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Review

Insights into Gastrointestinal Virome: Etiology and Public Exposure

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Abstract: Recycled wastewater is widely used owing to the potential shortage of water resources for drinking purposes, recreational activities, and irrigation. However, gut microbiomes of both human beings and animals negatively affect this water quality. Wastewater contamination is continuously monitored, using fecal contamination indicators or microbial source tracking approaches, to oppose arising enteric infections. Viral gastroenteritis is considered a principal manifestation of waterborne pathogenic virome-mediated infections, which are mainly transmitted via the fecal-oral route. Furthermore, acquired enteric viromes are the common cause of infantile acute diarrhea. Moreover, public exposure to wastewater via wastewater discharge or treated wastewater reuse has led to a significant surge of public health concerns. In this review, we discussed the etiology of waterborne enteric viromes, notably gastrointestinal virus infections, and public exposure to municipal wastewater. Conclusively, the early human virome is affected mainly by birth mode, dietary behavior, and maternal health, and could provide a signature of disease incidence, however, more virome diversification is acquired in adulthood. A multi-phase treatment approach offered an effective means for the elimination of wastewater reuse mediated public risks. The insights highlighted in this paper offer essential information for defining probable etiologies and assessing risks related to exposure to discharged or reused wastewater.

Keywords: virome; wastewater; etiology; viral gastroenteritis; exposure

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1. Introduction

Virome diversity accounted for approximately 1031 members worldwide, including bacteriophages, as the major division according to a ten-fold diversity evaluation compared to their bacterial hosts' diversity [1]. Likewise, phage community dominates the early human enteric virome, along with the bacterial communities' expansion acquired by maternal-mediated vertical transmission and after weaning [2,3]. On the other hand, enteric viruses in infants are minimally acquired from their mothers [4], however, the enteric viromes mostly persist after the first two years [2,5]. Several enteric viruses could transfer to infants, and even children, via maternal transmission, through direct exposure, or through the use of contaminated water, such as hepatitis E virus (HEV) and hepatitis A virus (HAV) causing gastroenteritis or, in severe cases, fulminant hepatitis [6–8].

However, adenovirus, rotavirus, norovirus, hepatitis A virus, and astrovirus represent the most commonly acquired enteric viruses and contribute to virome shaping in its early phases [6,9–12]. Moreover, these viruses are of high persistence in various water environments. For example, noroviruses can survive in ground water for 1266 days at 25 °C with 1.76 $\log_{10}$ reduction [13]. However, adenoviruses can last for 36 and 132 days at 20 °C and 4 °C, respectively, and are associated with a 1 $\log_{10}$ reduction [14]. Rotaviruses can also persist in fresh water and drinking water for 10 [15] and 64 [16] days, respectively, at 20 °C with 2 $\log_{10}$ reduction.

People are frequently exposed to wastewater via surface water usage, toilet flushing, recreation water, and wastewater—or greywater—dependent irrigation [17–21]. Most commonly occurring enteric viruses are self-limiting, whereas their infection risk is determined by the prevalence of infectious viral particles in the appropriate environmental condition, since some enteric viruses are significantly influenced by seasonal variation (e.g., rotavirus favoring late autumn and early winter [22]) or their prevalence in water environments that people are exposed to. For instance, the prevalence of HAV was found to be higher in raw water (16/27; 59%), than in treated water (5/26; 19%) [23].

Wastewater discharge to surface water resources imposes public health concerns and directly affects water resources, causing both enteric and non-enteric diseases, especially with the recent COVID-19 pandemic [24–26]. On the contrary, wastewater reuse was proposed mainly because of the shortage of water supplies [27,28]. This demanded technical solutions for reuse of treated water for both non-potable uses, such as irrigation, with reported limitations (e.g., alterations of soil physicochemical parameters, microbiota [29], soil fertility, and subsequent productivity [21] and soil pH [29]) to be considered and de facto wastewater reuse associated with raised concerns (e.g., increased drinking water risks in case of wastewater effluent in source water [30]). Integration of these technical solutions with a water safety plan (WSP) could offer organized management solutions for limitations and concerns. Thus, the current review highlighted the etiology of enteric viromes in various water environments and the associated concerns related to public exposure to municipal wastewater via wastewater discharge or treated water reuse.

2. Enteric Virome in Infants

The microbiome is established as early as the gestation period, and develops into a steady state as the individual reaches early adulthood [2,31–34]. Infant microbiomes were shown to be influenced by various factors involving birth mode, gestational age, antibiotic usage, geographical location, lifestyle, diet, and age [35–37]. For instance, a greater virome diversity was observed in spontaneous vaginal delivery (SVD) than in caesarean section (CS) [38]. Moreover, microbiome diversification during the early months after birth was found to be followed by a secondary expansive phase owing to diet alterations that occur after weaning [2,3,39]. Furthermore, microbiome composition of the infants' gut is linked to that of the maternal gut [4,40,41]. However, it was demonstrated that vertical transmission of the virome was considerably lower than that of bacterial microbiome [4].

Interestingly, antibiotic usage acts as a stressor, causing microbiome imbalances that are reported to cause sepsis in newborn infants by vertical transmission [42]. Antibiotic treatment reduces both the size and diversity of the bacterial community, initiates pro-phage activation, and enriches phage-encoded antibiotic resistance genes that further influences the prokaryotic microbiome, which is associated with long-term implications [37,43–45]. Thus, such influences on the microbiome via these trans-domain interactions can be associated with probable metabolic deficiencies and inflammatory conditions [46–49]. On the other hand, the infant virome is affected by dietary behavior and could serve as a signature of malnutrition. For instance, members of the Anelloviridae and Circoviridae were found to discriminate between both healthy twin pairs and twin pairs developing malnutrition [50].

Although the microbiome is acquired during pregnancy or even at birth, the gut virome develops postnatally, since the meconium was found to lack any virus-like particles (VLPs) [51]. However, VLP numbers begin to surge to about 10^8 per g feces in the first birth week, along with the primary colonizers that arise from dietary and maternal sources in addition to the surrounding environment [52]. Consequently, the infantile virome expands and includes significant shifts in the phage community along with age because of the expansion and diversification of the bacterial communities [2]. Moreover, enteric virus communities in infants, accounting for 15%, are acquired from their mothers [4]. The virome peak is reached at adulthood, displaying persistent viruses of about 80% that persist for >2.5 years [2,5]. Moreover, eukaryotic viruses, including adenovirus, herpes simplex virus,

cytomegalovirus (CMV), human parvovirus B19, enterovirus, respiratory syncytial virus, and Epstein–Barr virus, were characterized from healthy mothers' amniotic fluid, while neonates were healthy [53]. Furthermore, placental and vaginal transmission of viruses, comprising of HIV, influenza, hepatitis, CMV, rubella, and herpes zoster virus, were also detected, rendering extra evidence of maternal-mediated infantile virome modification [54]. This eukaryotic virome encompasses these conventional pathogenic viruses and viruses of unidentified host interactions. Despite the presence of these classical pathogens, infected hosts can remain asymptomatic.

On the other hand, waterborne enteric viruses, further, nourish the infantile virome either through maternal-based vertical transmission [55] or ingestion of contaminated water or infant formula, as reported elsewhere [56]. For instance, acute maternal HAV infection could result in infant infection during the last trimester or the postpartum period [6]. Moreover, piped drinking water crossing sewage channels in India led to higher hepatitis E virus incidence in mothers, that was then vertically transmitted to fetuses [7]. Subsequently, two fetuses were aborted and four pre-matured babies were delivered [8]. Therefore, an obvious relationship between the gastrointestinal virome in infants and waterborne diseases or enteric viruses in wastewater is well-established and tightly linked to community behavior, life style, and infection risk via direct or indirect contact with contaminated water.

3. Viral Etiology

Viral gastroenteritis is mainly transmitted by the fecal-oral route. Currently, five common groups of viruses account for the most frequently occurring acute diarrheal cases worldwide: adenovirus, rotavirus, norovirus, hepatitis A virus, and astrovirus.

3.1. Adenovirus

Adenoviruses are members of the family *Adenoviridae* and the genus *Mastadenovirus*, comprising of more than 80 human serotypes [57]. Human adenoviruses are non-enveloped icosahedral particles with a double-stranded linear DNA genome of ~34–36 kb [58]. They are currently grouped into seven human adenovirus species (A–G), alongside novel adenovirus types that are continuously emerging [59,60]. Virus types were identified in cross-neutralization assays as serotypes up to type 51, however a genotype designation was used for the more recent types based upon phylogenetic analyses of genes encoding the major capsid proteins [61].

Adenovirus infections can lead to a wide spectrum of clinical symptoms. Gastrointestinal infections are commonly caused by subgroup A, D, and F, while subgroup B is the main cause of infections of the lungs and the urinary tract. Subgroups C and E are, however, mainly related to infections of respiratory tract. Amongst subgroup F, serotypes 40 and 41, with serotype 31 of subgroup A, are mainly associated with gastroenteritis [62]. Adenovirus infections are mostly self-limiting, with the exception of immunocompromised individuals. However, a strain of adenovirus 14 that emerged previously resulted in a fatal respiratory disease in healthy personnel [63].

Human adenoviruses (HAdV) are specific to humans even though adenoviruses infect a range of animals. In domestic sewage, HAdV existed in notably high concentrations and their seasonal variability was insignificant [64–66]. As with most enteric viruses, adenoviruses are more persistent in various water environments, including lakes, irrigation water, and treated sewage (Table 1), than the currently used fecal indicator bacteria [67,68]. For instance, adenovirus was detected in rivers (18–100%), recreational water (40–93.1%), raw sewage water (0.4–100%), and treated effluents (25–100%, except for that reported in earlier study conducted in Tunisia) as shown in Table 1. Moreover, adenovirus was of the highest concentrations, estimated at 9.8×10^8 GC/mL, in treated water influents and in treated effluents, at 4.9×10^8 GC/mL, in Italy. HAdV was of the highest frequency (100%) in raw sewage water in all countries, except for the U.K. and Italy, wherein the encountered frequency was 90% and 96% in the same source, respectively. However, the highest HAdV

concentration was obtained from lagoons and beaches in Brazil (10^9 GC/L). Furthermore, adenoviruses are highly resistant to UV light and this significant resistance might be due to the host cell-mediated DNA repair mechanism [69]. In addition, adenoviruses have another mechanism that ameliorates the DNA damage response, mediated by the E4 or F4 protein, which are involved in efficient adenovirus replication [70]. Therefore, adenoviruses were proposed as a virological index for water quality control due to their potential environmental stability [71].

Table 1. Occurrence of adenovirus in various water environments.

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Species (Serotype)	Assessment Tools	Reference
Saudi Arabia	Treated effluents	44.44–61.11%	April 2018–March 2019	-	F (41)	PCR and direct sequencing	[72]
	Lakes	75–77.78%					
	Wastewater landfill	83.33%					
	Irrigation water	52.78%					
Egypt	Raw sewage water	84.4%	January–December 2017	4.3×10^5–8.7×10^6 GC/mL	-	Conventional PCR and Real-Time PCR	[73]
	Treated effluents	50%		1.22×10^4–3.7×10^6 GC/mL			
	Irrigation water (Nile River)	62.5%	September–December 2017	1.5×10^7 GC/L [a]	-	Real-Time PCR and amplicon cloning	[74]
Japan	Raw sewage water	100%	July 2003–June 2004	320 PCR units/mL [a]	-	TaqMan PCR and quantification by the MPN (Most probable number method	[75]
	Secondary treated water **	99%		7 PCR units/mL [a]			
	Treated effluents ***	100%					
Tunisia	Raw sewage water	0.4%	January 2003–April 2007	-	F (41)	PCR and direct sequencing	[76]
	Treated effluents	0%			-		
Uruguay	River	18%	June 2015–May 2016	1.5×10^4 GC/L [a]	B (3)	Real-Time PCR, cell culture, ICC-qPCR, nested PCR and amplicon sequencing	[77]
	Underground water	0.7%	November 2013–September 2014	-	-	Nested PCR	[78]
South Africa	River	30.56%	August 2010–July 2011	8.49×10^4 GC/L [b]	C (1, 2, 5 & 6) and F (41)	Real-Time PCR and Multiplex PCR (Serotype-specific)	[79]
	Treated effluents	64%	September 2012–August 2013	2.37×10^5 GC/L [b]	C (2) and F (41)	Real-Time PCR and serotype-specific PCR	[80]
Pakistan	Tap water	20%	-	-	-	PCR	[81]
USA	Raw sewage water	100%	August 2005–August 2006	1.15×10^6 viruses/L	F (41) and A (12)	Real-Time PCR, Molecular cloning and sequencing	[67]
	Combined sewer overflows	100%	February–June 2008	5.35×10^5 viruses/L	-		
	Primary treated water	-	August 2005–August 2006	1.12×10^6 viruses/L	F (41) and A (12)		
	Secondary treated water	-		2×10^4 viruses/L	-		
	Tertiary treated water	-		8.3×10^4 viruses/L	-		
	Surface water	30%	2006-2007	7.76×10^3 viruses/L	-		
	Raw sewage water	100%	Fall 2007	-	-	Nested PCR and sequencing	[82]
	Treated effluents	25%		-	-		

Table 1. *Cont.*

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Species (Serotype)	Assessment Tools	Reference
Brazil	Recreational water (Lagoons and beaches)	93.1% [c]	March 2015–July 2016	10^9 GC/L [b]	C	qPCR, ICC-qPCR, Nested PCR and sequencing	[83]
Italy	Raw sewage water	96%	May–September 2007	9.8×10^8 GC/mL	-	TaqMan real-time PCR	[84]
	Treated effluent	76%		4.9×10^8 GC/mL			
	Raw sewage water	60%	January–December 2013	-	F (41)	Nested PCR, Sanger sequencing and Next generation sequencing	[85]
UK	Raw sewage water	90%	March 2016 and August 2016–August 2017	6×10^5 GC/L [b]	-	SYBR Green qPCR	[86]
	Treated effluent	87%		10^3 GC/L [b]			
	Surface water	88%		10^5 GC/L [b]			
Netherlands	Drinking water influents ****	54%	2012	2.5 Log_{10} GC/L [a]	F(40, 41)	Real-Time PCR and mpnPCR	[87]
China	Recreational water (Swimming pool)	40%	May 2013	-	E (4)	Conventional PCR, sequencing and cell culture	[88]
Canada	River upstream	50% [c]	June 2012–May 2013	2.66 Log_{10} GE * copies/L [a]	-	qPCR and ICC-qPCR	[89]
	River downstream	92% [c]		4.55 Log_{10} GE copies/L			
France	River	100%	January–June 2016	3.6×10^3 GC/L [a]	F (41)	MPN assay, ddPCR (digital droplet PCR) and ICC-qPCR	[90]
Sweden	Raw sewage water	100%	November–December 2015	9.07×10^4 GC/mL [a]	F (41)	Nested PCR, Library construction, Ion-Torrent sequencing and qPCR	[91]
	Conventionally treated water			1.06×10^3 GC/mL [a]			
	Ozone treated water			8.25×10^3 GC/mL [a]			
	Raw sewage water	100%	January–May 2013	3.3×10^5 virus/L [b]	-	Real-Time PCR and sequencing	[92]

[a]: mean adenovirus concentration, [b]: maximum adenovirus concentration, [c]: maximum detection limit (frequency), GC: genome copy. *: genome equivalent, **: treated water before chlorination, ***: treated water after chlorination, ****: last storage reservoir before treatment of drinking water, (-): not defined.

3.2. Rotavirus

Rotavirus is a double stranded RNA virus composed of 11 segments of a genome size of ~18,550 bp [93]. These segments differ in size from 667 to 3302 nucleotides (Figure 1). Viral capsid proteins (VP1, VP2, VP3, VP4, VP6, and VP7) are encoded by segments 1, 2, 3, 4, 6, and 9, respectively. The non-structural proteins (NSP1, NSP2, NSP3, NSP4, NSP5, and NSP6) are encoded by segments 5, 8, 7, 10, and 11, respectively. All segments have methylated cap structures at the 5′ end and a 3′UGACC consensus sequence instead of the poly-A tail [94,95].

Rotaviruses are divided into seven serogroups (A–G) [96]. Rotavirus A is considered the principal cause of severe acute gastroenteritis throughout the world and predominantly results in severe acute diarrhea in children [97,98]. Moreover, the incidence of rotavirus diarrhea in developing countries accounts for 0.07 to 0.8 episodes per child annually [99] or at least one diarrheal episode by five years of age [9]. Rotaviruses showed a high prevalence in different water sources (Table 2). This could be owing to its broad tolerance to a wide range of temperatures (−20 °C to 37 °C) and pH levels (3 to 11) without a significant infectivity loss [100–104]. However, rotavirus A prevalence is influenced by seasonal variations, favoring lower temperatures in temperate countries [22,105], unlike the endemic manner of rotavirus in tropical countries [106]. In terms of rotavirus frequency, sewage influent of Brazil and, surprisingly, wastewater treatment plant (WWTP) effluents in China recorded the highest frequency, even higher than that reported in Chinese raw water, indicating a

deficiency in the WWTP performance or probable sampling cross-contamination, as shown in Table 2. Moreover, rotaviruses were detected in rivers (18.75–83.33%), raw sewage water (21.2–100%), and treated effluents (5–100%). Furthermore, rotaviruses were detected at significantly high concentrations, up to 1.16×10^7 GC/L, in treated water influents and in treated effluents, at levels of 2.8×10^6 GC/L, in Brazil and the USA, respectively, as displayed in Table 2.

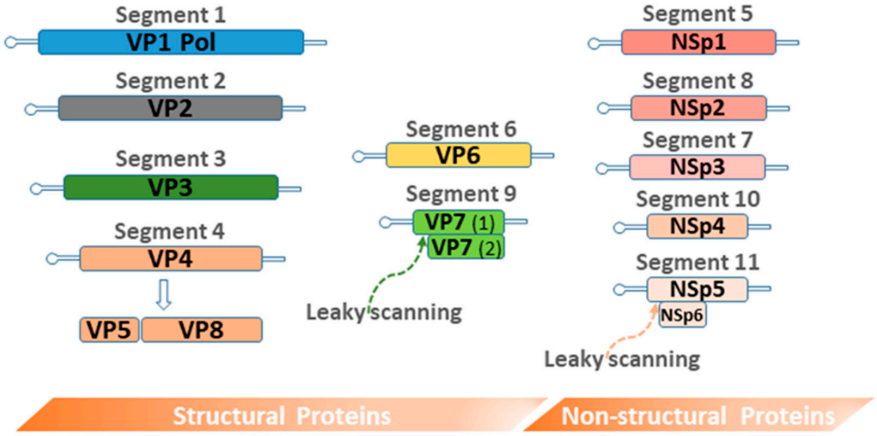

Figure 1. Rotavirus genome structure.

The rotavirus outer capsid consists of two distinct neutralization antigens that are responsible for rotavirus attachment and entry, termed VP7 and VP4. They serve for virus classification, with each categorized into a G-genotype (16 genotype) and P-genotype (27 genotype thus far) [98]. Despite the wide spectrum of rotavirus genotypes resulting from G/P combinations, epidemiological studies showed that the most prevalent genotypes are G1P(8), G3P(8), G4P(8), G9P(8), and G2P(4), which cause up to 90% of severe RVA infections worldwide [107,108]. Furthermore, there is no clear relationship between rotavirus genotypes and the severity of disease [109].

Table 2. Rotavirus frequency and dominant genotypes in different water sources.

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Dominant Genotypes	Assessment Tools	Reference
Saudi Arabia	Treated effluent	5.56–13.89%	April 2018–March 2019	-	G2	RT-PCR and Sanger sequencing	[22]
	Lakes	27.78–30.56%		-	G2		
	Wastewater landfill	63.89%		-	G2		
	Irrigation water	5.56		-	G2		
	Dams	13.33%	February–April 2017	-	-	RT-PCR	[110]
Japan	Drinking water effluent	86% [a]–95% [b]	June 2017–August 2018	5.5 [b]–6.3 [a] $\log_{10}$ GC/L	-	RT-PCR, semi-nested PCR and direct sequencing	[111]
Egypt	Nile river	18.75 %	June 2016–May 2017	-	G1P(8) and G1P(4)	RT-PCR and Multiplex semi-nested PCR	[112]
	Irrigation water (Nile river)	50%	September–December 2017	2.7×10^5 GC/L [d]	-	RT-PCR, amplicon cloning and qPCR	[74]
Tunisia	Raw sewage water	21.2%	January 2003–April 2007	-	GxP(8) and GxP(4)	RT-PCR and direct sequencing	[76]
	Treated effluent	10.8%					
Uruguay	River watersheds	41 % [c]	June 2015–May 2016	1.3×10^5 GC/L [d]	-	RT-PCR and Real-Time PCR	[105]
	Underground water	32 %	November 2013–September 2014	1.72×10^3 GC/L [a]		RT-PCR and qPCR	[78]

Table 2. *Cont.*

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Dominant Genotypes	Assessment Tools	Reference
South Africa	Treated effluents	41.7% [e]	September 2012–August 2013	5.2×10^3–1.2×10^5 GC/L [f]	-	RT-PCR and Real-Time PCR	[113]
Pakistan	Treated effluents	5%	February–July 2014	-	-	Enzyme-linked immunosorbent assay (ELISA)	[114]
	Drinking water	5%					
	Surface water (River and dam water)	23%	November 2014–February 2015 and April 2015–July 2015	-	G3 and G9	RT-PCR, Nested-PCR and sequencing	[115]
USA	Treated effluents	83%	August 2011–July 2012	2.8×10^6 GC/L [f]	-	RT-PCR and qPCR	[116]
Brazil	Raw sewage water	100%	August 2009–July 2010	2.40×10^5–1.16×10^7 GC/L [e]	G2P(4) and G2P(6)	RT-PCR, qPCR, Nested PCR and amplicon sequencing	[117]
	Treated effluents	71%		1.35×10^3–1.64×10^5 GC/L [e]			
Italy	Raw sewage water	60.4%	2010–2011	-	G1P(8) and G2P(4)	RT-PCR, Nested PCR and amplicon sequencing	[118]
Netherlands	Drinking water	48%	1999–2002	2.2×10^3 PDU/liter [f]	-	RT-PCR, and molecular cloning	[119]
China	Surface water (Rivers)	75-83.33%	September 2014–August 2015	-	-	(RT-)qPCR and sequencing	[120]
	Treated effluent	100%					
	Raw sewage water	91.67%					
	Tap water	91.67%					
Canada	Surface water (Rivers)	37% [g]–75% [h]	June 2012–May 2013	4.5 $\log_{10}$ GE * copies/L [f]	G1	(RT-)qPCR, cell culture and ICC-qPCR (integrated cell culture with qPCR) and sequencing	[89]

[a]: in epidemic season, [b]: in non-epidemic season, [c]: mean detection frequency, [d]: mean rotavirus concentration, [e]: maximum detection frequency, [f]: maximum rotavirus concentrations, [g]: in upstream sites, [h]: in downstream sites. *: genome equivalent, GC: genome copy, (-): not defined.

3.3. Norovirus

Norovirus (NoV) is a member of the family Caliciviridae, with a polyadenylated, positive-sense, single-stranded RNA genome sized ~7.5 kb. The ≥40 genotypes are classified into seven genogroups (GI–GVII) [121,122]. NoV infection is considered the most prevalent non-bacterial mediated gastroenteritis, causing ~20% of entire gastroenteritis cases worldwide [123], particularly in five years old and younger children [124]. NoV causes ~685 million diarrheal episodes [125] and 200,000 deaths per year [126]. Norovirus infection symptoms occurs after an average incubation period of 24 to 48 h, typically involving vomiting, nausea diarrhea, dehydration, fever, and abdominal cramps [127].

The NoV genome organization involves three or four open reading frames (ORFs). The first ORF (ORF1) encodes for six non-structural (NS) proteins, including NS1/2 (N-Term), NS3 (NTPase), NS4 (3A-like), NS5 (VPg), NS6 (Protease), and NS7 (RNA-dependent RNA polymerase; RdRp), which are responsible for viral replication. However, the other two ORFs (ORF2 and ORF3) encode two structural viral proteins (VP), comprising of VP1 (major) and VP2 (minor capsid protein), respectively (Figure 2) [128]. Norovirus typing was conventionally based upon sequence diversity within the capsid protein sequence. Noroviruses could be grouped into ten genogroups (GI-GX). Generally, genogroups vary by around 40–60% of their amino acid sequence: less sequence variance (20–40%) in the case of genotypes [129]. Moreover, genotypes can be sub-divided into variants [130]. Currently,

the RdRp-encoding region is used for dual genotyping of norovirus based on genotype and P type; GI.1[P1], for example [129].

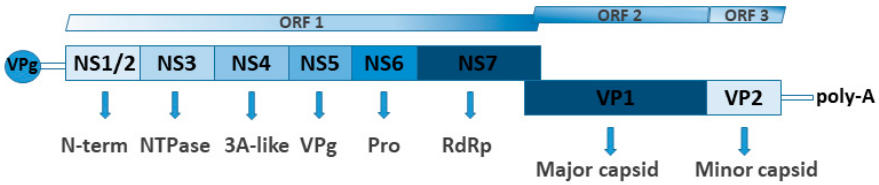

Figure 2. Genome organization of norovirus.

Humans can be infected by more than 30 genotypes of noroviruses. Furthermore, noroviruses show significant host specificity, which is at variance with evidence suggesting inter-species transmission [131–133], in addition to the detection of viral RNA from human strains in different animals [133–137]. Initially, human strains of viral RNA displayed a potentially limited replication capacity in animals [138–140]. Moreover, GI and GII viruses are mainly responsible for human infections [130], GIII viruses are associated with ovine and bovine species [141,142], GV viruses are specific for murine species (mice and rats) [143,144], and GIV, GVI, and GVII viruses are associated with various carnivorous species, notably felines and canines [145–147]. Furthermore, GVIII and GIX, which are novel genogroups, were detected in humans, while GX was described in bats [129]. However, there are some exceptions to the species specificity of GII and GIV genogroups. For instance, GII.11, GII.18, and GII.19 were described in pigs [148], but not detected in humans, while GIV.1 and GIV.NA1 were associated with humans only, but not found in canines or felines [149].

Analyses of outbreaks identified GII noroviruses as the most frequently circulating strains causing gastrointestinal infections worldwide [150]. Over the past 20 years, GII.4 became the predominant genotype, resulting in 70–80% of NoV outbreaks in various countries [151]. This genotype is potentially evolving, yielding new pandemic variants, including Grimsby 1995 (or US95_96), Farmington Hills 2002, Hunter 2004, Den Haag 2006b, New Orleans 2009, and Sydney 2012 [152,153]. This strain diversity arises from both genome recombinations and mutational events, since significantly higher non-synonymous changes were observed in comparison with other NoVs, supporting the antigenic drift proposal, although occurring at a higher rate [154,155].

Noroviruses are mainly transmitted via the fecal-oral route, through the ingestion of contaminated food or water, or by oral contact with a contaminated fomite existing in the surrounding environment [156]. Moreover, high rates of secondary infection arise via airborne transmission, although the fomite route is more dominant [157,158]. The biological characteristics of norovirus were extensively studied through human feeding study volunteers [159–162]. Norovirus inocula as low as 10 viral particles were sufficient to initiate infection [161,163]. This potentially low count-mediated infection is regarded as highly critical when discussing norovirus survival. Strikingly, norovirus was depicted to be of stable infectivity under freezing and thawing conditions [164], although a more recent study showed altered stability upon exposure to three cycles of freezing and thawing [165]. Moreover, it shows a high capacity of survival in a wide spectrum of water bodies (Table 3), as well as thermal resistance, despite being exposure time-restricted to up to 21 min decimal reduction time (time required at a given temperature to perform a log reduction) in the temperature range of 50–72 °C [166,167]. Furthermore, longer exposure time was detected at 50–60 °C, despite irreversible capsid disruption at >65 °C and loss of binding capacity at 72 °C [168]. This high survival capacity can be demonstrated in a norovirus outbreak that occurred in a long-term care facility in which fomite-mediated survival of norovirus resulted in a continuous infection for 14 days following the initial peak of illness [169]. Notably, noroviruses were detected in rivers (0–100%), recreational water (25–50%), raw sewage water (2.8–100%), and treated effluents (1.6–100%), as displayed in Table 3. Furthermore, noroviruses were detected at the highest concentrations, of 7.9 $\log_{10}$ GC/L, in combined wastewater in the USA (Table 3).

Table 3. Norovirus occurrence in various water bodies.

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Genogroups (Genotype)	Assessment Tools	Reference
Saudi Arabia	Raw sewage water	19%	January 2009–February 2010	-	-	One step RT-PCR	[170]
Egypt	Raw sewage water	25%	April 2017–March 2018	-	GI ‡ and GII	Semi-nested RT-PCR	[171]
	River	0% *–16.6% **					
	Irrigation water	31.25%	September–December 2017	3.5×10^3 GC/L [a]	GI	One step RT-PCR, Amplicon cloning and Real-Time PCR	[74]
	Urban sewage water	33.3%	October 2017–September 2018	-	GI ‡ and GII	RT-PCR and Semi- nested RT-PCR	[172]
	Treated effluents	25%			GI and GII		
Japan	Raw sewage water	-	October 2006- December 2007	-	GI(8) ***, GI(4), GII(4) ‡, GII(6) and GII(13)	RT-PCR and DNA Sequencing	[173]
	Raw sewage water	50%	March 2005–February 2006	6.9×10^4 GC/L [b]	GIV	RT-PCR and TaqMan-based real-time PCR	[174]
	Treated effluents	25%		4.8×10^3 GC/L [b]			
	River water	31%	April 2003–March 2004	1.5×10^4 GC/L [b]			
Tunisia	Raw sewage water	2.8%	January 2003–April 2007	-	GI(2), GI(5), GI(9) and GII(4) ‡	RT-PCR, Second-round typing PCR and amplicon sequencing	[76]
	Treated effluents	1.6%					
South Africa	Raw sewage water	72.2%	April 2015–March 2016	6.0×10^5 GC/L [b]	GI(4) ‡, GII(2) ‡ and GII(17) ‡	Real-time reverse transcription-PCR, semi-nested RT-PCR, conventional PCR, amplicon cloning and clone sequencing	[175]
	Treated effluents	83.3%		6.8×10^6 GC/L [b]			
	Rivers	62.9%	2008–2010	2.37×10^5 GC/L [b]	GI(5) ‡, GI(4) ‡, GI(3), GII(6) ‡ and GII(4) ‡	one-step real-time RT-PCR, two-step real-time RT–PCR, conventional PCR, semi-nested PCR, amplicon cloning and clone sequencing	[176]
India	Tap water [u]	16.67%	June–July 2015 and April–October 2017	1.9×10^4 GC/L [†, b] and 8.0×10^4 GC/L [¥, b]	GI and GII	RT-PCR, ddPCR (singleplex and multiplex probe-based assays)	[177]
USA	Untreated graywater	6%	December–April, June, July	2.5 $\log_{10}$ GC/L	GII	two-step RT-qPCR and duplexed RT-ddPCR	[178]
	Combined wastewater	39% [†]–96% [¥]		4.0 $\log_{10}$ GC/L [†,b] and 7.9 $\log_{10}$ GC/L [¥,b]	GI and GII ‡		
Mexico	Recreational water (karst aquifer)	40% [¥]–50% [†]	-	1.6×103 GC/L [†,b] and 2.9×10^2 GC/L [¥,b]	GI(2) and GII(17) ‡	RT-qPCR, Nested PCR, amplicon cloning, and Sanger sequencing	[179]
Norway	Raw sewage water	100%	February 2008–February 2009	6.1 $\log_{10}$ GC/L [†, b] and 6.3 $\log_{10}$ GC/L [¥, b]	GI and GII	RT-PCR, two genogroup-specific monoplex PCR and direct sequencing	[180]
	Treated effluents	95% [c]		5.65 $\log_{10}$ GC/L [†, b] 5.75 GC/L [¥, b]			

Table 3. *Cont.*

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Genogroups (Genotype)	Assessment Tools	Reference
Brazil	Raw sewage water	38.5% [†]–96.1% [¥]	May 2013–May 2014	6.2 $\log_{10}$ GC/L [†, b]–7.3 $\log_{10}$ GC/L [¥, b]	GI, GII.4 [‡], GII.17, GII.5, GII.2, GII.3 and GII.1	RT-PCR, qPCR and Sanger sequencing	[181]
	Primary effluent	40.4% [†]–96.1% [¥]					
	Final effluent	1.9% [†]–5.8% [¥]					
Italy	Treated urban wastewater stream	30%	May–September 2018	13 GC/L [b]	GI(4) and GII [‡]	Real-time RT-qPCR and Qualitative nested (RT)-PCR	[182]
	Recreational (bathing) water	25%		3.2 GC/L [b]			
Netherlands	Raw sewage water	100%	November 1998–April 1999	8.5×10^6 PDU [§]/liter [b]	GI(2), GII(1), GII(2), GII(3), GII(4) [‡] and GII(7)	RT-PCR, Southern blotting, amplicon cloning and sequencing	[183]
	Treated effluents			2.7×10^5 PDU/liter [b]			
	Surface water (Rivers)	100%		4.6×10^4 PDU/liter [b]	GI(2),GI(4), GII(3), GII(4) [‡] and GII(7)		
China	Drinking (barreled) water	45.5% [d]	February 2014	-	GII	RT-PCR	[184]
	Tap water (Secondary Water Supply System)	50%	May 2017	-	GII(17)	RT-PCR, Targeted gene (RdRP) sequencing	[185]
Canada	River upstream	50% [d]	June 2012–May 2013	3.24 $\log_{10}$ GE copies/L	-	Two-step RT-qPCR	[89]
	River downstream	75% [d]		4.43 $\log_{10}$ GE copies/L			
France	River	100%	January–June 2016	6.1×10^2 GC/L [a, †]–3.7×10^3 GC/L [a,¥]	GI and GII	ddPCR	[90]
Sweden	Raw sewage water	100%	November–December 2015	4.3×10^4 GC/mL [b, †]–6.5×10^4 GC/mL [b,¥]	GI and GII	RT-PCR, nested PCR, library construction, Ion-torrent sequencing and qPCR	[91]
	Conventionally treated effluents			3.9×10^2 GC/mL [b]	GII		
	Ozone treated effluents	33.3%		61 GC/mL	GII		
	Raw sewage water	100%	January–May 2013	3.5×10^3 virus particle/L [b, †]–3.2×10^5 virus particle/L [b,¥]	GI and GII	RT-PCR and qPCR	[92]

[a]: mean norovirus concentration, [b]: maximum norovirus concentration, [c]: mean norovirus frequency, [d]: maximum norovirus frequency. *: before mixing with wastewater, **: after mixing with wastewater, [‡]: dominant genotype, [†]: genogroup I, [¥]: genogroup II, [ᵘ]: dead-end ultrafiltration (DEUF) samples, [§]: PCR-detectable units (PDU), GC: genome copy, (-): not defined.

3.4. Hepatitis A Virus (HAV)

The hepatitis A virus belongs to the family Picornaviridae, genus Hepatovirus, and is a non-enveloped positive-sense, single-stranded RNA virus of ~7.5 kb genome packaged within a 27–32 nm icosahedral capsid [186]. The HAV genome is composed of a single ORF, whose translation occurs by means of a cap-independent mechanism, making the use of the internal ribosome entry site (IRES) located upstream of the genome producing a polyprotein composed of ~2230 amino acids [187]. This polyprotein consists of three distinct domains (P1, P2, and P3), which are further processed into 10 mature proteins by the virus-encoded proteinase, $3C^{pro}$ [186,188]. P1 encodes the four major capsid proteins VP1-VP4. The nonstructural viral proteins are comprised of the polyprotein domains P2 and P3, and also "processed" by $3C^{pro}$ [189]. HAV displays a high degree of conservation of the antigenic determinants—notably in amino acid sequences of viral capsids—now expanded to include the recently identified HAV-like viruses [190,191]. This could have resulted from negative selection pressures imposed upon any naturally-occurring mutants, producing the observed consensus conservation [192]. Despite the high conservation of HAV, a degree of genomic sequence divergence exists defining the various HAV genotypes and the identity of sub-genogroups [192,193]. Consequently, HAV genotyping is dependent on different regions of its genome used to recognize HAV variants, including the VP1 entire region, notably the VP1 amino terminus, the 168 bp VP1–2A junction, the VP1–2B region, the VP3–2B region, the VP3 carboxy-terminus, and the 5′ untranslated region [194,195]. Based on VP1–2A junction region variability (of ~15%), seven genotypes of HAV were primarily defined. However, according to the 23.7% variation denoted by the entire VP1 sequence analyses, six HAV genotypes (I–VI) are currently defined, encompassing genotypes 1A, 1B, II, III, IV, V, and VI [196,197]. Genotypes I, II, and III infect humans and are divided into A and B subtypes, however genotypes IV to VI are called simian HAV (SHAV) since they infect non-human primates [196,198]. Amongst human HAV genotypes, subtype IA was found to be the most frequently circulating subtype worldwide [199]. Interestingly, individuals cannot be re-infected by HAV since the presence of a single HAV serotype results in the neutralization of IgG production against HAV, elicited upon vaccination or even natural infection [200].

On the other hand, HAV infections can range in associated severity from asymptomatic to fulminant hepatitis-mediated deaths [201,202]. However, HAV commonly causes self-limiting infections that do not lead to chronic liver disease [200,203]. Moreover, clinical manifestations can increase with age, manifested by jaundice, and unusually high serum aminotransferase levels as the common symptoms, which are exhibited by over 70% of infected adult patients [201,204]. Furthermore, the incubation period of HAV lasts for ~15–50 days, with an average of 28 days [205]. A wide range of symptoms occur upon HAV infection, including gastroenteritis, malaise, fever, nausea, anorexia, jaundice, dark urine (genitourinary symptom), and abdominal discomfort [206]. Fulminant hepatitis is considered as a rare complication associated with HAV infections that occurs in less than 1% of infected patients, wherein the highest incidence rates occur in young children and the elderly with reported underlying liver illnesses [205,207]. Nucleotide substitutions at the 5′ UTR, P2, and P3 regions of the HAV genome were found to be associated with this fulminant disease [207,208].

HAV is mainly transmitted via the fecal-oral route, as well as through personal contact and exposure to contaminated water/food supplies, whereas transmission routes of the other typically hepatitis-causing viruses, in particular hepatitis B and C, involve contaminated blood or other body fluids via injection, intimate contact, or perinatal period vertical transmission [209]. Remarkably, waterborne HAV outbreaks are uncommon in developed countries owing to proper sanitation procedures, as well as water supply facilities [210]. On the other hand, HAV was found to be of high stability and abundance in the surrounding water environments (Table 4) for long periods, whenever associated with organic matter [207,211]. For instance, HAV was detected to be infectious after more than one year of storage at 4 °C in bottled water, with <1 log reduction owing to

concentrations of the added proteins [211,212]. Moreover, HAV shows significant resistance to surprisingly low pH, since it was reported that infectivity remains after treatment at pH 1 for up to 5 h at room temperature, and for 1.5 h at 38 °C and a pH 3 for up to 21 days at 4 °C [213,214]. The environmental stability of HAV, displayed by its low pH as well as heat resistance (60 °C for 1 h), could be due to the inherent molecular stability of the HAV capsid, concurrent with its particular codon usage, along with the unique folding pattern of the VP2 protein [190,215,216]. Moreover, HAV was detected in rivers (1.19–76%), recreational water (0–13.95%), raw sewage water (1.75–100%), and treated effluents (0–64.7%), as shown in Table 2. In addition, HAV was detected at potentially high concentrations, up to 6.0×10^6 GC/L, in treated effluents and, at 2.7×10^6 GC/L, in raw sewage water in Tunisia.

Ingestion of HAV-contaminated food accounts for 2–7% of all HAV-mediated outbreaks worldwide [217]. Epidemiological investigations provide a potential solution since they have succeeded previously in identifying the source of contamination. For example, a large and persistent food-borne mediated multi-state HAV outbreak occurred in Europe, from 2013 to 2014, which was determined to be due to the ingestion of HAV-contaminated frozen berries. This led to over 1589 cases and 2 deaths [218,219]. Moreover, bivalve molluscan shellfish was reported to have significant HAV levels, showing various prevalence spatially and temporally [220–222]. For example, the prevalence of HAV severely declined over the years from 40% to <8%, according to the 20 year-systematic survey conducted on bivalve molluscan shellfish from three estuaries in Spain [220], accompanied by a reduction in HAV cases. However, the reduction in cases could be due to the increasing availability of the HA vaccine, alongside increased surveillance that can rapidly identify contaminated food [217,223].

3.5. Astrovirus

Human astroviruses (HAstV) are members of the family Astroviridae, genus Mamastrovirus. They are non-enveloped icosahedral viruses, with a linear positive sense, single-stranded, RNA genome ranging from 6.4–7.9 kb [238]. The genome consists of three ORFs, comprising of ORF1a, ORF1b, and ORF2, which are flanked by 5′ and 3′ UTRs (85 and 83 nts, respectively) and a 3′ poly-A tail (Figure 3). ORF1a and ORF1b encode two functional polyproteins (nsp1a and nsp1ab), encompassing a serine protease and a RNA-dependent RNA-polymerase (RdRp). ORF2 encodes the capsid proteins precursor, translated from a sub-genomic RNA (sgRNA), and comprises of two principal domains: the highly conserved amino (N)-terminus and the hypervariable carboxy (C)-terminus [239,240]. In addition, the viral genome encodes genomic linked protein (VPg) that plays a major role in viral infectivity (notably the TEEEY-like tract), the replication of the virus genome, and protein synthesis [241,242].

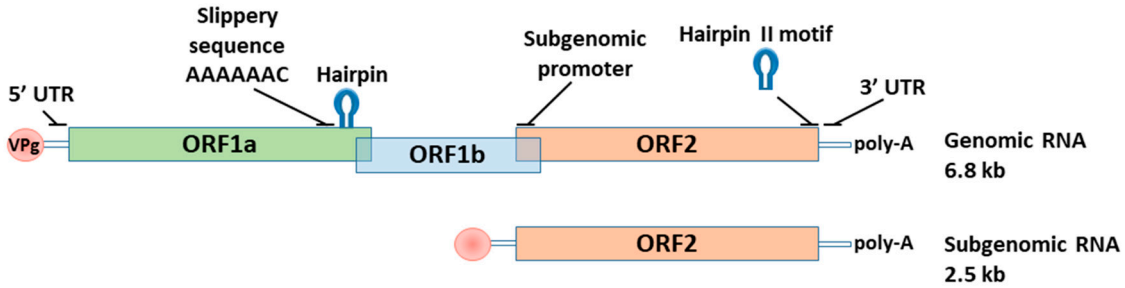

Figure 3. Genome structure of astrovirus. The hepanucleotide slippery sequence and the RNA hairpin structure acts as the frameshifting signal that produces ORF1b translation. ORF2 is a subset of sgRNA produced during virus replication.

HAstV was commonly associated with the incidence of acute gastroenteritis in young children, immunocompromised individuals, and the elderly. HAstV is responsible for sporadic non-bacterial diarrheal cases, representing up to 20% and 0.5–15% of related

outbreaks [243–245]. HAstV is considered the second or third major cause of infantile gastroenteritis after rota- and calciviruses [246]. Nonetheless, regional studies demonstrate a significantly different relative prevalence of HAstV in water resources (Table 5) and clinical settings. For instance, in particular developing countries, 30% of all diarrheal cases were due to HAstV infection [94,247]. Moreover, HAstV was detected in rivers (8.3–100%), seawater (4–11%), raw sewage water (40.2–100%), and treated effluents (0–84%), as displayed in Table 2. Moreover, HAstV was detected at the highest concentration estimated, 4.3 × 10^7 GC/L, in raw sewage water in Uruguay in comparison to other countries.

Gastroenteritis caused by HAstV is characterized by symptoms involving 2–3 day-watery diarrhea, vomiting, abdominal pain, malaise, and headache [248]. The incubation period is somewhat longer than gastroenteritis caused by other types of virus at an average of 4.5 days [96,249]. HAstV encompasses eight genotypes, HAstV-1 to HAstV-8 [250], while HAstV-1 is the most common genotype identified in both wastewater and stools [251].

Table 4. HAV abundance in water environments and prevalent genogroups.

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Genotypes-Subgenotype	Assessment Tools	Reference
Bahrain	Raw sewage water	12.5%	January–February and May–June	-	-	RT-PCR	[224]
	Tertiary treated effluents	0%					
	Bay downstream water (effluent discharge)	0%					
Egypt	Irrigation water	34.4%	September–December 2017	1.2 × 10^4 GC/L [a]	-	One-step RT-PCR and Real-Time PCR	[74]
	Raw sewage water	97.4%	2014	-	IB	RT-PCR, cell culture and direct sequencing	[225]
	Treated effluents	47%					
Tunisia	Raw sewage water	66.9%	December 2009–December 2010	2.7 × 10^3 GC/mL	IA [‡] and IB-	One-step real-time RT-qPCR, semi nested RT-PCR and sequencing	[226]
	Treated effluents	40.7%		6.0 × 10^3 GC/mL			
	Raw sewage water	68.3%	2007–2008	3.5 × 10^5 GC/L [a]	IA [‡] and IB	RT-PCR, nested RT-PCR, sequencing, qPCR	[227]
	Treated effluents	64.7%		2.5 × 10^5 GC/L [a]			
Uruguay	Surface water (rivers and logoon)	13.95%	2009–2012	3.7 × 10^3 GC/L	-	qualitative PCR and TaqMan-based qPCR	[228]
	Drinking water	0%		-			
	Raw sewage water	2.3%					
	Treated effluents	0%					
South Africa	Surface water (Rivers and dams)	76%	August 2010–December 2011 [ϒ], and January 2012–August 2012 [¥]	-	IB	One-step RT-qPCR, nested PCR, amplicon cloning and sequencing	[229]
	Treated effluents	37%					
	Irrigation water	73%	January, March and May 2013	2.37 × 10^5 GC/L [b]	V	real-time RT-PCR, molecular cloning and sequencing	[230]

Table 4. *Cont.*

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Genotypes-Subgenotype	Assessment Tools	Reference
Pakistan	Surface and subsurface water	12.63%	June 2014–May 2015	-	-	RT-PCR	[231]
USA	Well water	60%	September 1995–December 1995	-	1A	IC (immunocapture)-RT-PCR and amplicon sequencing	[232]
Brazil	River water	1.19%	2012–2014	1.5×10^4 GC/L	-	RT-TaqMan probe-mediated qPCR and ICC-RT-qPCR	[233]
	Recreational water (Lagoons and beaches)	0%	March 2015–July 2016	-	-	RT-PCR	[83]
Italy	Raw sewage water	28.16%	2015–2018	-	IA ‡ and IB	RT-nested-PCR and amplicon sequencing	[199]
	Coastal discharge water	3.97%					
	Seawater	12.8%					
	Raw sewage water	33.3%	January–December 2013	-	IA and IB ‡	nested RT-PCR and sequencing	[234]
	Treated effluents	14.3%			IA ‡ and IB		
	River water	7.4%			IB		
Spain	Raw sewage water	1.75%	2019	-	-	Real-time RT-PCR	[235]
	Tertiary-treated effluent	0.35%					
Hong Kong	Seawater §	57.14%	2011	1.028×10^3 particle/L [b]	IB	RT-PCR, amplicon cloning, sequencing and TaqMan real-time PCR	[236]
Canada	Drinking water	10%	1974–2001	-	-	◊	[237]
France	Raw sewage water	59.3%	October 2014–October 2015	-	IIIA and IA	RT-PCR and sanger sequencing	[23]
	Treated effluents	19.2%			-		
Sweden	Raw sewage water	100%	January–May 2013	1.4×10^4 virus/L [b]	-	Two-step real-time RT-qPCR	[92]

[a]: mean HAV concentration, [b]: maximum HAV concentration. ϒ: for surface water samples, ¥: for WWTP outflow water, ‡: dominant genotype, §: sewage polluted sea water, ◊: outbreaks data summary, GC: genome copy, (-): not defined.

Table 5. Prevalence of waterborne astroviruses, predominant genogroups, and assessment tools.

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Genogroups-Genotypes	Assessment Tools	Reference
Egypt	Raw sewage water	40.2%	April 2017–March 2018	-	A and B	Semi-nested RT-PCR	[171]
	River	8.3% *–25% **					
	Urban sewage water	58.3%	October 2017–September 2018	-	B ‡ and A	Semi-nested RT-PCR	[172]
	Treated effluent	33.3%			A and B		

Table 5. *Cont.*

Country	Water Source	Frequency (% Positive)	Study Period	Concentration	Genogroups-Genotypes	Assessment Tools	Reference
Japan	Raw Sewage water	91.67%	July 2015–June 2016	-	A(1), MLB1 ‡ and MLB2	RT-PCR and sequencing	[252]
Kenya	Raw sewage water	98% [d]	April 2015–April 2016	30.8 ∫	-	Real-time RT-PCR	[253]
	Urban river	60% [b]	May 2007–February 2008	-	-	Qualitative singleplex real-time RT-PCR	[254]
	Rural river	41.7%					
	Urban sewage water	87.5% [b]					
Uruguay	Raw sewage water	45%	March 2011–February 2012	4.3×10^7 GC/L [a]	-	Qualitative RT-PCR and qPCR	[255]
South Africa	River water	21.6%	June 1997–May 1998	-	-	Cell culture, RT-PCR, dot-blot Hybridisation assay	[256]
	Dam water	5.9%					
Nepal	Ground water	8.1%	August 2009–May 2011	-	A(1,2,4,5 and 8) ‡ and MLB	RT- semi-nested PCR and Next-generation amplicon sequencing	[257]
	River water	100%			A, B, MLB and VA		
USA	Raw sewage water	75% [b]	August 2011 and July 2012	-	A ‡, B, MLB and VA	RT- semi-nested PCR and Next-generation amplicon sequencing	[257]
	Treated effluent	63% [b]					
Brazil	Surface water (basins)	15.4% [b]	August 2004–June 2005	-	A(1)	RT-PCR, nested PCR and amplicon sequencing	[258]
Italy	Seawater (receiving treated water)	9%	February 2019–August 2020	1×10^2 GC/L	A(1)	Real-time (RT) qPCR, OneStep RT-PCR, nested or semi-nested PCR and sequencing	[259]
	Seawater (receiving non-treated water)	7%					
	Seawater (receiving rain drain and raw water)	4%					
	Seawater receiving mixed waters	11%					
UK	Water supplies	1%	1992–2003	-	-	‡	[260]
China	Sewage treatment plant water	6.3%	November 2006–October 2007	-	-	RT-nested PCR	[261]
Canada	River upstream	42% [b]	June 2012–May 2013	2.52 Log_{10} GE § copies/L [a]	-	Two-step RT-qPCR	[89]
	River downstream	92% [b]		4.1 Log_{10} GE § copies/L [a]			
France	River water	36%	May 2013–May 2014	10^3 GC/L [a]	-	Real-time RT-qPCR	[262]
	Tributaries water	16%		10^3 GC/L [a]			
	Treated effluents	84%		10^4 GC/L [a]			
Sweden	Raw sewage water	100%	November–December 2015	1.1×10^6 GC/mL [a]	A(4)	RT-nested PCR, Library construction, NGS sequencing and qPCR	[91]
	Conventionally treated effluents	33.3%		1.8×10^2 GC/mL			
	Ozone treated effluents	0%		-			
	Raw sewage water	100%	January–May 2013	4.6×10^5 virus/L [c]	-	Two-step real-time RT-qPCR	[92]

[a]: maximum astrovirus concentration, [b]: maximum astrovirus detection frequency, [c]: mean astrovirus concentration, [d]: mean astrovirus frequency, GC: genome copy. *: before mixing with wastewater **: after mixing with wastewater, §: genome equivalent, ‡: dominant genogroup/genotype, ∫: average quantification cycle (Cq), where low Cq values reflects high virus concentrations and vice versa, ‡: review study of epidemiological and microbiological characteristics of 89 waterborne infectious intestinal outbreaks affecting England and Wales, (-): not defined.

4. Public Exposure to Municipal Wastewater

People are exposed to wastewater by various means (recreational activities, food production, and agriculture). However, the infection risk due to waterborne enteric viruses is dependent on the infectious enteric viruses' prevalence or their infectivity in various water environments that humans interact with (Table 6). For instance, infection risk due to HAdV in drinking water accounted for 10^{-4}/year for each person, which was quite similar to astrovirus infection risk detected earlier in surface water in Mexico [87,263]. Moreover, HAdV and EV were found to be of the highest infectivity rate in secondary treated water and even in post-disinfection final effluent confirmed by cytopathic effect detection. However, a lower infectivity rate of HAdV and EV was detected in raw sewage (64%) and dam water (~65%), respectively (Table 6). Furthermore, infection risk was more reduced in surface water (10,000x/180 days and 10,000x/30 days) than in ground water (1000x/'213 days and 10x/30 days) in the case of RV and AstV, respectively. The main exposure routes frequently include recreational activities and surface water drinking. Moreover, shellfish production is regarded as an indirect route of exposure, since molluscs are filter feeders and, consequently, contaminated water pathogens become concentrated and lead to consumer infection [264,265]. Moreover, enteric viruses were detected using nested PCR for entero-, norwalk-like, and hepatitis A viruses and real-time PCR for adenovirus in 50% to 60% of the total mussel samples (18) obtained from a bioremediation mussel farm [266]. Notably, non-enveloped viruses, such as noroviruses and the hepatitis A virus, can survive in the bivalves' tissues and are highly resilient to degradation [267,268]. Moreover, virus particle size was found to determine whether the particle is degradation resistant or susceptible [265]. For example, <200 nm VLPs are typically of higher degradation resistance when compared to bacteria [269]. Human infectious diseases owing to consumption of contaminated filter-feeders and recreational activities in wastewater-polluted coastal waters account for USD 12 billion annually [270]. Moreover, wastewater-mediated irrigation, in particular sprinkler irrigation, generates aerosols that can cause infection upon direct exposure or ingestion of irrigated crops [271]. It is important to note that the RNA of the pandemic SARS-CoV-2 was detected in treated wastewater, representing a critical issue for usage in irrigation [272]. Therefore, SARS-CoV-2 RNA was investigated in various water resources for their incidence frequency (Figure 4) and prevalence using different genes (e.g., RdRP, S, N1, N2, N3, ORF1ab, and E) as genetic tracers [273–285]. However, the highest SARS-CoV-2 detection specificity was obtained when RdRP was applied in RT-qPCR and compared to other SARS-CoV-2 genes [286]. Furthermore, detection of SARS-CoV-2 RNA in treated wastewater is not usually associated with SARS-CoV-2 infection risk, as reported in treated sewage of nine WWTPs in Germany [286]. This could be owing to the significantly higher persistence of SARS-CoV-2 RNA than infectious SARS-CoV-2 in water environments. Moreover, the persistence of infectious SARS-CoV-2 in water environments is reliant on many factors, such as water source, temperature, and the initial virus titer. For instance, a T90 of infectious SARS-CoV-2 at room temperature was found 1.7 and 1.5 days in tap water and wastewater, respectively, that extended to 7 days when a higher initial titer (10^5 TCID50/mL) was applied [26]. By comparison, the T90 values declined in wastewater to a total of 15 min and 2 min at 50 and 70 °C, respectively [26]. Toilet flushing and groundwater production render other routes of direct exposure to wastewater [100,287].

Table 6. Infectivity of enteric viruses in different water resources.

Water Source	Virus	Genotype	Infectivity Rate	Number of Samples	Infection Risk (IR) ◊			Detection Method	Reference
					IR/person	Infection Risk Reduction			
						Period (days)	RA (Log_{10} or fold)		
Recreational water	HAdV	C	1 IVP/90% of sites *	159 (144 [9 sites] and 15 [3 sites])		-		Integrated cell culture-qPCR assay	[83]
Raw sewage water	HAV	IIIA and IA	64.3% (9/14) **	14		-		Cell culture	[23]
Treated effluents			100% (1/1) **	1					
Drinking water (40 mJ/cm^2 UV-treated)	HAdV	F(40, 41)	1/1700 (5.88×10^{-4}) ***	35	10^{-4}/year §	-	5 ¥	Integrated cell culture PCR	[87]
Drinking water (73 mJ/cm^2 UV-treated)							6.5 ¥		
Groundwater	RV	-	-	35	-	90	100 ¥	Immunoperoxidase focus infectious assay	[263]
						150	1000 ¥		
						~213			
Surface water				35		30	40 ¥		
						150	1500 ¥		
						180	10,000 ¥		
Ground water	AstV	-	-	20	-	30	10 ¥		
					2.0×10^{-3} ‡	60–120	2000 ¥		
Surface water				5	10^{-4} ‡	30	10,000 ¥		
Pre-DIS influent	HAdV and EV	-	100% †	30	-	-	-	Cell culture	[288]
Post-DIS influent							4.2 ¥,a		
Raw sewage water	HAdV	F	64% (32/50) **	50	-	-	-	Cell culture	[289]
Dam water	EV		64.6% (31/48)–66.7% (44/66) **	114 (48 samples at Jan.–Dec. 2012 and 66 samples at Oct. 2013–Oct. 2015)	-	-	-	Cytopathic effect detection and Direct immunofluorescence assay	[290]

HAdV: human adenovirus, RV: rotavirus, AstV: astrovirus, EV: enterovirus, ◊: infection risk (IR), including two parameters: infection risk per person and infection risk reduction. Infection risk per person refers to the probability of infection occurrence for each person exposed to various water sources, whereas, infection risk reduction refers to the amount of risk reduction (RA) in case of water treatment (e.g., via disinfection or UV-treatment) or in case of being exposed for a period of time (represented in days) to different water environments. ¥: Log_{10} reduction ¥: x fold reduction, a: average reduction, IVP: infectious virus particle, Pre-DIS: pre-disinfection (after secondary biological treatment), Post-DIS: post disinfection (final effluent), *: minimum infectivity rate (i.e., minimum number of infectious virus particles/site), **: % of samples that showed cytopathic effect (i.e., detection frequency of infectious virus particles), ***: average count of infectious virus particles out of total virus particles enumerated by qPCR and MPN PCR, §: in all four-treatment scenarios, ‡: residual infectivity (x of the original virus titer), †: defined by cytopathic effect detection, (-): not defined.

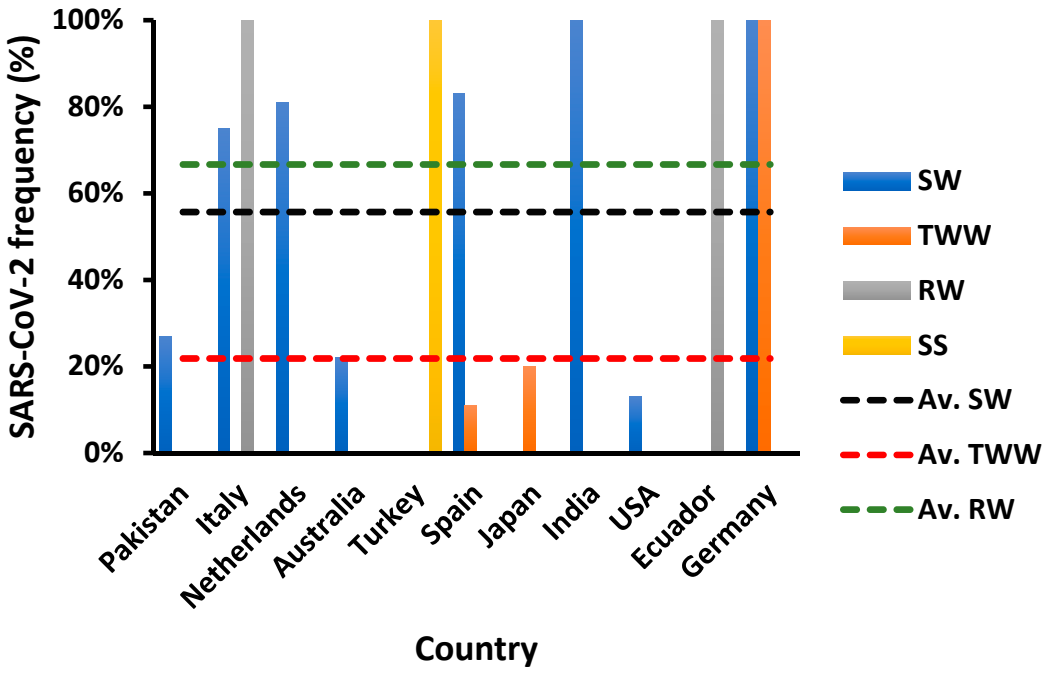

Figure 4. Frequency of SARS-CoV-2 RNA in various water environments [274,276–278,281–286,291]. SW: sewage water, TWW: Treated wastewater, RW: River water, SS: Wastewater sludge samples, Av.: Average frequency, for example, Av. SW: Average frequency of SARS-CoV-2 RNA in SW of countries that involved SW in their evaluation.

5. Discharge of Wastewater

Wastewater is commonly discharged into surface water resources. In addition to the public health concerns, fecal contamination of wastewater can negatively influence water environments essential for fishing, drinking water, and recreation. Enteric viruses are considered the main cause of waterborne illnesses associated with recreational water, including pools, spas, rivers, etc., and can reach waters via the accidental release of feces or body fluids [292]. Moreover, a surge in non-enteric diseases was reported to arise from wastewater contaminated with significant viral contamination [24,25]. Wastewater treatment (WWT) performance guidelines were established for reclamation and reuse (Table 7). These guidelines are concerned with microorganism levels and the degree of treatment, whereas receiving waters risk management mainly depends on fecal indicator bacteria monitoring [293]. Unfortunately, these bacterial indicators cannot meet the full criteria of the ideal water quality indicators [294]. On the other hand, excreted enteric viruses can be detected in wastewater, but a wastewater treatment plant (WWTP) may not completely eliminate viruses in terms of their concentration and infectivity, thus demonstrating a continued water-related health risk [295]. Furthermore, enteric virus presence in water does not necessarily link to the bacterial indicators' detection as *Escherichia coli* and coliforms [296]. Additionally, bacteriophage survival in water is more similar to human enteric viruses than the presently used bacterial indicators [293]. For instance, cross-assembly phage is currently implemented alongside pepper mild mottle virus (PMMoV) as the microbial source tracks markers simultaneously in this toolbox approach. This is owing to their inclusive distribution, associated with ever higher densities in sewage, than other detected viruses and the fact they follow a similar pattern to enteric viruses prevalence in different water bodies. Consequently, they are efficient as indicators of virus-mediated fecal pollution in lakes, rivers, and recreational waters [297–301]. Thus, traceability procedures provide a mandate to determine fecal contamination sources so that the risk can be assessed to initiate a proper water management to counteract it at its source.

Table 7. Microbial guidelines for wastewater reuse.

Usage	Guideline Category	Allowed Limit	Average Limit	Reference
Irrigation (unrestricted)	Enteric viruses	<2 Virus/50 L	-	[302]
Toilet flushing, primary contact recreation, food aquaculture and car wash	Total coliform	<10 cfu/100 mL	-	[303]
Irrigation (unrestricted)	Total coliform	<10 cfu/100 mL	-	[304]
Gardens with access, ponds parks, crops and secondary contact recreation	Total coliform	<100 cfu/100 mL	-	[305]
Gardens and parks with no public access during irrigation and passive recreation	Total coliform	<1000 cfu/100 mL	-	
Non-food crops, Pasture and fodder irrigation	Total coliform	<10,000 cfu/100 mL	-	
Food crops	Total coliform	<23 cfu/100 mL	2.2 cfu/100 mL	[304]
Non-food crops	Total coliform	<240 cfu/100 mL	23 cfu/100 mL	
Recreational reuse (unrestricted)	Total coliform	<240 cfu/100 mL	23 cfu/100 mL	
Irrigation (unrestricted)	Fecal coliform	<1000 cfu/100 mL	-	[305]
Food crops	Fecal coliform	<400 cfu/100 mL	200 cfu/100 mL	[304]
Non-food crops	Fecal coliform	<400 cfu/100 mL	200 cfu/100 mL	
Recreational reuse (unrestricted)	Fecal coliform	<23 cfu/100 mL	2.2 cfu/100 mL	
Irrigation (unrestricted)	Fecal coliform	<1 cfu/100 mL	-	[302]
Irrigation (unrestricted)	Nematode egg	<2 egg/L	-	[305]
Irrigation (unrestricted)	(Oo)cysts	<1 cyst/50 L	-	[302]

(-): not applicable.

6. Reuse of Treated Water

The reusing of wastewater is determined by economic factors as it is often either used for the recirculation of organic matter, to act as natural fertilizers, or due to a shortage of water resources [27,28]. For instance, wastewater and greywater (households' wastewater with no fecal contamination) were used for irrigation of agricultural products, as well as indoor activities involving toilet flushing and even for potable use [17–21]. However, intensive treatment measures are required to meet the suggested wastewater reuse guidelines and, in particular, for greywater in which significant coliform loads may exist. However, the performance of treatment procedures relying on coliform elimination may be biased and exaggerated owing to the capability of these bacteria to multiply within the greywater system.

Wastewater reuse is currently a frequent practice in many countries. For example, treated wastewater is utilized in agriculture and landscaping in many countries, including Egypt, Saudi Arabia, Italy, Cyprus, Malta, Spain, and the USA [306–310]. It is, for instance, used in Egypt for the irrigation of sandy soils to raise the organic matter content of soil and improve the capacity of cation exchange [311]. In Saudi Arabia in 2010, 25% of treated wastewater was used to irrigate landscapes in the public parks of a number of cities [312]. In the Netherlands, particularly in Amsterdam, wastewater is regarded as a rich resource of organic matter, including alginic acid, cellulose, bioplastic, biogas, and phosphorus obtainment, that can be recovered and reused [313]. Moreover, wastewater reuse has converted Singapore into a universal hydro-hub via the implementation of novel water technologies that allowed the nation to meet 30% of its water demands, a number that is

set to increase to 55% by 2060 [314]. Wastewater reuse usually demands higher standards of treatment, since it may well contain higher pathogen content than greywater [315]. Greywater reuse is, therefore, much easier when separated from wastewater [316]. However, water contamination is possible in all pathways to an extent that necessitates adequate safety measures prior to the establishment of new systems. In this regard, Singapore has approved a potential multi-phase approach to water reuse, involving primary sedimentation, followed by activated sludge and microfiltration, and then ultrafiltration, reverse osmosis and, eventually, disinfection by ultraviolet radiation exposure [314]. This approach can also be highly beneficial to eliminate or significantly reduce public health risks associated with the reuse of various wastewater streams. However, the targets should be well defined and technical solutions and proper assessment tools should be made available to ensure that it meets the recommended guidelines of safe water reuse.

Technical solutions for reuse of treated water includes: (i) the employment of innovative tools and technologies, such as the replacement of old equipment used for water treatment with new technologies, including membrane bioreactor (MBR)-based treatment [317,318], (ii) the establishment of an evaluation approach for determining water cost, that is energetic and equivalence-dependent, alongside treatment strategies [319], and (iii) solving the gap between water supply and water demand via desalination methodologies [320,321], control of runoff water [322], wastewater reuse [323], and cloud seeding [324]. However, the technical solution selection mandates the inclusion of a short costs analysis that depends on the nature of water reuse projects being chargeable or not [325]. For instance, regenerated water use for industrial purposes or course irrigation in the private sector required investment costs that reached AUD >3/m^3 in Australia [326] and up to EUR 736/m^3 produced/day in Spain, with an additional EUR 0.06/m^3 to EUR 0.45/m^3 for operational costs that varied according to the regenerated water uses and the required treatment [327]. On the contrary, regenerated water for water resources restoration and maintenance, the recharging of aquifers, or reduction of treated effluent discharge into essential water bodies is not chargeable [325,328]. Technical solutions for water reuse should be assessed for, in particular, viral load reduction efficacy to avoid any associated health concerns due to direct exposure. The MBR treatment process was found to be of higher efficiency, in terms of both bacterial and virus removals, than the activated sludge process, which results in up to 2 $\log_{10}$ bacterial load reduction and lacks virus removal capability [329]. For example, adenoviruses and enteroviruses, and even infectious enteroviruses, were 3.7, 1.7, and 2$\log_{10}$ reduced, respectively, following MBR-based treatment in Saudi Arabia [318].

Nevertheless, such efforts for the reuse of treated water, alongside the offered technical solutions, were opposed by serious limitations raised against irrigation using treated water. The alteration of the texture properties and physicochemical parameters of soil, due to agricultural reuse, led to changed microbiota and biomass [29]. Moreover, probable modifications of soil microbiota could influence soil fertility and subsequent productivity [21]. In addition, organic matter mineralization [330] and nutrients and metals availability [331,332] were affected by altered soil pH caused by irrigation with WWTP effluents. Therefore, reuse of insufficiently treated wastewater, or even raw water, could serve as alternative sources for irrigation, avoiding these risk factors [29]. However, other risk factors may emerge from the high burden of enteric pathogens. The norovirus disease burden due to the consumption of lettuce irrigated with untreated greywater was assessed by QMRA model and revealed an annual disease burden fluctuation above the range of 2×10^{-8} and 5×10^{-4} [333].

On the other hand, wastewater reuse is commonly practiced for potable purposes owing to the incidental presence of treated wastewater in a water supply source, termed de facto wastewater reuse. Upstream WWTP discharge was reported by the EPA as influencing drinking water treatment plants (DWTPs), which included 2–16% of upstream wastewater discharges [334]. For instance, DWTPs, containing 50% upstream WWTP discharges, were used to serve over 10^4 U.S. people, as reported in [335]. However, extensive risk assessment

studies were concerned with the associated risks due to de facto reuse [30,336,337] and an annual risk of >1 infection/10^5 people was recorded [338]. Moreover, the median norovirus risk per year was the highest in the case of de facto reuse, when compared to other treatment scenarios, to such an extent that de facto reuse scenarios exceeded risk benchmarks (10^{-o}). Alarmingly, 1% wastewater effluent was predicted to potentially surge drinking water risks if contributed to the source water [30]. De facto reuse is still applicable globally and de facto reuse is expected to increase in the future due to an increased frequency of water supplies shortages and droughts [339].

The Water Safety Plan (WSP) is receiving increasing attention as a recommended risk management approach for water reuse. The establishment of the WSP approach organized drinking-water-related management practices and assured the applicability of these practices to drinking-water quality management. A WSP encompasses, at least, a system assessment and effective operational monitoring and management to ensure drinking-water safety. Moreover, a WSP integrates various principles of other risk management approaches including, of a particular interest, the multiple-barrier approach and HACCP [340]. HACCP development presented an earlier framework for the improvement of drinking water treatment processes to minimize the probability of waterborne disease incidence [341]. Moreover, repairing and maintaining the drinking water distribution network was highlighted as a means of preventing drinking water contamination. In this regard, the necessity of HACCP implementation was reported in terms of avoiding microbial contamination incidence in drinking water treatment lines [342].

7. Conclusions

The high persistence of enteric viruses in various water environments enabled their detection in almost all water sources with a significantly higher frequency. However, detection frequency of enteric viruses could vary according to the virus type, geographical location, water source, and the assigned period for sampling, irrelevant to virus concentration. Second, virus detection is not usually associated with virus infectivity, wherein the presence of infectious virus particles indicate infectivity and the resultant infection risk. Moreover, infection risk relies on detection specificity since the virus origin, whether of human origin or not, could determine the course of infection. For example, the RDRP gene of SARS-CoV-2 was found to be of higher specificity than other genes. On the other hand, exposure to wastewater discharge should be monitored and controlled for probable health issues. Consequently, a toolbox approach, implementing both pepper mild mottle virus and cross-assembly phage together, was highly encouraged for the traceability of any possible fecal pollution. Moreover, MBR-based treatment for wastewater reuse was much more efficient in both bacterial and viral burden reduction than activated sludge, which cannot achieve virus removal. A WSP could likewise help in the quality management of de facto wastewater reuse through the employment of HACCP throughout the wastewater treatment strategies. This review article provided the information necessary for decision making in terms of determining the most probable viral etiologies as well as evaluating the resultant risks associated with direct or indirect exposure to both discharged or reused wastewater.

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