Contribution to risk profile on foodborne viruses

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March 3, 2020

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Abstract

Foodborne viruses have been recognized as the highest ranked food safety priority in a recent report by risk assessment experts. Human norovirus (NoV) and hepatitis A virus (HAV), which cause acute gastroenteritis and viral jaundice, respectively, are the predominant pathogenic foodborne viruses with hepatitis E virus (HEV) being a minor contributor to foodborne outbreaks. NoV are responsible for an estimated one third of all global foodborne gastroenteritis cases, making it the lead cause of foodborne illnesses. HAV is endemic in geographical areas with poor hygiene and sanitation infrastructure, and causes 2% of foodborne illnesses worldwide.

The Danish Veterinary and Food Authority is currently developing a risk profile for foodborne viruses and product combinations that have most frequently given rise to disease among consumers. The present report is a contribution to this risk profile and reviews the current knowledge about the biology and occurrence of relevant foodborne viruses, contamination pathways, products at risk and the efficacy of prevention and mitigation methods. The objective of the report is also to identify gaps in our knowledge pointing to research needs for the development of better risk assessments and more targeted control in food production and processing.

Foodborne virus are excreted in high titres in faeces of infected people, and due to their low infectious dose and high environmental persistence, transmission occurs via ingestion of contaminated food and water as well as through direct person-to-person contact. Common contamination routes for food are via infected food handlers and/or exposure to contaminated water and materials during primary production of bivalve shellfish, lettuce, fresh or frozen fruits and vegetables, and products of pork and wild boar meat.

Food safety experts agree that efficient surveillance and virus control measures are required throughout the food production chain from “farm to fork”, i.e., at the sites of primary production, processing, and food preparation in retail or commercial kitchens. However, our understanding of the utility of these controls and how to properly validate their effects is still lacking. For example, we lack insights in the impact of personal hygiene and sanitation practices within food companies, knowledge about the effect of food processing on viral inactivation and accurate methods to distinguish between infective and inactive viruses.

Resumé

Fødevarebårne virus er anerkendt som værende den højest rangerende fødevaresikkerhedsmæssige udfordring i en ny rapport fra eksperter i risikovurdering. Human norovirus (NoV) og hepatitis A virus (HAV), som resulterer i henholdsvis gastroenteritis og viral gulsot, er de mest almindelige patogene fødevarebårne virus, med hepatitis E virus (HEV) som ansvarlig for en mindre andel af fødevarebårne udbrud. NoV er årsagen til cirka en tredjedel af alle globale fødevare-relaterede tilfælde af gastroenteritis, og er dermed den mest almindelige årsag til sygdom forårsaget af fødevarer. HAV findes endemisk i geografiske områder med ringe infrastruktur inden for hygiejne og sanitet og kan på verdensplan tilskrives ca. 2% af fødevarebårne sygdomme.

Fødevarestyrelsen er ved at udarbejde en risikoprofil for de forskellige fødevarebårne virus og produkt kombinationer, som oftest giver anledning til sygdom hos forbrugeren. Denne rapport er et bidrag til denne risikoprofil og gennemgår vores nuværende viden om biologi og forekomst for relevante fødevare-relaterede virus, smitteveje, udsatte produkter og effekten af forebyggende og kontrol metoder. Formålet med denne rapport er også at identificere mangler i vores viden og pege på behov for forskning til at skabe et bedre grundlag for risikovurderinger og målrettede kontrolindsatser i fødevareproduktionen.

Fødevarebårne virus udskilles i et højt antal i fæces fra inficerede individer. Grundet deres lave infektiøse dosis og overlevelse i miljøet foregår smitten ofte ved indtag af forurenet fødevarer og vand så vel som ved direkte overførsel mellem personer. Kendte smitteveje kan relateres til inficerede medarbejdere i fødevarevirksomheder og/eller eksponering til forurenet vand og råvarer i den primære produktion af skaldyr, salat, frisk og frossen frugt og grøntsager, samt svine- og vildtsvinekød.

Eksperter i fødevaresikkerhed er enige om, at effektiv overvågning og metoder til kontrol af virus er nødvendige igennem hele produktionskæden fra ”jord til bord”, inklusiv hos primærproducenterne, i fødevareindustrien, og ved produktion af spiseklare produkter eller måltider i detailledet eller kommercielle køkkener. Vi mangler dog viden om effekten af disse kontroller, og hvordan de kan valideres. For eksempel, så kendes effekten af personlig hygiejne og industrielle rengøringsprotokoller ikke, lige som vores viden om effekten af konserveringsmetoder er mangelfuld. Til slut skal det nævnes, at vi for mange virus (fx NoV) mangler robuste metoder til at skelne mellem aktive (infektiøse) og inaktive virus.

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0. Background and objectives

Illnesses associated with foodborne viruses remain the cause of the majority of foodborne outbreaks. This clearly indicates that we lack proper controls and mitigation strategies. The lack of good detection methods also means that the actual number of virally implicated cases of foodborne illness may be underestimated. Propagation of viruses requires a host, i.e., in this case a human (or mammalian) host. Viruses are inactive outside their hosts and the risk of transmission through contaminated food, water or persons depends on the ability of the viruses to remain infective. The root cause of foodborne outbreaks of viral disease is therefore events where contaminated food and water have become the passive carriers of infectious virus particles from one host to the next.

The Danish Veterinary and Food Authority is currently developing a risk profile for foodborne viruses and product combinations that have most frequently given rise to disease among consumers. The present report is a contribution to this risk profile and reviews the current knowledge about the biology and occurrence of relevant foodborne viruses, contamination pathways, products at risk and the efficacy of prevention and mitigation methods. The objective of the report is also to identify gaps in our knowledge pointing to research needs for the development of better risk assessments and more targeted control in food production and processing.

1. Biology and epidemiology of foodborne viruses

Viruses are obligate intracellular parasites that require susceptible host cells for propagation and host infection. The structure of the extracellular infectious viral particle is simple, as it consists of a nucleic acid molecule comprised of single or double stranded DNA or RNA, covered by a protein coat (a capsid) that for some viruses are further surrounded by an envelope consisting of viral proteins and a lipid bilayer derived from membranes of the host cell. Based on their size and shape, nucleic acid composition and structure of the genome, as well as mode of replication, viruses are distributed into families, a few of which are grouped into orders (Green 2013). In practice, the viruses, which are most commonly implicated in reported viral foodborne illnesses, are human norovirus (NoV) causing gastroenteritis and hepatitis A virus (HAV) causing hepatitis. However, any virus present in the human

gastrointestinal tract is likely to be excreted in high numbers and if it is able to cause disease after ingestion then it could in theory be considered potentially foodborne and/or waterborne (Table 1) (Bosch et al. 2018). Other viral agents, less frequently reported in food and/or waterborne transmission of illnesses are rotaviruses (RV), sapoviruses (SaV), astroviruses (AsV), adenoviruses (AdV) (all causing gastroenteritis), hepatitis E virus (HEV) (causing hepatitis) and tick borne encephalitis virus (TBEV) (causing encephalitis) (Bosch et al. 2018). Extremely high numbers of viruses (10^{13} and 10^{10} virus particles, respectively, per gram of stool) may be shed in stools of patients suffering from gastroenteritis or hepatitis (Costafreda et al. 2006; Ozawa et al. 2007). The symptoms of viral gastroenteritis include nausea, vomiting and abdominal pain and occasionally fever and headache (FAO/WHO 2008a). While bacterial gastroenteritis agents are usually responsible for the most severe cases, viruses such as NoV, are responsible for the largest number of cases (Patel et al. 2009).

Table 1: Viruses documented to be found in the human gastrointestinal tract (Bosch et al. 2018).

Genus	Genome	Popular name	Disease caused
Enterovirus	ssRNA[a]	Poliovirus	Paralysis, meningitis, fever
		Coxsackie A, B virus	Herpangina, meningitis, fever, respiratory disease, hand-foot-and-mouth disease, myocarditis, heart anomalies, rush, pleurodynia, diabetes[b]
		Echovirus	Meningitis, fever, respiratory disease, rash, gastroenteritis
Hepatovirus	ssRNA	Hepatitis A virus	Hepatitis
Kobuvirus	ssRNA	Aichi virus	Gastroenteritis
Parechovirus	ssRNA	Human parechovirus	Respiratory disease, gastroenteritis, central nerve system (CNS) infection
Orthoreovirus	segmented dsRNA	Human reovirus	Unknown
Rotavirus	segmented dsRNA	Human rotavirus	Gastroenteritis
Norovirus	ssRNA	Human norovirus	Gastroenteritis
Sapovirus	ssRNA	Human sapovirus	Gastroenteritis
Hepevirus	ssRNA	Hepatitis E virus	Hepatitis
Mamastrovirus	ssRNA	Human astrovirus	Gastroenteritis, CNS infection
Flavivirus[c]	ssRNA	Tick-borne encephalitis virus	Encephalitis, meningitis
Coronavirus	ssRNA	Human coronavirus	Gastroenteritis, respiratory disease, SARS, MERS
Orthomyxovirus	segmented ssRNA	Avian influenza virus	Influenza, respiratory disease
Henipavirus	ssRNA	Nipah virus, Hendra virus	Encephalitis, respiratory disease
Parvovirus	ssDNA	Human parvovirus	Gastroenteritis
Mastadenovirus	dsDNA	Human adenovirus	Gastroenteritis, respiratory disease, conjunctivitis
Polyomavirus	dsDNA	Polyomavirus	Progressive multifocal leukoencephalopathy, diseases of urinary tract
Alphatorquevirus	ssDNA	TT (Torque Teno) virus	Unknown, hepatitis[b], respiratory disease[b] haematological disorders[b], cancer[b]

[a] The genomes consist of single stranded (ss) or double stranded (ds) DNA or RNA

[b] Uncertain whether the disease is caused by the virus.

[c] Has been found in food (milk) but not in gastrointestinal tract.

1.1. Caliciviruses: Norovirus (NoV) and Sapovirus (SaV)

1.1.1. Virus characteristics

Norovirus (NoV), previously known as 'Norwalk-like virus' or 'small-round-structured-virus', is the major cause of gastroenteritis globally and the most common cause of sporadic infectious gastroenteritis among people of all age groups (Patel et al. 2008, 2009). Moreover NoV is the most frequent cause of foodborne outbreaks of acute gastroenteritis in developed countries (Scallan et al. 2011; Van Duynhoven et al. 2005). Sapovirus (SaV) also causes acute gastroenteritis in humans but is mainly associated with sporadic gastroenteritis in young

children (Hansman, Oka, Katayama, et al. 2007; Johnsen et al. 2009; Khamrin et al. 2007; Monica et al. 2007). Compared to NoV, SaV is in general less commonly reported (Svraka et al. 2010) in foodborne gastroenteritis outbreaks (Hansman, Ishida, Yoshizumi, Miyoshi, et al. 2007; Hansman, Oka, Okamoto, et al. 2007; Hansman, Saito, Shibata, Ishizuka, et al. 2007; Johansson et al. 2005) .

NoVs and SaVs constitute two of the five closely related genera within the *Caliciviridae* family (Green 2013; Kroneman et al. 2013). They have a non-enveloped symmetrical icosahedral capsid of 27-40 nm with a single stranded positive sense RNA genome of approximately 7.6 kilobases (Green 2013; Oka et al. 2015). The NoV genome has three open reading frames (ORFs), of which the ORF1 at the 5' end of the genome encodes six non-structural proteins, including the RNA dependant RNA polymerase (RdRp), while ORF2 and ORF3 at the 3' end encode the capsid structural proteins; VP1 and the in between strains highly variable VP2, respectively (Atmar 2010; Green 2013; Seah et al. 1999). The SaV genome is organized into two ORFs, with ORF1 encoding non-structural proteins and the VP1, and ORF2 encoding VP2 (Oka et al. 2015).

Based on variation in the sequence for capsid structural proteins, the NoV genus is divided into seven genogroups (GI-GIIV) of which the GI and GII, as well as GIV although less frequent and more sporadic, are known to infect humans (Atmar 2010; Vinjé 2015). More than 30 human NoV genotypes have been reported, with an intra-genotype nucleotide diversity as high as 15% (Zheng et al. 2006). NoVs from GIII, GV and GVI-GVII infect bovine, murine and canines species, respectively, while besides humans some strains of NoV GII infect porcine species, and some strains of GIV infect feline and canine species. The SaV genus is divided into eight genogroups (GI-GVIII) of which the more than 21 genotypes within GI, GII, GIV and GV have been detected in humans (Oka et al. 2015). SaV has been detected in bats (Tse et al. 2012), dogs (Li et al. 2011), and sea lions (Li et al. 2011). No zoonotic potential has been demonstrated for the NoV and SaV genotypes infecting humans (Atmar 2010; Bank-Wolf et al. 2010; Vinjé 2015).

The diversity of NoV and SaV variants is constantly evolving with the generation of new variants as a result of random mutations in the RNA genome during viral replication, and for NoV the occurrence of inter-genotype recombination events at the junction between the

polymerase and the capsid genes (Farkas et al. 2004; Tsinda et al. 2017; Lindesmith et al. 2011). The different NoV genotypes potentially vary in their ability to cause disease and new variants or recombinants within mainly GII.4 have every 2–3 years through the past two decades been associated with epidemics due to the ability to escape herd immunity (Bull and White 2011; de Graaf et al. 2015; Karst and Baric 2015).

Except for a recently reported replication of NoV in human enteroid cells (Ettayebi et al. 2016), NoV and SaV have not yet been effectively cultivated *in vitro* (Duizer et al. 2004; Oka et al. 2015; Vinjé 2015), which prevents classification of serotypes and detection of viral infectivity or "viability" (Atmar 2010). Due to the lack of cell culture systems, proper risk assessment that requires determination of viability and genotype specification can be a challenge. The detection and determination of the NoV and SaV genotype(s) implicated in outbreaks or detected in contaminated foods have until now relied on the reverse transcription (RT) - PCR amplification, cloning and classical sequencing of selected segments of their genome. The target segments for NoV strain typing are typically located in the polymerase and/or capsid genes to account for possible recombination (Kroneman et al. 2013).

NoV is characterized by long-term stability and persistence in the environment (Glass et al., 2009). NoV appear to survive well on inanimate surfaces. This has frequently been demonstrated in outbreaks occurring in hospitals, residential homes, cruise ships (EFSA 2011; Wu et al. 2005), and in catering and kitchens where contaminated surfaces were detected in food preparation areas (Cheesbrough et al. 2000; Clay et al. 2006; D'Souza et al. 2006; Evans et al. 2002; Kuusi et al. 2002; Lamhoujeb et al. 2008, 2009; Mattison et al. 2007; Taku et al. 2002). NoVs are estimated to exhibit a higher resistance to heat, disinfection and pH changes than most other viruses (EFSA Panel on Biological Hazards (BIOHAZ) 2011) and vegetative bacteria (Duizer et al. 2004; Jimenez and Chiang 2006; Whitehead and McCue 2010) and can survive industrial food preservation methods such as refrigeration, freezing, acidification, reduced water activity and modified atmosphere packaging (Baert et al. 2009). NoV remains infective after heating at 60 °C for 30 min and it is unclear whether NoV can be completely inactivated during pasteurisation (FAO/WHO 2008b). NoV remains infectious for extended periods of time in seawater, especially during the winter months when temperatures are low

(Lees 2000). NoVs are inactivated by 10 mg chlorine/L, a concentration which is commonly used to treat a drinking water supply system after a contamination event, but are considered resistant in to the routinely applied drinking water disinfection dosage of 0.5-1.0 mg/L (Dolin et al. 1972; Keswick et al. 1985).

1.1.2. Outcome of exposure

1.1.2.1. Susceptibility in humans

Particularly young children, elderly, travellers and immunocompromised patients are considered highly susceptible to NoV infection and related complications (Glass et al. 2009). A higher number of outbreaks have, however, been observed in kinder gardens compared with child care and elder care facilities and a greater number of different genotypes have been detected in children (0–14 years old) compared to in older people (>65 years old) (Sakon et al. 2015). Although the excreted median NoV load of any genotype is high, the NoV load decreases with increasing age, especially in young children aged <5 years (Matsushima et al. 2015). It has been speculated that a reason for this could be that infants and children are more susceptible to a greater diversity of NoV genotypes due to a lower acquired immunity compared to the older generation (Kumazaki and Usuku 2016). Thus, it is likely that NoV outbreaks initially spread among young people.

The individual susceptibility to NoV infection relies on the heterogeneous host–virus interactions (Lindesmith et al. 2003), thus some individuals are resistant to infection and disease. The susceptibility to NoV is largely dependent on the specific genotype combined with the presence or absence of specific histo-blood group antigens (HBGA) on the gut epithelial surfaces of the human host (de Graaf et al. 2016). The synthesis of these HBGAs is regulated by the fucosyl- and glycosyltransferases, FUT2 (secretor), FUT3 (Lewis) and ABO(H) genes. Persons having an inactivated FUT2 enzyme, the non-secretors, do not express blood group antigens and are resistant to several NoV genotypes, including the predominant GII.4. Significant genotypic and phenotypic diversity in HBGA expression exist between different human populations, with non-secretor individuals occurring in approximately 5–50% of different populations worldwide (Bucardo et al. 2009; Castanys-Muñoz et al. 2013; Le Pendu et al. 2006). Bacteria that express HBGA and induce fucosylation in the gut may also be

intermediary factors that govern NoV susceptibility (Jones et al. 2014; Meng et al. 2007; Miura et al. 2013; Wacklin et al. 2014).

1.1.2.2. Disease

The pathogenesis of NoV illness is not well understood (de Graaf et al. 2016). Infection by NoV and SaV, and the resulting symptoms of acute gastroenteritis can occur among people of all age groups including neonates (Menon et al. 2010; Patel et al. 2008, 2009). The incubation times for NoV and SaV are usually 12–48 hours; with a median 1.1 and 1.2 days for NoV GI and GII, respectively, and 1.7 days for SaV (Lee et al. 2013). NoV and SaV cause similar symptoms, which typically are self-limited vomiting, (explosive) non-bloody diarrhoea and abdominal gurgling and pain, but also nausea, fever, and headache, (de Graaf et al. 2016; Robilotti et al. 2015; Yamashita et al. 2010). The severity of symptoms of NoV and SaV illnesses vary among people receiving the same titre of inoculum (Dolin et al. 1971; Oka et al. 2015). Vomiting has been reported to occur more frequently among children than diarrhoea (Green 2013). In one study, 74% of patients experienced onset of vomiting on the first day of NoV infection, while this was less common in young children below 1 year (59%) (Rockx et al. 2002). The symptoms last on average 12-60 hours (Green 2013; Kaplan et al. 1982; Rockx et al. 2002) .

While NoV illness is typically self-limiting, it may be life threatening for children, elderly people, and for immunocompromised patients (Green 2013). Thus, the majority of morbidity and mortality occurs among children, older adults and immunocompromised individuals (Koo et al. 2010). NoV infection in neonates have been associated with necrotizing enterocolitis (Turcios-Ruiz et al. 2008), diarrhoea associated benign infantile seizures (Chen et al. 2009) and inflammatory bowel disease (Khan et al. 2009). Among children (<5 years old), NoV causes 12% of all severe (hospitalized) gastroenteritis cases and an estimated 200,000 fatalities in developing countries, which is second highest for this age group after Rotaviruses (Green 2013; Patel et al. 2008). NoV infection may cause acute diarrhoea, serious illness, increased hospitalization and death in elderly (>64 years) (Mattner et al. 2006) (Ruzante et al. 2011; van Asten et al. 2011). An estimated 80 fatalities per year in UK (Harris et al. 2008) make infections life threatening in institutional settings or nursing homes (Estes et al. 2006; Green et al. 2002). Underlying conditions like cardiovascular disease, renal transplant and

immunosuppressive therapy have been suggested to be co-factors in cases with severe complications associated with NoV illness (Mattner et al. 2006).

NoV infections were shown to lead to symptoms lasting more than two weeks in 20% of cases in a community-based cohort study in the Netherlands (Rockx et al. 2002). Older patients (79-94 years) experienced persisting non-specific symptoms like headache, thirst or vertigo for 19 days past the initial diagnosis (Goller et al. 2004). This concurs with NoV infections in patients having underlying secondary illnesses, like immunodeficiency, being reported to cause prolonged and recurring illness and shedding (up to 182 days) (Siebenga et al. 2008), and a higher risk for nosocomial diseases (Lemes et al. 2014).

Asymptomatic infections, where people are shedding virus without showing any clinical symptoms, have been described for both SaV and NoV in all age groups (Phillips et al. 2010; Yamashita et al. 2010). Asymptomatic NoV infections have been reported in 7% of infants in developed countries (Ahmed et al. 2014), 7-30% of the population in some African countries (Huynen et al. 2013) and for more than 5% of adults in England (Phillips et al. 2010).

Among community cases of gastroenteritis, 4.7% had mixed infections, primarily involving adenovirus, NoV, and SaV (Tam et al. 2012).

1.1.2.3. Incidence rate in humans

NoV causes the largest number of foodborne disease illnesses and overall burden in the world (Ahmed et al. 2014; Bitler et al. 2013; Fankhauser et al. 2002; Green 2013; Karst et al. 2014; Vinjé 2015; WHO 2015a). The exact number of illnesses and fatalities are difficult to determine with a high level of accuracy due the disease being self-limited and often not reported to the medical system. Various researchers have however, come up with a range of estimates, which are described in the following section. NoV is estimated to being associated with nearly 50% of all-cause acute gastroenteritis outbreaks (Patel et al. 2009) and the leading cause (12% estimated) of mild to moderate acute diarrheal illness globally in all age groups (Patel et al. 2008). The World Health Organization (WHO) has estimated NoV to be responsible for approximately one third of an 1.8 billion diarrheal diseases caused by nine etiological agents commonly transmitted by food (Pires et al. 2015). Of an estimated 677

million cases of diarrheal disease caused by NoV, an estimated 213,515 cases result in fatalities every year (Pires et al. 2015). In the USA between 1996-2007, the annual mean number of hospitalizations due to illnesses associated with NoV infections was estimated to be 71,000 (swelling up to 110,000 cases in epidemic seasons) at an annual cost of 493 million USD to the healthcare system (Lopman et al. 2011). Another estimate is for NoV to be responsible for more than 124 million foodborne illnesses (one fifth of the estimated >600 million cases of foodborne illnesses) and 34,929 fatalities every year (WHO 2015a).

1.1.3. Treatment and vaccination

NoV infection is self-limiting in general and does not typically require medical intervention for remedy, but in rare severe cases of dehydration interventions including oral electrolyte replacement therapy may be necessary (Green 2013).

NoV does not naturally induce long term immunity after infection (Esposito et al. 2014) and despite the severity of infections and outbreaks, and attempts to develop vaccines, no commercially available safe and clinically efficient prophylactics are yet available (Arias et al. 2013; Atmar et al. 2011; Debbink et al. 2014; Green 2013). Successful development of NoV vaccines and other therapeutics have been limited due to the poor understanding of human immunity against NoV (Arias et al. 2013), the lack in NoV tissue culture systems, high diversity of strains and frequent antigenic shifts and genomic drift (Kaufman et al. 2014). Passive immunization using antibodies that block binding of NoV to human histo-blood groups may provide protection against the virus (Richardson et al. 2013), as reported in a study using antibodies from egg yolks from anti-NoV antibodies immunized chickens (Dai et al. 2012).

Diagnosis of SaV and NoV infections is based on molecular analysis of faecal samples from patients (Oka et al. 2015). The same method can be used to detect - and distinguish between - the presence of SaV or NoV in food samples.

1.1.4. Epidemiology

NoVs and SaVs are primarily transmitted via the faecal–oral route including direct person-to-person transmission or indirectly through aerosols from projectile vomiting contaminating food, water, or environmental surfaces (Franck et al. 2015b; Glass et al. 2009; Hall et al. 2013;

Lian et al. 2019). NoV is highly contagious with an infectious dose of 18–2800 viral particles. Infected persons including asymptomatic carriers, exhibit a prolonged period (4 weeks on average; range of 13–56 days) of viral shedding in faeces and vomitus as determined in human feeding trials (Ao et al. 2018; Teunis et al. 2008). In outbreaks, the average attack rate is high - typically 45% or more (Vinjé et al. 1997) and limited long-term immunity increases the risk of secondary spread through person-to-person transmission (Teunis et al. 2008). NoV is therefore easily transmitted and spread via the environment, food and water, factors which sometimes result in large outbreaks (Atmar et al. 2008, 2014; Hall et al. 2013; Patel et al. 2009).

Factors that contribute to NoV transmission are high population density, crowding, high contact rates and social mixing in closed populations (Rohayem 2009). Other factors are consumption of food prepared by infected food handlers and consumption of contaminated foods and water produced in insanitary conditions (Franck et al. 2015). For these reasons, NoV has repeatedly been implicated in disease outbreaks in institutional settings such as hospitals, nursing homes for elderly, schools and day-care centres, military-camps, cruise ships, restaurants and events with catered meals (Fankhauser et al. 2002; Green 2013; Green et al. 2002). The most common setting for NoV outbreaks in the United States and Europe are the acute and long-term healthcare facilities (e.g., nursing homes) (Division of Viral Diseases, National Center for Immunization and Respiratory Diseases 2011; Franck et al. 2015; Fretz et al. 2005; Hall et al. 2012; Vega et al. 2014; Wikswo et al. 2012). In Asian countries (Japan, Taiwan, Hong Kong and China), schools and childcare facilities account for >90% of all NoV outbreaks (Kumazaki and Usuku 2016; Lau et al. 2004; Lian et al. 2019; Wu et al. 2015).

Consumption of ready-to-eat food contaminated by infected and asymptomatic food handlers are the most common cause of foodborne NoV outbreaks (Daniels et al. 2000; Franck et al. 2015; Safaa Lamhoujeb et al. 2008). Bivalve shellfish grown and harvested in wastewater polluted areas can concentrate NoV, which are inadequately eliminated by standard depuration procedures (Muniain-Mujika et al. 2002); leading to outbreaks of gastroenteritis after consumption of shellfish (Le Guyader et al. 2006, 2008; Webby et al. 2007).

NoV outbreaks generally peak in winter and early spring (between October and March) (Greer et al. 2009; Lian et al. 2019). This is in particular the case for GII.4 strains, while non-GII.4

strains appears to exhibit a weaker seasonal pattern (Kroneman et al. 2008), and non-GII.4 outbreaks caused by person-to-person transmission occur significantly less in the fall and winter seasons than in the spring-summer season (Vega et al. 2014).

The increase of gastrointestinal diseases by e.g. NoV during winter has been associated with lower temperatures and greater rainfall (Rohayem 2009). However, a further explanation might be that NoV accumulates more efficiently in oyster tissue during fall and winter, which could significant increase the exposure of NoV amongst consumers of oysters during that period, and thus contribute to efficient re-circulation of the virus back to the human population (Maalouf et al. 2010).

GI strains are detected less frequently in clinical samples than GII strains although GI strains are clearly present in the environment (Boxman et al. 2006; Hasing et al. 2013; Lopman et al. 2004; Vega et al. 2014; Williams and Zorn 1997). GI strains have been reported to be found relatively more often in school children than in infants (Kroneman et al. 2008), which could be due to school children coming into contact with more various genotypes including GI strains than infants, because school children have a wider sphere of activity than infants.

In addition to the food association, numerous outbreaks of NoV have originated from sewage-polluted drinking water (Hewitt et al. 2007; ter Waarbeek et al. 2010; van Alphen et al. 2014) and recreational water bodies (Hoebe et al. 2004; Sartorius et al. 2007). This may be due to the resistance of NoV towards wastewater treatment and its ability to remain infectious in the aquatic environment (Bae and Schwab 2008; La Rosa et al. 2009; Nordgren et al. 2009; Skraber et al. 2009).

1.2. Hepatitis A virus (HAV)

Hepatitis A virus (HAV) causes viral jaundice and is an important water- and foodborne pathogen (Collier et al. 2014; WHO 2016).

1.2.1. Virus characteristics

The 30 nm diameter icosahedral non-enveloped HAV with a single stranded positive sense RNA genome of approximately 7.5 kb is the only member of the *Hepatovirus* genus in the family of *Picornaviridae* (Hollinger and Martin 2013). The genome consist of an untranslated region (UTR) at the 5' end and a single ORF encoding a protein, which is cleaved and processed into the non-structural and structural proteins, VP1, VP2, VP3 and VP4 (Hollinger and Martin 2013; Stuart et al. 2018; Weitz et al. 1986). Host susceptibility to the HAV is reported to be exclusive to humans and several monkey species (Hollinger and Martin 2013).

HAV is highly persistent and can survive for long periods in the environment notably in water, food and soil (Rzezutka et al. 2004). Water is considered to be the most important source of transmission, as the virus can remain infectious after up to 60 days and 30 weeks in tap- or sea water, respectively (Crance et al. 1998; Enriquez 1995), and for more than six and eight weeks in river- or ground-water, respectively (Sobsey et al. 1989; Springthorpe et al. 1993). HAV is also able to survive in various types of soil, where it can remain infectious for 12 weeks (Sobsey et al. 1989). Due to the ability to resist drying, freezing, food preservatives and acidification, HAV is persistent in the environment and has frequently caused food-borne outbreaks among susceptible populations worldwide (Baert et al. 2009; Collier et al. 2014; Linder and Malani 2017; Mollers et al. 2018; Rossati et al. 2017; Severi et al. 2015; Werber et al. 2017). HAV is therefore considered a major food hazard (FAO/WHO 2008b).

1.2.2. Outcome of exposure

1.2.2.1. Susceptibility

Age dependent immunity and susceptibility against HAV infection has been reported, while sex does not play a role in susceptibility to HAV (Jacobsen 2010).

HAV transmission, infection and illnesses are highly associated with regions of poor sanitation and hygiene practices (Hollinger and Martin 2013). In low income regions, such as Asia and sub-Saharan Africa, where the level of endemicity is high, almost all people contract immunity to HAV infection and illness (Jacobsen and Wiersma 2010). In contrary, in high income regions with better sanitation, e.g., Australia, Canada, Japan, New Zealand, Republic of Korea,

Singapore and Western Europe, a very low level of HAV infections are reported with a consequently high proportion of susceptible adults (Jacobsen and Wiersma 2010). In the Western and South-western regions of United States, consistent higher incidence rates have been observed compared to other parts of the country (Fiore 2004). WHO reported that in high income countries in the Asian Pacific region, nearly 100% of the children between the age of 1-10 are at risk of HAV infection (Jacobsen 2010).

In recent years, the geographic distribution of HAV infections has been changing due to improved sanitation and personal hygiene in endemic countries (Hollinger and Martin 2013). Between 1975-1990, approximately 95% of the population of EU/EEA countries were living in high endemic areas, whereas the number was reduced to 20% in 2014 (ECDC 2016). In 2016 ECDC classified 28 EU/EEA countries' 'susceptibility-in-adults profile' of HAV infection for which seroprevalence data were available. Three countries were graded 'Low' (>20 cases per 100,000 populations) (Romania, Bulgaria, Portugal), ten countries 'Moderate' (Spain, Malta, Lithuania, France, Italy, Poland, Cyprus, Slovakia, Greece, Slovenia), ten countries 'High' (Croatia, the Netherlands, Ireland, Czech Republic, UK, Germany, Luxembourg, Belgium, Austria and Estonia) and five countries 'Very high' (Norway, Sweden, Iceland, Finland and Denmark) (ECDC 2016).

1.2.2.2. Disease

The general incubation period of HAV infection is 15-50 days before onset of symptoms. Acute HAV illness may include symptoms such as fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice (Fiore 2004; Pintó et al. 2010). Recovery can be expected within two months (Fiore 2004; Pintó et al. 2010), although a small number (6-10%) of cases may experience prolonged relapsing symptoms of HAV illness over a period of up to 40 weeks (Glikson et al. 1992; Schiff 1992; Sjogren et al. 1987). Symptoms of HAV infection are age dependent, where children below the age of 5-6 experience asymptomatic to subclinical infections and less than 10% cases of jaundice, compared to the usually symptomatic infection and often evident hepatitis in 80% of adults (Jeong and Lee 2010; Lednar et al. 1985). Between 21-53% of HAV infected patients needs hospitalization, where the rates are lowest for children and highest for persons over 60 years. Once hospitalized, the mortality rate

among HAV infected patients is 0.23% below the age of 30 and 1.8-2.21% above the age of 49 (Hollinger and Martin 2013).

In HAV infected individuals, the virus is excreted in the bile and shed in the stool. The shedding peaks two weeks prior to onset of jaundice, a fact which may increase the risk of large outbreaks. Although a chronic carrier state does not exist in children, they may excrete the virus for longer than adults. The stool concentration of virus drops after the appearance of jaundice (Koopmans and Duizer 2004; Tassopoulos et al. 1986).

1.2.2.3. Incidence rate in human

Worldwide HAV infections are estimated to cause 14 million cases of illness yearly and approximately 28,000 deaths in 2010 (Havelaar et al. 2015; WHO 2015a).

1.2.3. Epidemiology of HAV

HAV transmits primarily via the faecal-oral route through person-to-person contact or through contaminated food and water (Bitler et al. 2013; Hollinger and Martin 2013; Iorio and John 2018; Linder and Malani 2017; Martínez et al. 2015; Severi et al. 2015; Werber et al. 2017).

HAV is frequently implicated with recurring epidemics and is the most common cause of foodborne viral jaundice (Hollinger and Martin 2013).

Contaminated fruit imported from endemic areas has in recent years been identified as the source of several large, and often multistate, outbreaks of HAV in Europe (EFSA 2014). Consumption of frozen raspberries and/or blueberries were the suspected sources of HAV outbreaks in the Netherlands in 2017, in four Nordic countries including Denmark in 2012-2013 and in Italy, Germany, Ireland and Norway 2013-2014 (Lassen et al. 2013; Mollers et al. 2018; Severi et al. 2015). The last mentioned outbreak resulted in 1,589 hepatitis A cases, including two deaths. In 2018, dates were for the first time linked to a transnational HAV outbreak in Denmark and Norway (Migley et al., *in prep*; Rajiuddin et al., *in review*; Rajiuddin 2019).

Besides, consumption of contaminated green onions (Dentinger et al. 2001; Wheeler et al. 2005), semidried tomatoes (Donnan et al. 2012; Gallot et al. 2011; Petrignani et al. 2010), pomegranates (Collier et al. 2014) and bivalve shellfish have been associated with foodborne HAV outbreaks (Boxman et al. 2016; Guillois-Bécel et al. 2009; Manso and Romalde 2013).

1.3. Hepatitis E virus (HEV)

Hepatitis E virus (HEV) causes liver infection and continuously poses a serious threat especially in developing countries with many large hepatitis outbreaks and approximately 20 million cases occurring every year (Hakim et al. 2017; Rein et al. 2012).

1.3.1. Virus characteristics

HEV is a 30-34 nm diameter spherical non-enveloped, 7.2 kb positive sense single-stranded RNA virus with a morphology that is similar to *Calicivirus* (Cook and van der Poel 2015), although they belong to the *Hepeviridae* family, Hepevirus genus (Balayan et al. 1983; Emerson and Purcell 2013). Although there seems to be only one serotype, HEV has based on the genomic sequence been divided into four genotypes Gt1-4 (Lu et al. 2006). HEV Gt1 and Gt2 are relatively conserved and reported to primarily infect humans, while Gt3 and Gt4 are infectious to a whole range of mammalian animals including swine, wild boar and domestic pigs which occasionally may cross-transmit to humans (EFSA 2017; Meng 2010; WHO 2015). Of all animal species, domestic pigs are most abundantly examined worldwide, and found to be massively infected with HEV belong to mainly Gt3 and Gt4, which also has been detected in wild boars (EFSA 2017).

The Gt1 and Gt2 cause the majority of human HEV infections and epidemics in Asia, Africa and Mexico, while only sporadic cases of human Gt3 and Gt4 infections are observed in more industrialized countries, including the USA, Japan, China and Europe (Herremans et al. 2007; Mushahwar 2008; Zhou et al. 2004).

HEV has at least two distinct epidemiological profiles: (1) large outbreaks and epidemics in developing countries, usually caused by HEV Gt1, resulting in high morbidity and mortality among pregnant women and young children, and (2) very few symptomatic cases of HEV Gt3,

most cases without symptoms or clear source(s) of infection, but frequent seroreactivity in 5%-21% of asymptomatic persons in developed countries. Though the first is largely considered to be the result of a water-borne infection, the latter is suspected to result from frequent contact with pigs or consumption of meat and meat products from pig or wild boar.

HEV can be detected using serological assays. However, RT-PCR is increasingly used for detection (Garson et al. 2012; Jothikumar et al. 2006). Although an internationally validated standard (Althof et al. 2019) including standard material (WHO 2019) is available for HEV RNA detection in meat and meat products, no formal international standard exists for the detection of HEV in food products. HEV has been detected in various foods such as pork products (Di Bartolo et al. 2012), shellfish (Diez-Valcarce et al. 2012) and leafy vegetables (Kokkinos et al. 2012). There has also been progress in development of a cell-culture assay for HEV (Okamoto 2013) although it seems to be selective for a limited number of HEV strains (Johne et al. 2016).

1.3.2. Outcome of exposure

1.3.2.1. Susceptible populations

Sporadic HEV infections have been identified in at least 63 countries, half of which are large epidemics (WHO 2010, 2015b). HEV is prevalent all over the world, although epidemics and outbreaks are mainly reported in developing countries where the more virulent HEV strains, Gt1 and Gt2, are transmitted through water (Emerson and Purcell 2013; Meng 2010).

In the developing HEV endemic countries, sporadic hepatitis is believed to predominantly be caused by HEV with the young adults in highest risk of severe illness and death among in particular pregnant women (Emerson and Purcell 2013; Meng 2010; Rein et al. 2012). Pregnant women, immunosuppressed or pre-existing liver diseased persons, as well as refugees, travellers and displaced persons suffer the highest attack rates of HEV Gt1 and Gt2 due to their weakness or nature of living conditions that include poor hygiene and overcrowding (WHO 2015b).

HEV is endemic in swine all over the world (Meng 2003). In industrialized countries with better sanitation and food safety, the less virulent HEV strains, Gt3 and Gt4, are clinically

predominant and mainly observed in individuals, who are in contact with swine and swine products, such as pig-farmers, handlers and veterinarians (Emerson and Purcell 2013; Meng 2010; Pavio et al. 2010). The incidence of HEV infection has however, increased in industrialized countries (EFSA, 2017); with locally acquired infections in men over 60 years of age in UK believed to be associated with the consumption of processed pork products.

1.3.2.2. Disease

HEV infection in humans can be asymptomatic, as many individuals in industrialized countries are seropositive for antibodies against HEV without a history of prior illnesses (Drobeniuc et al. 2001; Meng et al. 2002). The incubation period of HEV infection before disease onset may be 2-8 weeks (Aggarwal and Naik 2009; Emerson and Purcell 2013). HEV infected patients may have jaundice, anorexia and hepatomegaly in general, while abdominal pain, tenderness, nausea and vomiting has been reported in approximately half of the cases (Emerson and Purcell 2013). Viremia in patients have been reported from 1 week prior to onset of clinical symptoms of the disease and 3 weeks post exposure of HEV, which is also concurrent with faecal shedding that may continue for weeks (Emerson and Purcell 2013). Despite that the clinical symptoms of HEV infection varies among infected species, the histopathological lesions have been reported to be similar in infected humans, pigs and chickens (Meng 2010).

While HEV Gt3 initially was thought to only cause acute infection where most patients remain asymptomatic (Hoofnagle et al. 2012), chronic infection rapidly leading to cirrhosis and liver failure has been demonstrated mainly in immunocompromised organ transplant recipients (Zhou et al. 2013).

In general, the mortality due to HEV illness is 0.1-4%, while in pregnant women in their third trimester the fatality rate is between 10-50% (WHO 2015b). HEV infection in patients with chronic liver disease may cause fatalities in up to 30% cases (Emerson and Purcell 2013).

After 7-8 weeks post HEV infection, viremia may reduce, while liver enzyme values are at their highest. Khuroo et al. (1993) reported that anti-HEV antibodies in patients might persist for years after exposure.

Compared to a 0.2% fatalities among HAV infected patients, the in general infrequent HEV infections with mild onset of symptoms in immune competent patients may be more severe, as they may cause up to 1% fatality (Emerson and Purcell 2013; WHO 2015b).

1.3.2.3. Annual incidence rate in humans

In developing countries the prevalence of HEV can be very high. For example in Egypt, the general population shows a more than 70% prevalence of HEV antibodies (Stoszek et al. 2006).

In Asia and Africa, an estimated 20.1 million HEV infections may occur annually, which may result in 3.4 million symptomatic cases, 70,000 deaths and 3000 stillbirths. Among all age groups, the highest increase in prevalence of HEV was observed among children and young adults between 5-20 years of age, while the highest numbers of symptomatic cases and fatalities were observed in East and South Asia compared to the accounted nine Global Burden of Disease (GBD) areas (Rein et al. 2012). In Asian and African regions, the rate of HEV incidents is highest (1.0-1.4%) for ages 15-20, and decreases for ages 0-15 (0.5-1.0%) and further for ages older than 30 years (≤0.2%) (Rein et al. 2012).

1.3.3. Treatment and vaccination

HEV infection and illness is normally self-limiting and immune competent persons recover without complications (Emerson and Purcell 2013). No anti-HEV treatment or guideline from WHO exists and treatment for acute HEV is generally supportive (WHO 2015b).

Clinical trials have demonstrated that anti-HEV antibodies can be induced by vaccination. A subunit vaccine (Hecolin®) approved by the China Food and Drug Administration (Bin Park 2012), containing recombinant truncated capsid proteins of HEV Gt1 have been demonstrated to be highly effective in providing nearly lifelong prevention of the disease of HEV Gt1 - with possible cross reactivity to Gt4 – infections (Chen et al. 2015; Zhang et al. 2015; Zhu et al. 2010). It remains unknown whether Hecolin® could confer protection against HEV Gt2 or Gt3 and thus provide protection against the foodborne zoonotic Gt3 infections mainly acquired in Europe. The safety and efficacy of the HEV vaccines in pregnant women, among which a high case fatality rate has been observed, remains to be studied (Wu et al. 2012).

Such trials with Hecolin® are currently being conducted in a rural area in Bangladesh (NCT02759991). An additional HEV Gt1 vaccine candidate has shown efficient protection against HEV in a phase II clinical trial conducted in Nepal (Shrestha et al. 2007) and more HEV vaccines are now in different stages of development (Cao et al. 2017; Kulkarni et al. 2016; Wen et al. 2016; Xia et al. 2016)

1.3.4. Epidemiology

HEV is relatively stable and excreted in the environment through faeces of infected persons and animals, thus primary transmission of HEV is faecal-oral through water and food, particularly when faecal contaminated by e.g. manure (Krog et al. 2017; Van der Poel et al. 2018). However, since many cases are not obviously associated with travel to HEV endemic areas, or can be directly linked to live pigs or pork products, the route of transmission is not fully elucidated (EFSA 2017).

Five main routes of HEV transmission has been described (WHO 2010): i) faecal-oral transmission through contaminated water, ii) foodborne transmission through ingestion of food derived from infected animals, iii) zoonotic transmission through exposure to infected animals and their bodily fluids, iv) transmission through infected body fluids, and v) vertical transmission from mother to fetus.

Faecal contamination of drinking water has been reported to be the major route of HEV transmission in endemic regions (Rein et al. 2012). Waterborne transmission of HEV Gt1 or Gt2 have been reported in at least 30 countries in Asia, Africa and North America, (WHO 2015b).

In developed countries, where drinking water is safer, HEV transmission is largely zoonotic, through uncooked or undercooked pork products and wild boar meat (Li et al. 2005; Masuda et al. 2005; Kamar et al. 2012). In Japan, where 2% of pig livers sold to consumers are contaminated with HEV, sporadic cases of HEV infection have been associated by ingestion of raw or uncooked pig liver (Yazaki et al. 2003; Meng 2010). In USA, 11% of pig livers sold to consumers are contaminated of HEV (Feagins et al. 2007). In Denmark, infection of HEV was suggested to be through zoonotic transmission, which in one study was reported to involve largely asymptomatic cases (Christensen et al. 2008).

In both developed and developing countries contaminated shellfish, meats and direct contact with infected animals have been implicated in HEV diseases (Emerson and Purcell 2013; Meng 2010; Pavio et al. 2010)

1.4. Tick-borne encephalitis virus (TBE)

Tick-borne encephalitis virus (TBEV) is a zoonotic virus transmitted via tics to rodents, goats, sheep and cows with potential further transmission to human consumers of unpasteurized dairy products from endemic areas (Kríz et al. 2009).

1.4.1. Virus characteristics

TBEV is an enveloped, single stranded RNA virus, which belongs to the genus *Flavivirus* and is maintained in forests, which is the habitat for the tick vectors and their main hosts, rodents. A significant increase in reported cases (including foodborne) in the last 30 years due to ecology and climate changes, has led to an increased focus on this virus.

Three major subtypes of TBEV exist: the European or Western (TBEV-Eu), the Siberian (TBEV-Sib), and the Far Eastern or spring-and-summer-encephalitis (TBEV-Fe). The vectors of TBEV act as long term reservoirs of the viruses (Hubálek and Rudolf 2012). The vector of TBEV-Eu is *Ixodes ricinus* which is predominantly distributed in the mid to western regions of the European Union (EU) including Denmark (Lindquist and Vapalahti 2008; Demina et al. 2010; Lindquist 2014; Michelitsch et al. 2019). In the Netherlands in 2016, an endemic TBEV was reported, through the detection of a TBEV strain that was genetically different from the common TBEV (Weststrate et al. 2017).

The virus genome itself can be infectious and has in the appropriate host been shown to be capable of producing progeny viruses with same virulent characteristics as of a wild type TBEV (Mandl et al. 1997).

Simulation of a typical thermal regime utilized for cheese production could not completely reduce the infectivity of a tick-borne *Flavivirus* (Langat virus (TP21 strain)) inoculated in milk. Infectious TP21 was shown to be maintained for days in goat milk kept at refrigeration

conditions, and be stable for at least 24 hours in acidified dairy products and 24-48 hours in sour milk (Gresíková-kohútová 1959). However, the infectivity of TP21 in milk was reduced markedly at room temperature (22°C) after 24 hours and completely after 48 hours (Offerdahl et al. 2016). Further, infectious TP21 in goat milk could be completely inactivated after 20 min at 65˚C, as well as by HTST pasteurisation (72˚C, 15 sec following by cooling to refrigeration temperature) (International Dairy Foods Association 2016; Offerdahl et al. 2016). Similary, infectious TBEV in goat milk was shown to be reduced by up to 6.7 log after heating the milk at 72°C for 10 sec (Gresíková et al. 1961).

Another study using a Western TBEV strain Hypr suspended in milk, showed a slightly different reduction pattern in which the virus remained stable during storage at 8°C for five days, and could be reduced 4-4.5 log by heat treatments in the range of 60 to 80 °C (Saier et al. 2015).

Thus, TBEV infectivity in goat milk may persist for days at refrigerated temperatures, but is not likely to survive pasteurization. The kinetics may vary according to the virus tested and the study. However, it is clear, that proper milk handling and pasteurization processing in areas endemic for TBEV are important.

1.4.2. Outcome of exposure

The incubation period of tick-bite acquired TBEV infections can be 2-28 days (Bogovic and Strle 2015; Taba et al. 2017), while individuals affected by foodborne TBEV may show clinical symptoms already after 2-4 days (Dumpis et al. 1999; Taba et al. 2017). TBEV infection is normally asymptomatic but may be acute neuroinvasive (Taba et al. 2017). The clinical onset of TBEV is biphasic. In 2/3 of infected patients, a first phase may be induced showing influenza-like illness with fever, headache, muscle pain and fatigue that last 2-7 days. In 30% of cases, a second phase is induced that lasts up to 10 days with reappearing high fever and symptoms of inflammation of the central nervous system. Encephalitis developing during this second phase may result in paralysis, permanent sequelae or death (Taba et al. 2017). The clinical severity varies by subtype with a lower fatality rate of European TBEV (approximately 1%), than the other two subtypes of TBEV (Taba et al. 2017). Patients do not shed TBEV in faeces (Veje et al. 2018) .

On average, up to 3% ticks can be carriers of TBEV in endemic areas and approximately 0.3% of tick bites lead to disease manifestation (Kaiser 2016). Approximately half of TBEV infections develops into meningitis, 40% cases develop meningoencephalitis and the remaining 10% of cases develop encephalomyelitis (Kaiser 2016). TBE can be mistaken for nonspecific inflammatory disease due to the unspecific clinical presentation as shown for infected Swedish children (Hansson et al. 2011).

1.4.2.1. Susceptibility

In endemic areas, every case of meningitis, encephalitis or myelitis has the potential to be TBE (Taba et al. 2017). Non-vaccinated tourists in endemic regions is at risk of contracting TBE with an estimated 1 in 10,000 persons/month (similar to the risk of typhoid fever or malaria among tourists in India). With increased tourism, particularly in warm months to endemic areas, the risk of TBEV infection may increase (Bogovic and Strle 2015).

Among German patients in 2001-2018, increased severity of TBEV infections was shown to correlate with age, as well as fatalities increased from average 0.4% in all age groups to 2.1% among patients aged 70 years or older (Hellenbrand et al. 2019). This study further showed a highest mean incidence rate of TBE among 40-69 year olds, and confirmed that male patients in all age groups had more severe manifestations of the disease compared to females (Bogovic and Strle 2015).

1.4.2.2. Annual incidence rate in humans

According to European Academy of Neurology (EAN) consensus, an estimated 13,000 cases of TBE can occur in Eurasian northern hemisphere (Taba et al. 2017). In EU and Asia, 10,000 to 15,000 TBE cases are reported per year, with more than 10,000 complications that needs hospitalization (Kaiser 2016; Dobler 2010). This number is likely underestimated, as many countries do not have concrete case definitions and mandatory system of reporting TBE cases (Bogovic and Strle 2015). Considering the frequency of fatalities per year, TBEV illness are second highest among neurotropic *Flaviviruses* after Japanese encephalitis (Lindquist and Vapalahti 2008).

In EU, TBE disease has been notifiable since 2012 and a case definition has been proposed by ECDC only recently (Taba et al. 2017). In the European countries during the period of 2005-2009, pronounced yearly variations of registered TBE cases occurred with the following highest incidences per 100,000 inhabitants: 14.1 cases for Slovenia, 11.1 cases for Estonia, 10.6 cases for Lithuania and 8.8 cases for Latvia (Süss 2011). According to the latest available epidemiological data for Slovenia the incidence of the disease in 2013 was 15.0 cases per 100,000 inhabitants (Institute of Public Health of the Republic of Slovenia 2014). Between 2012-2016 in EU, 12,500 cases of TBE were reported, among which Czech Republic and Lithuania together accounted for 38.6% of cases (Beauté et al. 2018). In Denmark, 37 cases of TBE was reported during the period 1998 – 2009, which was lowest among the European countries, Belarus and Russia (Lindquist 2014). No data on TBE illnesses was reported from Denmark between 2012-2016 (Beauté et al. 2018).

In Czech Republic, 1997-2008, 7,288 TBE cases were reported, of which approximately 1% were foodborne (Kríz et al. 2009).

1.4.3. Treatment and vaccination

Patients infected with TBEV may require symptomatic treatment and in severe cases emergency management and intensive care (Taba et al. 2017). European TBEV is vaccine-preventable by two effective vaccines based on the European TBEV subtype (Šmit and Postma 2015; WHO 2011). However, effective treatment is not available for all TBEV (Kaiser 2016; Taba et al. 2017). The first developed veterinary vaccine for TBEV was reported recently, and showing promise in laboratory experiments (Salát et al. 2018).

1.4.4. Epidemiology

The predominant route of TBEV transmission is horizontal through bite of infected ticks, however foodborne transmission of TBEV by ingestion of raw milk or milk products from endemic areas have also been reported (Kríz et al. 2009; Taba et al. 2017). Person-to-person spread, except rarely through blood transfusion and breastfeeding, has not been reported (Mansfield et al. 2009). In central EU, the TBE mostly occur during the warm months coinciding with the highest tick activity period between April and November (Lindquist 2014; Lindquist and Vapalahti 2008).

TBEV RNA has been detected in samples of raw milk of goats (21%), sheeps (22%), and cows (11%) from Poland (Cisak et al. 2010) and in 5.4 of % of milk samples from cows in three municipalities in Norway (Paulsen et al. 2019).

Alimentary transmission of TBEV has been reported by consumption of unpasteurized goat milk in Austria, Estonia, Slovenia (Hudopisk et al. 2013; Kerbo et al. 2005; Markovinović et al. 2016), cow milk in Hungary (Caini et al. 2012), and goat and sheep cheese in e.g. Croatia (Dorko et al. 2018; Holzmann et al. 2009; Markovinović et al. 2016).

Pasteurization of milk products and vaccination of veterinary animals may prevent alimentary TBEV infection and transmission to humans (Salát et al. 2018).

1.5. Rotavirus (RV)

Human rotaviruses (RV) cause severe diarrheal disease in children all over the world (Estes and Greenberg 2013). RV is a 100 nm diameter icosahedral, non-enveloped and triple capsid structured virus with 18.5 kb segmented double stranded RNA genome (Rodríguez-Lázaro et al. 2012). Belonging to the genus *Rotavirus* in the *Reoviridae* family of viruses (Estes and Greenberg 2013), RV consist of 10 different species (A-J) based on genome sequence and antigenic variances (Crawford et al. 2017). Most human infections are caused by group A RV, although infections and outbreaks also occur to a lesser extent due to group B RV and C RV. Diverse genotypes of RVs are found in the intestinal tracts of many young mammals which can act as reservoir for human infections (Estes and Greenberg 2013).

Most children are infected by RV by the age 5, regardless of the socio-economic status of the region (Crawford et al. 2017), although most fatalities occur in the developing countries due to poor sanitation (Tate et al. 2016). Childhood infection may lower the risk of subsequent infection and disease onset (Velázquez et al. 1996). In spite of adults frequently becoming infected by RV, they seldom manifest clinical symptoms (Estes and Greenberg 2013). However, an estimated annually 24,000 hospitalizations still occur due to RV infection in individuals above 5 year (Lopman et al. 2011).

Rotavirus causes gastroenteritis with vomiting, diarrhoea, malaise and fever (Crawford et al. 2017).

Oral treatments, like rehydration therapy using oral saline and other liquid supplements may be challenged by the typical symptomatic vomiting (Hagbom et al. 2011; Leung and Robson 2007). In 2006, live attenuated vaccines against RV were licenced and are now used globally in more than 100 countries (Crawford et al. 2017). The introduction of vaccines may lead to the emergence of novel RV genotypes or the re-emergence of old strains, particularly from animal reservoirs (Iturriza-Gómara et al. 2004; Kang et al. 2005; Rzezutka et al. 2004; Steyer et al. 2008).

Being responsible for approximately 450,000 fatalities in children below 5 years of age, RV is the major cause of severe gastroenteritis in children globally (Tate et al. 2012). Even after the introduction of a global universal vaccination program, RV still causes considerable mortalities particularly in developing countries. Of an estimated 215,000 deaths in 2013 globally, 49% occurred in India, Nigeria, Pakistan and the Democratic Republic of Congo alone (Tate et al. 2016).

RV persist similarly to NoV, HAV and HEV in fresh water (Hurst and Gerba 1980) even when subjected to light exposure, which can seriously affect the stability and viability of other enteric RNA viruses, e.g., astrovirus (Fujioka and Yoneyama 2002; Lytle and Sagripanti 2005). Inactivation of virus infectivity in different types of water has been consistently found to correlate with higher temperatures (John and Rose 2005).

1.6. Aichi virus (AiV)

Aichi virus (AiV) belongs to the genus *Kobuvirus* in the *Picornaviridae* family and is responsible for human gastroenteritis (Racaniello 2013). The non-enveloped ~30 nm diameter icosahedral virus particles contain a single stranded positive sense RNA genome of approximately 8.25 kbs (D'Souza 2015; Yamashita et al. 1998). AiV has been detected in human faecal samples from all over the world (Kitajima and Gerba 2015). Studies suggest high (80-99%) and

widespread seroprevalence of AiV-1 antibodies in adults in countries such as Japan, Germany, France, Spain and Tunisia (Kitajima and Gerba 2015).

AiV has been detected in raw or treated sewage and surface water (Di Martino et al. 2013; Haramoto and Kitajima 2017; Kitajima and Gerba 2015; Lodder et al. 2013) and shellfish (Hansman et al. 2008; Terio et al. 2018). Kitajima and Gerba (2015) suggested that AiV may cause no or subclinical symptoms while circulating, or may be involved in mixed viral infections causing gastroenteritis.

The clinical symptoms of AiV infection may include diarrhoea, abdominal pain, nausea, vomiting, and fever (Yamashita et al. 2001). The onset of symptoms, however, may depend on patient condition (Yamashita et al. 2001). Another study suggested no association between AiV and gastroenteritis in children in China, proposing that the virus may replicate in humans without causing disease (Li et al. 2017).

In Thailand, 2.6% of paediatric gastroenteritis patients were found to be infected by AiV in one study of 923 cases (Chuchaona et al. 2017).

1.7. Astrovirus (ASV)

Astrovirus (AsV) is a member of the family *Astroviridae* with icosahedral non-enveloped capsid of 28-35 nm diameter and a 6.4-7.7 kbs positive sense single stranded RNA genome (Arias and DuBois 2017; Bosch et al. 2014; D'Souza 2015). The virus is prevalent in stool samples of symptomatic or asymptomatic individuals from around the world (Storch 2013). AsV is a major cause of acute gastroenteritis in children, elderly and immunologically compromised patients (Bosch et al. 2014; Johnson et al. 2017). The majority of the children have been reported to carry antibodies against AsV type-1 which makes adults less susceptible to infection (Bosch et al. 2014; Johnson et al. 2017). Bats and pigs carry the largest diversity of AsV strains and are suggested to be potential reservoirs (Vu et al. 2017). Common genetic features have been found among chicken, turkey and duck AsVs, which may suggest frequent cross-species transmission (Bosch et al. 2014; Johnson et al. 2017). The high genetic

variability of AsV and recombination due to simultaneous infection with multiple strains suggest AsV as major candidates of emerging zoonotic infections (Vu et al. 2017).

AsV infection has an estimated incubation period of 3-6 days (Lee et al. 2013) until the onset of symptoms such as watery diarrhoea, abdominal pain, fever, headache and anorexia (Johnson et al. 2017). Though AsV are in general self-limiting and asymptomatic in adults and adult children, AsV may cause fatal encephalitis and meningitis in immunocompromised patients (Pérot et al. 2017).

In Australia, an average of estimated 17,500 foodborne gastroenteritis illnesses occurred a year (in circa 2000) due to AsV and adenovirus (AdV) infections (Hall 2005).

Detection of AsV in fresh fruit and vegetables is not common (Shin et al. 2019). However, the virus has been detected in mussels in a 2014-2015 surveillance study in Italy (Fusco et al. 2017) and in patient stool samples obtained in connection with a foodborne disease outbreak in Japan (Mori et al. 2017).

1.8. Adenovirus (AdV)

Adenovirus (AdV) belong to the genus *Mastadenovirus* and are divided into subgroups (A-G) (Harrach et al. 2012). They have an icosahedral, 70-90 nm in diameter non-enveloped capsid and a single double stranded DNA genome of 26-49 kbp (Harrach et al. 2012). All AdV serotypes of these subgroups can cause gastrointestinal infections except for subgroup E (Wold and Ison 2013). Human AdV commonly cause infection in the gastrointestinal and respiratory tracts, as well as in the eyes, and occasionally the urinary tract, liver and pancreas (Wold and Ison 2013). AdV subgroup F and G consisting of serotypes 40, 41 and 52, exclusively cause gastrointestinal infections in humans (Wold and Ison 2013).

The incubation period for AdV is 8-10 days, before onset of the primary symptoms, watery diarrhoea and vomiting, which last for 7-8 days (Wood 1988; Uhnoo et al. 1990).

Worldwide an estimated 8% of clinically relevant viral disease are caused by AdV (Wold and Ison 2013), whereas in industrialized countries, 4-17% of acute diarrhoea among infants may

be due to AdV infection (Uhnoo et al. 1990). One study conducted in Thailand between 2011-2017 showed that children aged between 1-2 years had the highest rate of AdV illnesses among other age groups (Kumthip et al. 2019). In Australia, an average of estimated 1650 foodborne gastroenteritis illnesses occurred every year in 2010's due to AdV infections (Kirk 2014).

AdV are an important cause of nosocomial infection and gastroenteritis (Krajden et al. 1990; Rodriguez-Baez et al. 2002), in which non-enteric AdV may play an important role (Kumthip et al. 2019). The majority of human AdV infections are subclinical (Harrach et al. 2012), which in children has been suggested to produce lifelong immunity (Wold and Ison 2013).

2. Detection methods for viruses in foods

Methods for cell culture detection and titration of infective NoV and HAV in complex matrices such as foods have not yet been established. However, unreliable and time-consuming cell culture assays to test for NoV or HAV in clinical samples do exist (Ettayebi et al. 2016; Yeh et al. 2008). Therefore, detection of NoV and HAV in foods relies on the detection of viral genomes extracted from the food matrix (de Roda Husman et al. 2009). In general, these methods consist of two parts, i) elusion, concentration and extraction of viruses from the matrix followed by purification of the viral genome, and ii) molecular detection of specific sequences of the viral genome in question typically by the highly sensitive and specific reverse transcription-quantitative Taqman real-time PCR (RT-qPCR) (Vinjé 2015).

The first validated standard method for extraction and detection of viral RNA from foods was published in 2017 (ISO 2017).

For fresh produce, the method includes viral elution from the food matrices using a protein rich alkaline buffer requiring concurrent pH adjustments, followed by viral particle concentration, extraction and capsid lysis to release viral genomes. The viral genomes are then absorbed to magnetic silica particles forming a complex which are purified by several washing steps, before the genome is finally eluted from the particles prior to being analysed for the presence of genomic sequences of the virus in question using RT-qPCR (ISO 2017).

The number of steps in the ISO standard makes it laborious and time consuming and prone to loss of viral genomes. Thus, the method often fails to achieve the desired efficiency in viral genome recovery from the tested samples. In addition, food matrices such as fruits and vegetables contain organic or inorganic substances, which if remaining in the purified nucleic acid extracts may act as PCR inhibitors that hamper RT-qPCR amplification of target viral sequences (Bartsch et al. 2016; Perrin et al. 2015; Schrader et al. 2012).

To improve viral RNA recovery in extracts from soft fruits processed by ISO 15216 (ISO 2017), Bartsch et al. (2016) included a purification step using the commercially available MobiSpin-400 column (MoBiTec, Göttingen, Germany). This improved the detection frequency of target viruses, although it failed to comply with the extraction efficiency criteria described in the ISO standard method (15216). Therefore, the ISO standard method, although being a complex procedure, still faces major challenges with low viral RNA recoveries and inhibited RT-qPCR detection of target viral sequences, in extracts processed from diverse categories of foods.

Relevant and sensitive qPCR methods exist for all the viruses described in this document. However, the challenge of how to best isolate viral genomes from different food matrices remains the same for detection of all foodborne viruses and is an area of active research. Having reliable detection methods is naturally of great consequence both for the surveying food and health authorities and for the food industry.

3. Transmission routes of foodborne viruses

3.1. Transmission via food handler

The origin of most foodborne virus outbreaks can be pin-pointed to events in kitchens, where the food is prepared by symptomatic or asymptomatic food handlers, who are infected or have infected relatives, and served to the consumer without prior heat treatment (EFSA Panel on Biological Hazards (BIOHAZ) 2011; Kuo et al. 2009;Todd et al. 2007a). Buffet meals may also be contaminated by guests with subsequent transmission to other buffet guests (Franck et al. 2015). Food handler transmission of foodborne viruses have most often been reported

for NoV and HAV and to a lesser extent for SaV and RV, see Table 2 (EFSA Panel on Biological Hazards (BIOHAZ) 2011; Fiore 2004; Franck et al. 2015).

A study of foodborne disease outbreaks caused by infected food handlers, identified three main causes of NoV and HAV contamination: i) handling of food by infected person or carrier, ii) bare hand contact, and iii) lack of proper hand hygiene (Todd et al. 2007b). Among foodborne NoV outbreaks, infected food handlers could be identified as the origin of NoV transmission in 34% of 191 reported outbreaks in Denmark during 2005-2011 (Franck et al. 2015), and in 61% of 74 selected published outbreaks during 2003-2017 (Hardstaff et al. 2018). In both these studies, the transmitted NoV by food handlers involved a diverse range of foodstuffs in a wide variety of settings. In the Danish study, the implicated food handlers were reported as asymptomatic during food handling in the majority of outbreaks (64% out of 41). Before handling the food, some food handlers had been in contact with ill relatives and remained asymptomatic, while others developed symptoms shortly after or were post-symptomatic (Franck et al. 2015). That asymptomatic food handlers are more often reported to cause NoV disease outbreaks than symptomatic food handlers is not an uncommon observation (Boxman et al. 2007).

Practically all types of foods served after personal handling without prior heat treatment (i.e., ready-to-eat foods), may pose a risk of transmitting viruses to consumers, and a great number of such events have been described for both NoV and HAV (Chironna et al. 2004; Fiore 2004). For NoV, infected food handlers could be identified as the vectors in outbreaks due to e.g., contaminated sliced ham affecting 125 cases (Texas, 1998) (Daniels et al. 2000), side salads involving 333 persons (13 states, USA, 2001) (Anderson et al. 2001), sandwiches causing 59 cases (Spain) (Godoy et al. 2005), and bakery product affecting 231 cases (The Netherlands, 2001) (de Wit et al. 2007).

Similarly for HAV, transmission through infected food handlers affected 91 consumers of uncooked food served at a catered event in Kentucky in 1994 (Massoudi et al. 1999) and 269 people consuming raw beef in Belgium (Robesyn et al. 2009). Glasses, which became contaminated by pub staff, led to infection of eight drink-consumers (England, 2002) (Sundkvist et al. 2000). An interesting study, which reviewed all reports of salsa or guacamole

associated (SGA) disease outbreaks during 1984-2008, concluded that 32 outbreaks (987 illnesses) were caused by NoV, of which nearly all (30) were caused by foods prepared in restaurants or delis (Kendall et al. 2013). Fresh salsa and guacamole require careful preparation and storage and this study pointed to the importance of focussing on prevention strategies, which involve food handlers, in order to reduce virus transmission and the risk of illness among consumers.

Indeed, the most frequent cause of foodborne outbreaks due to NoV and HAV have been documented to originate from catering, canteens or restaurants where the surfaces of the kitchen environment and foods have been contaminated by infectious food handlers (Fankhauser et al. 2002; Franck et al. 2015). Surfaces of community buildings like hospitals, day care centres, offices, apartment houses, nursing homes, hotels, day care centres, schools, animal care facilities, bars, coffee shops and paediatric wards have been reported to be contaminated by foodborne viruses (Boone and Gerba 2007). Transmission of viruses between hands, melamine surfaces, door handles, telephone receivers or cleaning cloth has been reported in households (Barker et al. 2004). Transmission of foodborne viruses between hands and contaminated fomites have been demonstrated in several studies as reviewed by Barker et al. (2001). Two experimental transmission studies using hands inoculated with infectious virus showed transfers of 46, 18 or 13% of NoV surrogates (feline calicivirus) to ham, lettuce or steel disks, respectively (Bidawid et al. 2004), and 9.2% of HAV to lettuce (Bidawid et al. 2000).

Table 2: Some reported outbreaks of foodborne viruses due ill food handlers, 2009-2018

Cause of transmission	Virus	Year	Country of OB	Settings	No. OB	No. cases	Detection (Epi/stool/swab)	Reference
Kitchen stuff	NoV	2009	Austria	Healthcare facility	1	204	Epi	(Schmid et al. 2011)
Catered lunch	SaV	2010	Japan			3827	Epi/stool	(Oka et al. 2017)
Food served by ill cook and water	NoV	2011	France	Military canteen	1	147	Epi/stool(chef)/food	(Mayet et al. 2011)
Grain salad and beetroot dip (indicated food handler contaminated)	NoV	2014	Australia	Restaurant	1	46	Epi/stool	(Coutts et al. 2017)
Pork liver and lamb chops (indicated food handler contaminated)	NoV	2015	Taiwan	distillery	1	169	Epistool/food/swab	(M.-Y. Chen et al. 2016)
Schools & colleges (71.9%), kindergartens (23.4%), and factories (4.7%)	NoV	2016-2017	China		64	2953	Stool	(Fu et al. 2017)
Person to person	NoV	2017	China	Primary school		19	Stool	(J. Li et al. 2018)
Environmental surfaces and infected food handlers	NoV	2017	USA	Wedding event		159	Epi/stool	(Free et al. 2019)
Food handler	NoV	2017	Italy	cafeteria	2	45	Epi/stool/swab/	(Monini et al. 2019)
Food supplying chain	NoV	2017	Portugal	Army base	3	31	Stool	(Lopes-João et al. 2019)
Turkey dinner (indicated)	NoV	2018	Spain	Nursing home		137	Epi/stool	(Parrón et al. 2019)

3.2. Transmission during primary production

Fresh produce

Virus contamination of food during primary production can be due to inefficient sanitation of water and equipment or improper practice of personal hygiene among symptomatic or asymptomatic food handlers (pickers and packers), who shed virus particles (EFSA Panel on Biological Hazards (BIOHAZ) 2011; Kuo et al. 2009; EFSA Panel on Biological Hazards (BIOHAZ) 2014b). Examples of fruits, vegetables and lettuce, which became contaminated during primary production and later resulted in viral disease outbreaks among consumers, are listed in Table 3.

Fresh food, such as soft-fruits, are sold as ready-to-eat food in the market place, and come directly from production establishments, therefore risk evaluation of food contamination at primary production level is a key factor in foodborne disease control (Macori et al. 2018). Fresh produce may be subjected to both pre- and post-harvest contamination (Beuchat 1996).

Before harvest, fruits and vegetables may be contaminated by faeces, soil, water used for irrigation or to apply insecticides or fungicides, green or inadequately composed manure, air (dust), wild or domestic animals, insects and human handling (Beuchat and Ryu 1997). After harvest, fruit and vegetables may be contaminated by faeces, improper human handling by workers or consumers, harvesting equipment, transport containers, wild or domestic animals, insects, air (dust), wash or rinse water, processing equipment, ice, transport vehicles, storage condition, packaging condition, cross-contamination, and improper handing after purchase (Beuchat and Ryu 1997).

Often fresh produces such as berries are picked by hand, which may facilitate contamination and entry of human pathogenic viruses in the food chain (Alegbeleye et al. 2018; Anderson-Coughlin and Kniel 2019; Beuchat and Ryu 1997). The type of cultural or irrigation techniques may also play a role in contamination of fresh produces (Macori et al. 2018). At the production level, irrigation with contaminated water has been reported to have contaminated fresh lettuce (Barker et al. 2013; Werneck et al. 2017), and leafy greens and berry fruits (Bouwknegt et al. 2015). Domesticated animals have also been reported to be the source of contamination at the farm level (Salaheen et al. 2015).

Foodborne viruses, which are known to be transmitted via primary production of fresh produce, are primarily NoV and HAV but also HEV and RV. Contaminated water is the most common cause of NoV, HAV and HEV transmission (Jacobsen 2010). Waterborne transmission of HEV (genotype 1 or 2) have been reported in at least 30 countries in Asia, Africa and North America (WHO 2015b).

In a study in Mexico, NoV was found on 31% of workers' hands during the harvest of green bell peppers, while 45 or 30% of field or packed green bell peppers were found contaminated with NoV (León-Félix et al. 2010).

Seaweed has just recently been reported associated with NoV illness (Kwan et al. 2017), see Table 3. The first reported outbreak of NoV gastroenteritis was in South Korea in 2012, where both the seaweed implicated in disease outbreak and seawater used to wash seaweeds were found contaminated by NoV (Park et al. 2015). Investigations suggested that the seaweed

were likely contaminated by either seawater before harvest, due to NoV contaminated wastewater disposal near seaweed farm, or during washing of seaweed after harvest using contaminated seawater (Park et al. 2015). In Japan, seven large outbreak of NoV gastroenteritis was reported due to dried seaweed possibly being contaminated by an infected food handler during packaging. This led to illness in 2094 persons (Sakon et al. 2018). More recently, in 2019, imported contaminated seaweed has been reported to have caused a NoV disease outbreak in Norway (RASFF 2019:3003). Seaweed may be processed in geographical areas, where NoV contaminated seawater may be used for washing (Park et al. 2015), or seaweed may be processed and packed by infected food handlers (Kusumi et al. 2017). These products, despite containing preservatives or being processed by desiccation, may still harbour high titres (360-2900 genome copies/g) of NoV, which could remain infectious even after a long preservation period (Kusumi et al. 2017; Park et al. 2015; Sakon et al. 2018).

Table 3: Some reported outbreaks of foodborne viruses due to produce, 2009-2018

Food Vehicle	Virus	Year	Country of OB	Settings	No. OB	No. cases	Detection (stool/epi?)	Source region	Reference
Semidried tomatoes	HAV	2009	Australia			562	case-control studies + serum + food		(Donnan et al. 2012)
raspberries	NoV	2009	Finland	Restaurant +day care + cafeteria	3	~200	Specimen + food	Poland	(Maunula et al. 2009)
Raspberries (indicated)	NoV	2009	Finland	School	15	525	Epi + stool	Poland	(Sarvikivi et al. 2012)
Salad (indicated)		2009	Germany	Military base	1	101	Epi + stool + environmental swab		(Wadl et al. 2010)
Raspberries	**NoV**	2009	Denmark		**1**	**6**	Epi + Stool + Food	**Serbia**	(Franck et al. 2015)
Semidried tomatoes	HAV	2009-2010	The Netherlands			66	Case-control study +		(Petrignani et al. 2010)
Semidried tomatoes	HAV	2010	France	Domestic	1	59	Serum+epi	Turkey	(Gallot et al. 2011)
Lettuce (Lollo Bionda)	NoV	2010	Denmark				France		(Ethelberg et al. 2010)
Romaine	NoV	2010	Denmark		1	40	Epi + Stool + Food	**Germany**	(Franck et al. 2015)
Lolo bionda	NoV	2010	Denmark		11	260	Epi + Stool + Food	**France**	(Ethelberg et al. 2010)
Raspberries	NoV	2010	Denmark		1	10	Epi + Stool + Food	**China**	(Franck et al. 2015)
Raspberries	NoV	1010-11	Denmark		7	224	Epi + Stool + Food	**Serbia**	(Franck et al. 2015)
Raspberries,	NoV	2010-2011	Denmark	Hospital canteen+	6	27	Epi + Stool + Food	Serbia	(Müller et al. 2015)
Raspberries	NoV	2011	Denmark		1	8	Epi + Stool + Food	**China**	(Franck et al. 2015)
Strawberries	NoV	2012	Germany		1	11000	Epi + Stool + Food	China	(Bernard et al. 2014)
Green seaweed	NoV	2012	South Korea	School	2	91	cohort study + stool + food	South Korea	(Park et al. 2015)
Strawberries	NoV	2012	Germany			10950	Epi + specimen + food	China	(Mäde et al. 2013)
Strawberries	HAV	2012-13	Denmark /Scandinavia		1	103	Epi + Stool + Food	**N Africa**	(Nordic outbreak investigation team 2013)
strawberries	HAV	2012-13	Denmark, Finland, Norway and Sweden			103	Epi + patients' specimen (	Egypt, Morocco and Turkey	(Lassen et al. 2013; Nordic outbreak investigation team 2013)
Pomegranate arils	HAV	2013	USA			165	Patients' specimen + food	Turkey	(Collier et al. 2014)
mixed frozen berries	HAV	2013-2014	13 EU/EEA countries (90% in Italy)			1589	Epi + microbiological	Possibly: Bulgaria (blackberries) and Poland (red currants)	(Severi et al. 2015)
Environment + mixed salad	NoV	2014	Germany	Restaurant	1	3	Stool + food + environmental swab		(Mäde et al. 2016)
green coral (Lollo Bionda) lettuce)	NoV	2016	Denmark		23	412	Cohort Study + Stool + food	France	(Müller et al. 2016)
strawberries	HAV	2018	Sweden			20	patients specimen + food	Poland	(Enkirch et al. 2018)
strawberries	HAV	2018	Austria			14		Poland	Enkirch et al., 2018)
Seaweed (Laver)	NoV	2017	Japan	School	4	1193	Specimen + food		(Somura et al. 2017)
Seaweed (dried shredded)	NoV	2017	Japan	School + office	7	2094	Epi + stool + food		(Sakon et al. 2018)

3.3. Bivalve shellfish

Bivalve shellfish are at constant risk of being exposed to pathogens from their surrounding water as a consequence of human or animal discharge originating from wastewater treatment plants and run offs from manured land (EFSA Panel on Biological Hazards (BIOHAZ) 2012; Krog

et al. 2014). Pathogens are taken up through the bivalve shellfish indiscriminate filter-feeding behaviour and will bioaccumulate to varying degrees in the digestive tissue (DT) of the different species (Carver and Mallet 1990; Winter 1973). If present in the growing water, NoV, HAV and HEV will be accumulated due to specific binding affinities to the tissue in the digestive gland, gills and mantle, with an efficiency depending of the species of shellfish, virus family and strain type, and seasonality (water temperature) (Burkhardt et al. 1992; Burkhardt and Calci 2000; Le Guyader et al. 2012; Maalouf et al. 2010, 2011; Muniain-Mujika et al. 2003).

The hygienic control of faecal contamination in shellfish beds is based on sanitary surveys (EU 2017) and the levels of the indicator bacteria, *Escherichia coli*, in shellfish meat (European Communities 2005). However, despite compliance with legislative requirements (European Communities 2004), NoV, HAV and HEV among other foodborne viruses are frequently detected in oysters and mussels during winter in European areas (EFSA Panel on Biological Hazards (BIOHAZ) 2011, 2012; Mesquita et al. 2016; Pol-Hofstad et al. 2014). Reasons for this are partly that bacteria are eliminated from shellfish more quickly than are viruses (Holm et al. 2015; Schwab et al. 1998). Also, the main foodborne viruses are more resistant to seawater conditions than most vegetative bacteria (Griffin et al. 2003; Mattioli et al. 2017). Besides, lying dormant in the sediment, viruses can be resuspended upon disturbance of the seabed and thus be absorbed by the shellfish long after first entering the sea (Meschke and Boyle 2007). For these reasons, viral and bacterial loads in shellfish correlate poorly.

As a consequence, consumption of raw or undercooked oysters, mussels and clams are regularly associated with disease of NoV, but also HAV and less commonly HEV (EFSA Panel on Biological Hazards (BIOHAZ) 2012), see Table 4. The first association with shellfish-borne viral gastroenteritis was already made in the UK in 1976/1977, when cooked cockles were epidemiologically linked to 33 clusters of nearly 800 people (Appleton et al. 1981; Appleton and Pereira 1977). Since then enteric viruses causing gastroenteritis have been epidemiologically linked to outbreaks of shellfish-vectored illness on numerous occasions in several countries (Bellou et al. 2013). In a study reviewing the 368 published shellfish borne viral outbreaks occurring between 1980 and 2012, NoV accounted for the majority (83.7%, n=300) of outbreaks followed by HAV (12.8%, n=46), AsV (0.5%, n=2), HEV, SaV, RV, AiV, EV (each virus 0.3%, n=1). Oysters were the most commonly involved type of shellfish (58.4%,

n=215) followed by clams (22.6%, n=83), cockles (1.1%, n=3) and mussels (0.5%, n=2). The reported outbreaks occurred in 17 different countries, with East Asia accounting for most of the NoV outbreaks (72.7%) while Europe accounted for most of the HAV outbreaks (83%). The one HEV outbreak was due to mussels from UK.

Human SaV has been detected in an 18-months surveillance study of Spanish mussels (Varela et al. 2016) and in catered lunch suspected to be the cause of disease outbreaks in Japan in 2010 (Oka et al. 2017).

Table 4: Some reported outbreaks of foodborne viruses due to bivalve shellfish, 2009-2018

Cause of transmission	Virus	Year	Country of OB	Settings	No. OB	No. cases	Detection (Epi/stool/food)	Source region	Reference
oysters (steamed) (indicated) + 2nd transmission	NoV	2009	USA	Restaurant	1	177	Epi/ study/stool	USA	(Alfano-Sobsey et al., 2012)
Shellfish	NoV	2009	UK	Restaurant	1	240	Epi/stool/food/ swab		(Smith et al., 2012)
Oysters	NoV	2010	Ireland			>70	Eoi/Stool/food		Marine Institute Ireland* (see Efsa 2011/2012 (EFSA Panel on Biological Hazards (BIOHAZ) 2011)
Oysters	NoV	2007-10	UK		6	287	Epi/Stool/Food	UK	(Lowther et al. 2012)
Oysters	NoV	2010	DK, UK, SE, Fr, NO				Epi/Stool/Food		(Westrell et al. 2010)
Oysters	NoV	2010	UK	Restaurant	1	11	Stool/ swab/food		(Baker et al. 2011)
Mussels	HAV	2012	The Netherlands	Domestic	2	89	Epi/serum	The Netherlands/UK	(Boxman et al. 2016)
Clams (carpet shell) (Tapes rhomboides)	NoV	2013	Norway	company Christmas celebration		43	Epi/food		(Lunestad et al. 2016)
Oysters	NoV	2013	Australia			306	Epi/stool/food		(Lodo et al. 2014)
Oysters (fermented)	NoV	2013	South Korea	School		8	Epi/ stool/food/swab		(Cho et al., 2016)
Raw oysters, Clams	NoV	2016	Denmark				Epi/Stool/Food	France	(Rasmussen et al. 2016)
Scallops	HAV	2016	Hawaii			292		Philippines	(CDC 2016; Disease Outbreak Control Division 2017)
Oysters (*G. gigas*) (raw)	NoV	2017	Denmark			10	Eoi/Stool/food	Denmark	Unpublished

3.4. Meat products

Foodborne transmission of HEV by meat and meat products may be attributed to for example consumption of raw liver from infected pigs or wild boar, or contamination of food products during preparation (BIOHAZ 2017). The exact stage, where meat become contaminated from infected animals, is not known. However, since the virus is shed in animal faeces and urine, poor evisceration practices have been assumed to be the main source of meat contamination by HEV (Velebit et al. 2015).

The European population are sporadically infected with HEV, due to the pig, wild boar and deer reservoirs of the virus, which can reach the food chain (Clemente-Casares et al. 2016). The seroprevalence of HEV in the populations of 11 EU countries have been estimated to be between 2.2 to 52.2% (Clemente-Casares et al. 2016), while in Denmark it is 19.8% among blood donors (Holm et al. 2015). In Denmark, infection of HEV was suggested to be through zoonotic transmission, which in one study was reported to be largely asymptomatic (Christensen et al. 2008). Apart from pigs, ferret, and rat reservoirs in Denmark, farmed minks were reported to carry distinct variants of HEV (Krog et al. 2013). In the USA, consumption of undercooked meat was reported to be the highest risk factor for HEV infection (Cossaboom et al. 2016). Consumption of wild boar meat have been reported to be connected with HEV infection in Japan in at least 2 studies (Li et al. 2005; Masuda et al. 2005). In UK, in 2009-2010, HEV was detected in slaughterhouses, processing plants and point of sale in pork food chain, suggesting pork meat to be a possible risk factor for foodborne transmission of HEV (Berto et al. 2012). HEV RNA has been detected in samples of pig liver (1-21%), meat (0-6%) and sausage (0-47%), in samples of wild boar liver (2-38%), meat (0-12%) and sausage (10%), and in samples of deer liver (0-22%) and meat (0-5%) collected in predominantly developed countries (Pavio et al. 2017). In a screening study in 2016 in Switzerland, approximately 11, 19 or 6% of meat products, liver sausages or raw meat sausages, respectively, were found to contain HEV RNA (Moor et al. 2018). Even exposure to pigs or pig-environment may increase risk of HEV transmission. In Netherlands, 11% of swine veterinarians were seroprevalent for HEV, while seroprevalence was 6% among non-swine veterinarians and only 2% in general population (Bouwknegt et al. 2008).

Table 5: Selected reported outbreaks of foodborne hepatitis E viruses due meat products, 2009-2018, (Extract of ECDC member state survey; ECDC, 2017)

Cause of transmission	Virus	Year	Country of OB	No. OB	No. cases	Reference
Unknown, assumed pork and pork products at pig-slaughtering feasts	HEV	2009–2011	Czech Republic	2	13, 8	(Trmal et al. 2012)
Raw figatelli	HEV	2010	France		2	(Renou et al. 2011)
Probably raw figatelli	HEV	2011	France		1	(Anty et al. 2012)
Tripe sausages made in farm and selling in butcher shop	HEV	2011	Czech Republic		36	(EFSA Panel on Biological Hazards (BIOHAZ) et al. 2017)
Raw pig liver sausage (figatelli)	HEV-3	2011	France		1	(Moal et al. 2012)
Possible factors: pork meat (3), butcher, home pig slaughter (3), excessive pork intake, minced meat/ liver sausage, brawn, liver sausage (3), raw pork meat, grilled pork meat, contact with HEV (2), greaves, minced meat, precooked sausage, home-made sausage, wild boar goulash, sausage	HEV	2009–2012	Czech Republic		27	(Chalupa et al. 2014)
Raw pork liver sausage, not thoroughly cooked pig meat	HEV-4	2011–2012	France		4	(Colson et al. 2012; Tessé et al. 2012)
Undercooked pig liver-based stuffing in spit-roasted piglet	HEV-3	2013	France		17	(EFSA Panel on Biological Hazards (BIOHAZ) et al. 2017; Guillois et al. 2016)
Raw pig liver sausage (figatelli)	HEV-3	2013	France		2	(Renou et al. 2014)
Likely raw pig liver sausage (figatelli)	HEV-3	2014	France		1	(Doudier et al. 2015)

3.4. Dairy products

Transmission through dairy products is relevant for TBEV, which can be acquired by milk producing domesticated animals being bitten by ticks carrying the virus. It should be noted as explained in section 1.4. that proper pasteurization will inactivate the virus.

Table 6: Some reported outbreaks of foodborne viruses due dairy products, 2009-2018

Cause of transmission	Virus	Year	Country of OB	No. OB	No. cases	Detection (stool/epi?)	Source region	Reference
Unpasteurised cow milk	TBE	2011	Hungary	1	7	Epi + blood (not in food)	Hungary	(Caini et al. 2012)
Unpasteurised goat milk (råw)	TBE	2012	Slovenia		3	Epi + blood + food	Slovenia	(Hudopisk et al. 2013)
Raw goat milk + cheese	TBE	2015	Croatia		7	Specimen (cerebral fluid) + serum + epi	Croatia	(Markovinović et al. 2016)
Unpasteurised goat milk, cheese	TBE	2016	Germany	1	32	Goats, Tick, cheese	Germany	(Brockmann et al. 2018)

3.5. Drinking water.

Although not the primary focus of this review, contaminated drinking water can also be the cause of virus outbreaks. This is highly relevant for the food industry, as the regulations require that drinking water is used in the handling and processing of foods.

Table 7: Some reported outbreaks of foodborne viruses due to contaminated drinking water, 2009-2018

Cause of transmission	Virus	Year	Country of OB	Settings	No. OB	No. cases	Detection (Epi/stool/water)	Source region	Reference
Water	NoV GI	2011	Sweden			173	Epi + stool + water		(Riera-Montes et al., 2011)
Tap water	NoV	2012	Denmark	Community	1	15	Epi + stool + water	Denmark	(van Alphen et al. 2014)
Tap water	NoV GI	2015	Greece			230	Stool + water		(Tryfinopoulou et al. 2019)
Private well connected to public water supply	HEV	2015	France			7			(EFSA Panel on Biological Hazards (BIOHAZ) et al. 2017)
Tap water	NoV	2016	Denmark	Community	1		Epi + Stool + water	Denmark	(Hellmér 2018)

4. Mitigation

Strategies to mitigate foodborne viruses can be divided into prevention of the occurrence in the raw material, and mitigation of the viruses in the food processing environment. The latter can be achieved through attention to the hygiene in processing facilities and where possible through food processing to inactivate the virus particles without compromising the quality of the food product.

In terms of decontaminating surfaces or foods, limited efficiency in disinfection of NoVs has been reported when using common disinfectants such as quaternary ammonium compound (QAC) or ethoxylated alcohols (Girard et al. 2010) and for HAV using commercial QAC (Jean et al. 2003). Sodium hypochlorite (50 ppm) or peracetic acid (85 ppm) have been demonstrated to reduce NoV surrogate murine norovirus (MNV) on surfaces of blueberries, strawberries and lettuce by up to 4 logs after 1 min of treatment (Girard et al. 2016). Free chlorine inactivation of HAV and bacteriophage MS2 on strawberries, cherry tomatoes and lettuce has been demonstrated to be effective, however, highly dependent on contact time (2-10 min) and type of food matrix (Casteel et al. 2008; Fraisse et al. 2011). Solomon et al. (2009) showed

that QAC at a concentration of 10 times (8480 ppm) the recommended level (848 ppm) reduced HAV by only 0.4 log, while oxidative disinfectant Virkon required an 1% concentration to achieve a reduction of over 3.2 log.

Ultraviolet light (UVC) can inactivate HAV, feline calicivirus and AiV on lettuce and green onion with log reductions between 2.5 and 5.6 (Fino and Kniel 2008), and can only marginally reduce bacteriophage MS2 on lettuce (up to 2 log) (Xie et al. 2016). For water, lettuce and green onion, ozone inactivation has been observed to be effective on MNV and Feline calicivirus (Hirneisen et al. 2011) or RV (Hirneisen et al. 2011; Khadre and Yousef 2002).

Heat inactivation studies of HAV in cockles showed a 4 log reduction of infectious viruses after heating to internal temperatures of 85-90°C for 1 min (Millard et al. 1987). Traditionally, thermal inactivation of viruses is a reliable process for food decontamination. Though, the process may be time consuming (Hirneisen et al. 2010) and may not be suitable for all surfaces in industrial or health care facility settings or for inactivation of viruses on fresh produce without compromising the quality of food (Berk 2009). Thermal processing of food can reduce the quality of the product visually by altering the texture, flavour, colour or appearance (Oliveira 2004), as well as compromising the nutritional value of food by for example destroying heat-labile vitamins (Awuah et al. 2007). Overall more research is needed into effective mitigation strategies.

5. Conclusions

- The issue of foodborne viruses in our food supply is recognized as an important food safety priority.
- The present report is a contribution to the foodborne virus risk profile being developed by the Danish Veterinary and Food Administration (Fødevarestyrelsen) and includes a review of the current knowledge about the biology of relevant viruses, contamination pathways and product relationships, detection methods and the efficacy of mitigation methods to reduce foodborne viruses.

- Human norovirus (NoV) and hepatitis A virus (HAV) are by far the predominant pathogenic foodborne viruses, with hepatitis E virus (HEV) recently having attained attention as an important contributor to foodborne illnesses.
- Common contamination routes for food are via infected food handlers and/or exposure to contaminated water and materials during primary production of bivalve shellfish, lettuce, fresh or frozen fruits and vegetables, and products of pork and wild boar meat.
- Efficient surveillance and virus control measures are required throughout the food production chain from “farm to fork”. Improved surface surveillance and control after cleaning of kitchen environments may for example reduce food handler transmitted virus outbreaks.
- Research is needed to devise better virus detection methods and mitigation strategies including methods to properly validate the effect of interventions. This would allow for the development of better risk assessments and more targeted control in food production and processing.

6. References

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