of the environment. This is true in settings where people reside or congregate such as long-term care facilities, acute care hospitals, cruise ships, and college dormitories as well as in the case of infected food handlers.

Unfortunately, empirical evidence for the effectiveness of exclusion and isolation strategies is limited; [241] these strategies are based on general infection control principles rather than direct evidence. The principle underpinning isolation is to minimize contact with persons during the most infectious periods of their illness. This includes the acute phase of illness, a period following recovery while the person is still shedding virus at high levels, and, in some situations in healthcare facilities, exclusion of exposed and potentially incubating individuals. Isolation of well persons (i.e., quarantine) may be useful during outbreaks in long-term care facilities and hospitals to help break the cycle of transmission and prevent additional cases.

In healthcare facilities, ill patients may be cohorted together in an isolatable unit, with the same dedicated nursing staff providing care only for infected individuals [242]. Ill patients should not generally be transferred to unaffected units in the facility – except in the case of medical necessity and after consultation with infection control staff. Analogously, passengers with AGE on cruise ships may be asked to remain isolated in their cabins during their illness and for a period of 24–48 h after recovery. To minimize the risk of spread from incubating or asymptomatically infected patients and staff in healthcare facilities, such individuals should not be transferred to or work in unaffected areas, typically for 48 h after exposure. In certain situations, units in a healthcare facility may be closed to new admissions to prevent the introduction of new susceptible patients, though guidelines differ on this point [236, 243–245]. Ill staff members in healthcare facilities as well as infected food handlers should be excluded during their illness and for 24–48 h following resolution of symptoms [108].

8.3 Food Handling

Food may also be potentially contaminated with enteric viruses during production if growing or irrigation waters are contaminated with human feces; thus, shellfish should be adequately cooked and fresh produce washed thoroughly before consumption [108].

8.4 Environmental Decontamination

Chemical disinfection is a central approach inactivate norovirus [246, 247]. The US Environmental Protection Agency maintains a list of approved products for norovirus disinfection (http://www.epa.gov/oppad001/list_g_norovirus.pdf) based on their efficacy against FCV. Notably, FCV exhibits different physiochemical properties than human norovirus and therefore might not reflect a similar disinfection efficacy profile. Largely due to the uncertainty from in vitro studies, CDC recommends chlorine bleach solution at a concentration of 1,000–5,000 ppm (5–25 tablespoons household bleach [5.25 %] per gallon of water) for disinfection of hard, nonporous, environmental surfaces whenever feasible [108, 172]. In healthcare settings, cleaning products and disinfectants used should be EPA registered and have label claims for use in healthcare settings [108]. Hand hygiene (discussed above) is also a key part of the environmental transmission cycle since contaminated hands can transfer virus to touched surfaces, and hands may be a vehicle for transferring virus from contaminated surfaces back to humans [175].

8.5 Vaccination and Treatment

No specific treatment exists for most AGE viruses, so treatment is supportive and includes therapy for dehydration and electrolyte imbalances. First-line treatment should be oral rehydration solutions, while severe dehydration or shock may warrant intravenous fluid therapy. Antiemetics, antimotility agents, and antibiotics are generally not recommended [248]. Certain compounds with antiviral properties have shown promise in laboratory studies, but their value in the clinic remains uncertain given the short and acute infection caused by caliciviruses.

No vaccines for noroviruses are currently available, but a number of norovirus vaccines are at various stages of development. The product furthest developed is based on recombinant virus-like particles (VLPs) produced by the expression and spontaneous self-assembly of the major capsid protein VP1. An intranasally delivered formulation was shown to be safe and immunogenic in phase 1 and 2 trials [249]. In a challenge study, where participant were vaccinated and

subsequently exposed to homotypic Norwalk virus, the vaccine was shown to be effective against disease and, to a lesser extent, infection [250]. A number of remaining questions and challenges include whether efficacy in the community against commonly circulating viruses can be achieved, whether more vulnerable groups (children and the elderly) will be protected, and whether duration of protection will be long enough to be clinically useful [251].

9 Unresolved Problems

A number of issues remain unresolved, hamper our understanding of norovirus, and preclude a solid basis to develop effective prevention and control strategies. Most fundamental is our inability to grow norovirus in a cell-culture system [252]. This limitation has restricted development of infectivity assays and our ability to differentiate infectious virus from inactivated particles. That capability could ultimately lead to a better understanding of the biology of noroviruses. Second, a perplexing result from many studies is the high level of asymptomatic infection, mainly in children, but occasionally in older age groups [44]. These findings raise questions about the interpretation of diagnostic results as well as the role of asymptomatic infection in transmission. For example, considering the long duration of asymptomatic shedding, we do not know how long infected food handlers or healthcare workers should be excluded from work. Finally, and most importantly, the burden of the noroviruses among economically poor populations in developing countries remains to be fully understood.

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