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Turning the Spotlight on Meat-borne Viral Diseases

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ABSTRACT

Food borne diseases are and have been an ongoing menace all over the globe. Meat or meat products constitute a major food in almost all classes of people worldwide. Unfortunately, meat when contaminated, serves as a major source and carriers of a number of viral diseases. Noroviruses (NoV), Rotaviruses (RV) and Hepatitis A and E viruses are among the major viruses transmitted by meat and its products causing serious conditions like acute gastroenteritis and hepatitis when consumed without treating and cooking properly. Other viral diseases like MERS, SARS, COVID-19, and Avian Influenza also possess the possibility of transmission through food (meat). Although treatment and prophylaxis for prevention of some of these diseases are available, but due to cosmopolitan nature of the viruses, it is easy for anyone to get afflicted with the disease. It is noteworthy that some of the aforementioned disease(s) have been speculated to have zoonotic implications as well. Control, prevention and strict microbiological testing of meat and meat products right at the level of the source still remain the best method in preventing these diseases. However, for maintenance of good public health standards, it is very important for us to acknowledge not only the food borne bacterial and parasitic diseases, but also the viral pathogens and the diseases they cause. This review highlights some of the important food-borne viral diseases from the etiological, pathological, clinical and prevention cum prophylactic point of view.

KEYWORDS: Food-borne, norovirus, rotavirus, gastroenteritis, hepatitis, COVID-19

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1. INTRODUCTION

Food-borne diseases constitute a major concern to public health in the global outlook. It has been estimated that the etiology of illnesses of 1 out of 10 people is food-borne and according to official WHO estimates, that consumption of unsafe or contaminated food results in 600 million cases of food-borne disease and 420,000 deaths annually (Ali and Alsayeqh, 2022; Anonymous, 2022b). A significant percentage out of those cases is caused/transmitted by the eating of contaminated meat and meat products, with person-to-person contact or through environmental contamination. The food products which are animal-based, like milk, meat and eggs are considered as an essential component of human nutrition (Mughini-Gras et al., 2018). As the global population increases, the demand for meat has also increased. Presently, the world produces about 340 metric tonnes of meat, and it is expected that by 2050, the world consumption of meat will be about 460–570 mt (Ali and Alsayeqh, 2022). Bushmeat, unhygienic backyard and intensive animal farming for meat has also indirectly increased the spillover, and amplification of pathogens important to human health (Espinosa, Tago, and Treich 2020). The animals to be slaughtered or the carcasses may show no signs of disease but they may be carriers or natural reservoirs for a variety of pathogenic microorganisms such as bacteria, viruses and parasites. Food (meat) borne viral infections are responsible for explosive outbreaks worldwide. Infective doses can be very low, only a few virus particles may be required to cause serious illness. Meat-borne viral infections, just like bacterial or parasitic infections, are transmitted either endogenously (animals themselves being the reservoir for the virus) or exogenously (the meat gets contaminated during the processes of transportation, slaughtering, dressing and handling), the latter being more common (Ijaz et al., 2021). The occurrence of meat-borne viral infections can be attributed, but not limited, mainly to the following factors: a) The change in eating habits, for example the consumption of raw and semi cooked meat, and the demand for exotic foods like bushmeats (Newell et al., 2010b) Meat getting contaminated due to environmental and human sources like water contaminated with fecal particles and improper handling by the handlers. c) The shift from low to high protein foods resulting in the increased global demand for meat and fish products.

The major diseases resulting from consumption of such contaminated meat are gastroenteritis and hepatitis (types A and E) which are caused by different viruses. However, new and emerging meat-borne viruses affecting other body systems like respiratory system are being documented too (Todd and Greig, 2015). We have tried to turn the spotlight towards those lesser-known meat borne viral diseases with particular reference to its transmission, pathogenesis, prophylaxis, control and important challenges faced to tackle them. A diagrammatic representation of transmission and infection cycle of the common meat-borne viral diseases has been depicted in Figure 1.

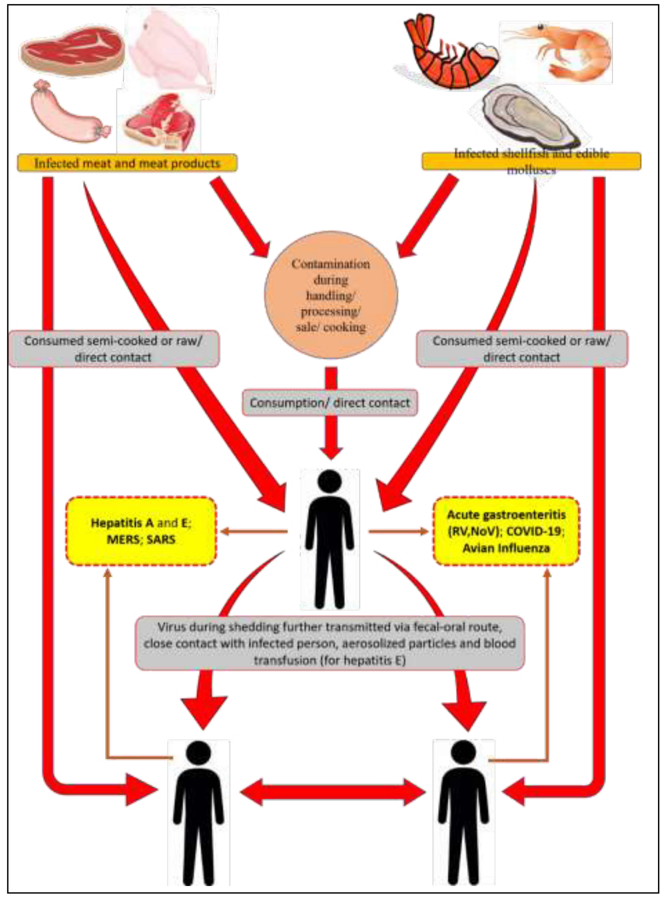

Figure 1: The transmission and infection cycle of the common meat-borne viral diseases

Naturally infected meat, when consumed raw, undercooked or contaminated and aquatic animals like shellfishes and molluscs serve as the major sources of human infection (Roselli et al., 2021). The same sources can also get contaminated via the various intermediary processes. The diseases are contracted either by consumption or by other routes of direct contact. The viruses are then further spread within the communities via faeco-oral and other routes. Therefore, strict policies for hygiene in the animal and meat industry should be made mandatory in order to prevent pathogens in food animals and thereby minimize meat-borne viral diseases (Lyu et al., 2021).

2. GASTROENTERITIS

Gastroenteritis is defined as the condition in which the lining of the stomach and the intestine are inflamed. Infectious gastroenteritis can be caused by bacterial, viral or parasitic pathogens. Bacterial organisms which usually cause severe gastroenteritis are *Campylobacter* spp. (*C. jejuni*, *C. coli*, etc.), non-typhoidal *Salmonellae* and Shiga-toxin producing *Escherichia coli* (STEC) (Fleckenstein et al., 2021; Hakeem and Lu, 2021; Moxley et al. 2020). Among all the enteric viruses, noroviruses (NoVs) and rotaviruses (RVs) have been regarded as the most common viral pathogens and a major cause of food-borne acute gastroenteritis which can result due to consumption of contaminated meat or meat products (Biscaro et al., 2018).

2.1. Norovirus (NoV)

NoVs, also commonly known as the 'winter vomiting bug', belong to the family *Caliciviridae*, a family of non-enveloped, icosahedrally symmetric viruses, measuring about 27–40 nm in diameter. Their genomes are linear, positive sense single stranded RNAs. They are the major non-bacterial cause of acute gastroenteritis outbreaks among the human population. It is caused mainly by consumption of contaminated food and meat products like deli meat, shellfish, oysters and ready-to-eat (RTE) foods (Velebit et al., 2015). NoVs are a large group of viruses which includes Norwalk-like viruses. The prototype strain of this group of viruses is the Norwalk virus (NV), which was first discovered by Kapikian et al., in 1972 (Kapikian et al., 1972). Among the seven NoV groups based on their genotypes, GI and GII are the most commonly found genogroups implicated in human diseases and up to 80% of the infections are caused by the GII.4 strains (Franco and Greenberg, 2012; Haddadin et al., 2020; Lindesmith et al., 2008). GIII and GV genogroups are known to infect the bovine and murine species respectively.

2.1.1. NoV associated meat-borne outbreaks

During the period from November, 2003 to January, 2004, there were 3 outbreaks of NoV infection in Australia mediated by the consumption of oyster meat; in 2005, in Colorado, USA, a NoV outbreak was reported where 137 people fell ill after eating contaminated meat; in December 2013, in Norway, a NoV outbreak occurred following consumption of insufficiently cooked shellfish (Hardstaff et al., 2018; Lunestad et al., 2016; Malek et al., 2009; Parrón et al., 2019; Webby et al., 2007). In the USA alone, 58% of the food-borne gastroenteritis outbreaks are due to NoVs (Bozkurt, D'Souza, and Davidson, 2015). Estimates suggest that human NoV infection leads to around 700 million cases and 220,000 deaths annually around the world (Bartsch et al., 2016; Lopman et al., 2016). In many developing countries where there are areas with poor hygiene, cases and minor outbreaks are often underreported.

2.1.2. Transmission

Contamination of products in the meat processing factories due to unhygienic handling of the products by the handlers and the consumption of the same can lead to noroviral gastroenteritis. Consumption of semi cooked oysters and shellfish has been linked to NoV infection in humans (Yekta et al., 2021). Since oysters are filter feeders, they can concentrate NoV particles if they are grown in water contaminated by faeces (Prato et al., 2004). It has also been found that molluscan shellfish tissues may house NoVs even if they are subjected to depuration for seven days (Cook et al., 2016). The prominent transmission routes are the fecal-oral route, direct contact with infected persons or fomites, ingestion of aerosolized vomit particles from infected individuals and consumption of contaminated water (Dábilla et al., 2017). The incidence of noroviral gastroenteritis has been found to be the greatest among children and older adults. Majority of the severe NoV cases and fatalities have been recorded in patients who are above 65 years of age (Harris et al., 2008).

2.1.3. Pathogenesis

The information on pathogenesis of human NoVs has been primarily derived from volunteer studies and none of the animal models fully replicates the human disease after oral inoculation of the virus. Severity of the disease ranges from mild to life threatening, although asymptomatic cases exist too. The incubation period of the virus in majority of cases ranges from 24–48 hours, but it may also range from 12–69 hours (Webby et al., 2007). The site for primary replication of NoVs is believed to be the upper intestinal tract (Bhar and Jones, 2019). Jejunal biopsy studies show broadening and blunting of the proximal small intestine, vacuolization of the cytoplasm, hyperplasia of the crypt cells, infiltration of mononuclear and polymorphonuclear cells into the lamina propria; and duodenal biopsy revealed a reduction in the villus surface area. However, the mucosa remains histologically intact (Bányai et al., 2018a; Troeger et al., 2009). In experimentally induced NoV infection in human, malabsorption of fat, d-xylose and lactose has been observed due to reduced brush border enzymatic activity, resulting in steatorrhoea and carbohydrate malabsorption (Agus et al., 1973). The body's innate immune response to the infection might also have a role in the symptoms. Shedding of the viruses occurs mainly through vomitus and faeces. However, NoV RNA has also been recovered from mouth washings, which suggest that oral-to-oral route transmission is possible (Ghosh et al., 2022).

2.1.4. Clinical signs

Clinical signs of viral gastroenteritis mainly present as watery non-bloody diarrhoea and acute onset vomiting along with nausea, abdominal cramps, fever, myalgia and malaise (Yekta et al., 2021). The resulting dehydration can further lead to life-threatening conditions like shock, coma and even death. Although most cases result in full recovery, severe outcomes may occur. The severity of the infection depends on a number of factors which include the immune status and genetics of the host and the strain of the virus. It has been found that GII.4 NoV strains cause more severe illness than other strains. Although, NoV induced gastroenteritis is self-limiting in immunocompetent hosts, immunocompromised, solid organ transplant recipients and elderly individuals are susceptible to a higher severity and longer duration of illness (Abbas et al., 2021; Rolfes et al., 2019; Strohmeier et al., 2023). The disease can last from several weeks to several years in such individuals (Bányai et al., 2018a). Children below 5 years of age are also susceptible to more hospitalizations and deaths (Shah and Hall, 2018).

2.1.5. Vaccines

Currently there are no vaccines against NoV fully approved for human use. Lack of a strong and reproducible *in vitro* cultivation system has proved to be the major constraint for the development of an effective NoV vaccine (Zhang et al., 2021). However, research is under way and several vaccine candidates are on their preclinical and clinical phases of development. The vaccines are mainly designed based on the virus-like particles (VLPs), which are produced by the expressed VP1 capsid proteins of the human NoV (Tan, 2021).

2.2. Rotavirus

Like NoVs, Rotaviruses (RV) are also considered as the one of the leading causes of severe acute gastroenteritis worldwide, particularly in children aged from 1 to 5 years (Dennehy, 2015). It accounts for 215,000 deaths globally of children aged 0–5 years (Markantonis et al., 2018). RV is a major foodborne virus which may be transmitted by all types of foods, including meat and meat-based products, provided that they are exposed to it, thus making them a concern to the global public health (Soares et al., 2022). RV belongs to the family *Reoviridae* and is a non-enveloped, double stranded RNA (dsRNA) virus with a diameter of approximately 70 nm. Until 1974, this virus was considered similar reo- or orbi- viruses and was named as 'reovirus- or orbivirus-like particles' found in faeces of young children with acute gastroenteritis and the virus causing acute diarrhea in newborn calves. That study substantially proved the distinct nature of this virus both in terms of its antigenicity and morphology from reo- and orbi-virus and proposed the term rotavirus for the first time in their work (Bishop et al., 1973; Flewett et al., 1974). It has a characteristic 'hubbed wheel with spokes' appearance. It has an icosahedral capsid with three layers, viz. outer capsid, inner capsid and a core. The genome consists of 11 dsRNA segments encoding 6 structural proteins (VP1-VP4, VP6, and VP7) and 6 non-structural proteins (NSP1-NSP6) (Kirkwood, 2010; Leung et al., 2005). On the basis of sequence and antigenic differences of VP6, RVs have been classified into ten species, viz. A-J. Out of these ten species, A is the most common cause of gastroenteritis in children (Crawford et al., 2017). Among the RVAs, 28 G types, 39 P types have been identified and for the remaining nine (B-J) RNA segments, 14 and 24 genotypes were recognized in 2015 (Anonymous, 2022a). Among the diverse genotypes encountered in RVA, the most common genotype is G1P[8] that predominantly found around the world (Sadiq and Bostan, 2020). Recently common shrew (*Sorex ananeus*) was shown to harbor two classes of prototype RV's with low sequence identity (50.1% to rotavirus C, 48.2% to rotavirus H) to mammalian and (or) avian RV's showing a distinct evolutionary trajectory. These were designated as RVK, closely related to RVC and RVL, closely related to RVH (Falkenhagen et al., 2022; Johne et al., 2019; Johne et al., 2022). The annual mortality of <5 year old children from RV-associated disease is much lower since the introduction of RV universal mass vaccination (UMV) programs (Tate et al., 2016; Troeger et al., 2018). One out of three hospital admissions related to moderate or severe diarrhoea in children can be attributed to RVs and it is responsible for around 400,000–600,000 deaths of children. Most of them are from developing countries in Asia and Africa, owing mostly due to weak public health and medical infrastructure (Kirkwood, 2010).

2.2.1. RV associated meat-borne outbreaks

Similar to human NoVs, there have been many outbreaks of rotaviral infections related to consumption of meat products. One such instance is of group C RV which caused a massive outbreak in seven elementary schools in Fukui city in Japan in 1988, infecting over 3000 school children and teachers. It was found that the origin of infection was from a common lunch preparation center and it was speculated that there may have been contamination of the pork provided, probably post preparation (Matsumoto et al., 1989). Another instance is of group A rotavirus infection which was reported among students at a university in the District of Colorado in 2000. Upon investigation it was found that the students who fell ill ate either tuna or chicken salad sandwiches from a common dining hall in the campus (Anonymous, 2022h). Like these two instances, there have been many outbreaks that have happened through food, be those were meat-borne or not. Nevertheless, since rotaviral infections are so widespread in nature, it is important to classify it as a major foodborne viral infection which can spread through meat and meat products.

2.2.2. Transmission

For meat-borne rotaviral gastroenteritis, contamination of meat during handling and in abattoirs remain a major concern. Contamination may occur through contact with faeces of infected animals post slaughter. In developed countries, diseased animals are generally not slaughtered, but older animals with subclinical symptoms may transmit the virus. Consumption of raw or semi cooked meat products as well as shellfish (which are filter feeders and may contain the virus due to exposure with contaminated water) as well as consumption of meat contaminated post preparation due to contact with fomites are also a probable cause of infection (Cook et al., 2004; Hale, 1999). However, like other enteric viruses, RVs are also transmitted mainly by fecal-oral route. Children aged 4–23 months have been found to be the most susceptible for rotaviral infections and due to less immunity at that particular age, reinfections are also a common occurrence (Bányai et al., 2018a).

2.2.3. Pathogenesis

Like NoVs and unlike bacterial gastroenteritis, infection caused by RV is characterized by non-bloody diarrhoea which lasts for short duration. It has also been seen that the diarrhoea is associated with a minimal inflammatory response. RV has affinity towards the mature enterocytes in the villi, enteroendocrine cells of small intestine and replicates in them. The attachment of the virus to the enterocytes has been attributed to its capsid protein VP4 (Crawford et al., 2017). The replication of RV in those cells are also linked to the increased release of serotonin from RV-infected human enterochromaffin cells, resulting in nausea and vomiting (Hagbom et al., 2011). Multiplication of the virus in the duodenal mucosa of infants and children leads to destruction and loss of villous cells and microvilli. There is also a marked proliferation of the secretory crypt cells. The secretion of NSP4 (a viral enterotoxin) from cells infected with RV induces an increase in cytoplasmic Ca^{2+} levels. This sudden rise in Ca^{2+} causes an influx of water into the intestinal lumen causing secretory diarrhoea (Parashar et al., 2013). Mononuclear cell infiltration in the lamina propria, distended endoplasmic reticulum and mitochondrial swelling in enterocytes are also observed. The destruction of villi and the filing of the intestinal crypts results in the loss of surface area for absorption. The virus is shed in large quantities mainly in the faeces. Only 10 virus particles can result in an infection and the shedding ranges from 4–57 days (Anderson, 2008; Crawford et al., 2017).

2.2.4. Clinical signs

The clinical signs of an acute rotaviral gastroenteritis can range from mild to severe watery diarrhoea accompanied with vomiting which can result in hypovolaemic shock, coma and death, induced by severe dehydration (Bányai et al., 2018a; Dian et al., 2021). The severe rotaviral gastroenteritis (SRVGE) is characterized by diarrhoea which is non-bloody and can last for around 3–8 days. Children who are younger in age and with immature immune systems present the highest susceptibility to more severe consequences of the illness. Nearly half of all infected children experience low grade fever. Most of the infected children may have temperatures greater than 102°F and may experience febrile seizures. In almost all cases, there is occurrence of non-bilious vomiting which lasts for 24 hours or less (Dennehy, 2015). In general, the duration of illness of RV infection is longer than a NoV infection. Extraintestinal clinical signs like respiratory symptoms, CNS manifestations are also not unusual in rotaviral infections.

2.2.5. Vaccines

The WHO recommends that in order to reduce morbidity and mortality associated with diarrhoea, prophylaxis against RV infection should be a part of prevention and treatment-oriented interventions. As of 2021, there are four globally licensed vaccines are available which are being used across the world (Cárcamo-Calvo et al., 2021). Two nationally licensed vaccines from Vietnam and China are also being used and available in their respective private markets. Rotarix is a monovalent vaccine derived from a human G1P[8] isolate. RotaTeq® is pentavalent, consisting of a mixture of human bovine RV mono-reassortants, carrying the genes encoding the human G1, G2, G3, G4 and P[8] proteins in a genetic background of the bovine rotavirus Wi79 (G6P[5]) The use of vaccines has significantly reduced the burden of the disease and it has resulted in substantial decline in severe rotaviral gastroenteritis in children (Bányai et al., 2018a; Burke et al., 2019). The effectiveness of these vaccines in children among the age group 12–23 months were found to be 84–86%, 54%, 58% in low, medium and high mortality countries (Burnett et al., 2020). The vaccines are discussed in brief in table 1. All of the vaccines are live attenuated and administered orally.

A study undertaken from 2006–2019 to review the impact of RV vaccine on acute gastroenteritis (AGE) based hospitalizations and death among children less than 5 years of age, found that there was clear reduction by 59% in hospitalizations and approximately 36% reduction in AGE mortality following RV vaccine introduction. Further, these reductions were very pronounced in countries with highest RV vaccine coverage (Burnett et al., 2020). In randomized controlled trails (RCT) conducted in 228, 233 subjects that evaluated the efficacy of Rotarix, RotaTeq, Rotasiil and Rotavac in 2019 found that Rotarix and RotaTeq promisingly reduced the incidences of severe RV diarrhea in low mortality countries, Whereas, all the four vaccines showed a lower efficacy in countries with high mortality cases (Bergman et al., 2021).

2.3. Treatment for acute viral gastroenteritis caused by NoV and RV

Oral rehydration therapy (50–60 mmol l^{-1} sodium) is the recommended first line of treatment for children with mild to moderate dehydration caused by acute diarrhoea. For

Table 1: List of vaccines developed against rotaviruses

	Trade name/name	Manufacturer	Dose
Globally licensed	Rotarix®	GlaxoSmithKline Biologicals, Rixensart, Belgium	3
	RotaTeq®	Merck and Co. Inc., Kenilworth, NJ, USA	2
	Rotavac®	Bharat Biotech, India	3
	Rotasiil®	Serum Institute of India, India	3
Nationally licensed	Rotavin-M1	POLYVAC, Hanoi, Vietnam	3
	Lanzhou lamb rotavirus vaccine	Lanzhou Institute of Biological Products, China	1 annually age 2 months to 3 years

*Table 1 Modified and updated from (Burke et al., 2019; Cárcamo-Calvo et al., 2021; Cates, Tate, and Parashar 2022; Vetter et al., 2022)

cases with severe dehydration, hypovolaemic shock, profuse vomiting, altered consciousness, intravenous rehydration is recommended (Bányai et al., 2018a; Parashar et al., 2013). Probiotics are also useful in reducing the duration of diarrhoea. Some of the common probiotics used for treating acute diarrhoea are *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus plantarum*, some strains of *Bifidobacteria* and *Enterococcus faecium* (SF68 strain), and yeasts like *Saccharomyces boulardii* (Crawford et al., 2017).

3. HEPATITIS

Hepatitis literally means inflammation of the liver which leads to damage of the liver and other body organs. Although there are other causes of hepatitis, viral infections are proved to be the most common cause for hepatitis. Viral hepatitis can be caused by any of the five viruses namely hepatitis A, B, C, D and E; all of which belongs to different genera. Of these, hepatitis A virus (HAV) and hepatitis E virus (HEV) are spread through contact and consumption of contaminated meat, food or water (Anonymous, 2022f.).

3.1. General characteristics of HAV and HEV

Hepatitis A virus and hepatitis E virus are both non-enveloped single stranded RNA viruses (Desbois et al., 2010; Smith and Simmonds, 2018). HAV belongs to the genus *Hepatovirus* under the family *Picornaviridae* (Costa-Mattioli et al., 2003). HAV was initially defined into seven genotypes out of which, genotype I, II and III and genotype VII (reclassified under genotype II) infect humans. Genotypes I and III, are reported most commonly, whereas genotypes IV, V, and VI infects non-human primates (Desbois et al., 2010; Lu et al., n.d.). HEV is whereas classified under the genus *Orthohepevirus* of the family *Hepeviridae* and comprises of 4 species A, B, C and D (Sridhar et al., 2017). Orthohepevirus A are classified into 8 genotypes where genotypes 1-4 and 7 have shown evidences of human infection out of which genotype 3 and 4 are considered to be zoonotic (Smith and Simmonds, 2018). Orthohepevirus C is sometimes termed as rat HEV. Humans contract only HEV 1 and 2 infection via contaminated drinking water whereas both human and animals can get affected by HEV 3 and 4 infection via consumption of contaminated animal products. HEV 7 and rat HEV have been seldom reported (Pallerla et al., 2020).

3.2. Hepatitis A

3.2.1. HAV associated meat-borne outbreaks

The first record of food borne HAV infection outbreak dates back in 1950s and since then there have been sporadic outbreaks. Approximately 25% of those outbreaks were due to consumption of seafood and 36% due to consumption of meat, milk products, bakery products, etc. Most of the HAV outbreaks are recorded in the developed nations of America and Europe (Di Cola et al., 2021). In 2004, in Belgium there was a major outbreak of hepatitis A in which total of 269 cases were registered. The outbreak occurred due to consumption of raw beef through cross contamination. The source of the virus was identified as a food handler at the level of distribution who had contracted hepatitis A, a month before the outbreak occurred (Robesyn et al., 2009).

3.2.2. Transmission

In case of Hepatitis A, transmission is through consumption of meat or food product which gets contaminated with HAV either during harvesting, processing, distribution or preparation of meat or meat-based dishes. Many outbreaks stated involvement of HAV infected food handlers handling raw or cooked food either during preparation or sale. However, there is uncertainty regarding whether the infected food handlers were ill at the time of transmission or whether they have recovered. Nonetheless, there is enough proof assuring that infected food handlers do play a major role in transmission. In case of HAV contamination during harvesting of meat products, shellfish are a proven example as the source of transmission. The main factors which contribute to contamination in shellfish, oysters and raw clams are harvesting them in untreated sewage water or near sewage plants (Acheson and Fiore, 2004).

3.3. Hepatitis E

3.3.1. HEV associated meat-borne outbreaks

Meat-borne HEV outbreak was first reported in Japan in 2003 with deer meat as the source of contamination. From 2003 to 2018 there were subsequently 12 outbreaks due to consumption of pork meat, wild boar meat, piglet meat and figatelli (pork sausages). France has the highest recorded HEV outbreaks (6 outbreaks in the year 2007–09 and 2013), followed by Japan (4 outbreaks 2003–2006) due to consumption of meat. The first reported outbreak of hepatitis E due to consumption wild boar meat was recorded in Spain in the year 2015. The latest outbreak was reported in China in the year 2018, the source of which is epidemiologically related and reported as pork liver. Seafood is also linked to HEV outbreaks but to a lesser extent in comparison to HAV outbreaks (Di Cola et al., 2021).

3.3.2. Transmission

Like HAV, HEV is also transmitted by consumption of raw or undercooked meat of wild boar, deer, rabbits, camels, goat, cattle and shellfish, causing hepatitis type E. Genotype 3 HEV infection is evidently linked to the consumption of pork products. The transmission between pigs is through the faeco-oral route. There is significant evidence on transmission of HEV by pork products and meat of wild boar and deer. Although there are traces of HEV found in milk and meat of cattle, camel, goat and rabbit meat too, but further investigation is going on in regards to distribution of HEV is in these group of animals and its implication on human transmission. Pollution of water sources with sewage water increases the possibility for shellfish to be affected by HEV contamination. HEV is also traced in dolphins but the transmission within dolphins is still unknown. Consumption of infected fishes by dolphins are suspected to be the source of transmission. Hence investigation regarding aquatic fishes as a source of HEV transmission to humans are currently under process (Treagus et al., 2021). Present evidences and studies by nested PCR and genomic sequencing have also found that infected pigs and wild boars are the main reservoirs of HEV (Johne et al., 2022; Pallerla et al., 2020). HEV RNA has been found to be mainly concentrated in pork livers and processed pork products like sausages. The virus is inactivated by heating the product for 72°C for 20 minutes, thus infection primarily indicates that the consumed meat was either undercooked or raw (Pallerla et al., 2021). The infected pigs also shed the virus in their faeces, which can contaminate the water bodies, thus infecting both healthy humans and pigs via waterborne transmission. The contaminated water, if used in the intermediary meat processing steps, can contaminate the meat as well (Beyer et al., 2020; Johne et al., 2022). Although the primary mode of transmission for both HAV and HEV are generally considered to be the faeco-oral route, either via direct contact with infected person or by ingestion of contaminated food and water, but unlike hepatitis A, human to human transmission of HEV is rare although alternative transmission routes are blood transfusion and vertical transmission from mother to child are reported (Shin and Jeong, 2018).

3.4. Pathogenesis

The pathogenesis of both hepatitis A and hepatitis E are almost similar. The incubation period is about 2–10 weeks. During this period HEV reaches the liver via intestinal tract. In case of hepatitis A, there is onset of mild chemical hepatitis. After reaching the liver both HEV and HAV undergo multiplication in the hepatocytes before entering into the circulation. There is a possibility of virus multiplying in the enterocytes but whether or not the virus replicates in the enterocytes before entering into circulation remains ambiguous. The replication of the viruses causes hepatocyte injury which is responsible for the appearance of clinical signs in humans. Viremia and faecal shedding of the virus begins before the onset of the symptoms. There is also rise in serum transaminase levels (Aggarwal and Goel, 2019; Lemon, 1997). HAV has two different forms, namely quasi-enveloped HAV (eHAV) and non-enveloped naked HAV. Quasi enveloped virus as the name suggests are enclosed in small extracellular vesicles (EV's) that are devoid of virus-encoded surface protein which are released non-lytically. These eHAV are the only form found in the sera from infected humans and after losing its lipid envelope due to its exposure to bile, the naked HAV is found in the faeces (Shin and Jeong, 2018). In case of acute liver failure (ALF) due to hepatitis A and B the liver size decreases, liver tissue shows varying degree of hepatocyte necrosis, pseudo-rosette formation, hepatocyte degeneration and infiltration by mononuclear inflammatory cells, portal and lobular inflammation, presence of plasma cells in portal tracts, bile duct proliferation, Kupffer cell activation and disruption of bile canaliculi. Marked swelling of brain leading to neurological complications can also be seen in certain cases of ALF (Aggarwal and Goel, 2019; Shin and Jeong, 2018).

3.5. Clinical signs

Both HAV and HEV generally cause acute viral hepatitis. HAV infection does not lead to chronic hepatitis whereas some people infected with genotype 3 of HEV might develop chronic infection (Aggarwal and Goel, 2019; Shin and Jeong, 2018). The clinical signs of Hepatitis A can be divided into asymptomatic and symptomatic infection. Fever, malaise, nausea or vomiting, abdominal discomfort, dark urine and jaundice are some of the common symptoms whereas diarrhoea, arthralgia, pruritus or developments of skin rash are some of the uncommon symptoms. The symptoms are more prevalent in adult patients in comparison to the children and persist for around 2–8 weeks in adults whereas asymptomatic infection generally heals spontaneously (Shin and Jeong, 2018). Clinical symptoms of Hepatitis E are almost similar to the ones of hepatitis A although the course of illness is divided into three phases namely: prodrome or prodromal phase, icteric phase and convalescent phase. It's in the prodromal phase, symptoms like malaise, myalgia, fatigue, low grade fever anorexia, nausea, vomiting, aversion to food, abdominal discomfort, right upper quadrant pain is observed. Prodromal phase lasts for 3.5 days on average. Jaundice onsets in the icteric phase along with mild itching and light-colored stools and recovery of appetite and other systemic symptoms. In the convalescent phase other symptoms completely relieved although mild jaundice may persist (Aggarwal and Goel, 2019). Symptomatic infections of both HAV and HEV either leads to acute liver failure (ALF), extra hepatic complications such as acute reactive arthritis, hemolysis, hemophagocytosis, pure red cell aplasia, acute pancreatitis etc. ALF or extra hepatic complications can lead to death (Aggarwal and Goel, 2019; Shin and Jeong, 2018).

3.6. Vaccines

Hepatitis A is a disease that can be prevented by vaccination. A number of vaccines have been approved that are currently being used worldwide. They can be broadly classified into two types as described in table 2.

Worldwide, there are no vaccines commercially available for hepatitis E, except in China. In China, a recombinant vaccine by the name Hecolin® (HEV 239) has been available since 2011 and is approved for use to people above 16 years (Yu et al., 2019). This vaccine is mainly effective towards genotypes 1 and 4 of HEV. The primary antigenic constituent of the vaccine consists of the ORF2 protein of the HEV1 strain. No vaccines are available for animal use (Harrison and DiCaprio, 2018).

3.7. Treatment for hepatitis caused by HAV and HEV

For both hepatitis A and E, there are no specific antiviral therapies. Hospitalization is generally not required until a case of acute liver failure or chronic hepatitis arises. Patients with co morbid conditions or symptomatic pregnant patients might require hospitalization. Treatment is generally supportive which includes bed rest, balanced diet, replacement of fluid losses and avoiding unnecessary medicines and alcohol. In few cases of cholestatic Hepatitis A, patients are treated with corticosteroids. In case of chronic Hepatitis E administration of antivirals is highly recommended along with reduction of immunosuppression. Administration of pegylated interferon-α is also recommended but it has certain side effects for patients who have undergone heart or kidney transplantation. In case of fulminant hepatic failure, the only feasible and widely acceptable treatment is live transplantation (*Hepatitis E*, n.d.; Kemmer and Miskovsky, 2000; Wedemeyer et al., 2012). In many cases, it is very difficult to clinically distinguish hepatitis A and hepatitis E from other types of acute viral hepatitis. Hence confirmatory diagnosis is essential. Definitive diagnosis can be done by detecting presence of anti HEV immunoglobulin M (IgM) for hepatitis A or HAV specific immunoglobulin G antibodies in blood for hepatitis A. RT-PCR is also widely used (*Hepatitis E*, n.d.).

3.8. Diagnosis

For effective control of an outbreak of any disease, immediate

Table 2: List of vaccines developed for HAV*

Type of vaccine	Attenuated HAV strain	Trade name/Name	Manufacturer
1. Formalin inactivated (killed)	HM-175	HAVRIX®	GlaxoSmithKline
	CR-326	VAQTA®	Merck
	GBM	AVAXIM®	Sanofi Pasteur
	TZ84	HEALIVE®	Sinovac Biotech Co LTD
	Lv-8	Weisairuian®	Institute of Medical Biology of the Chinese Academy of Medical Sciences; Kunming
	YN5	Veraxim®	Shanghai Wison bioengineering Inc
	RG-SB	EPAXAL®	Crucell/Berna Biotech
2. Live Attenuated	H2	Biovac A® (Freeze-dried)	Wockhardt Ltd/ Zhejiang Pukang Biotech Company
	LA-1	HAVAC freeze–dried live HAV vaccine	Changchun Institute of Biological Products

*Table 2 modified and updated from (Herzog et al., 2021; Lemon et al., 2018) diagnosis is required. For both noroviral and rotaviral gastroenteritis, the ideal specimen for laboratory diagnosis is diarrhoeic stool. Rapid immunochromatographic assays and commercially available enzyme immunoassays (EIAs) are available like IDEIA Norovirus (Oxoid Ltd., Hampshire, United Kingdom) and Ridascreen Norovirus (R-Biopharm, Darmstadt, Germany) for detecting NoV infection (Robilotti et al., 2015). These demonstrate a wide range of sensitivities and specificities. However, among the most broadly used detection methods for NoVs in specimens worldwide are end-point RT-PCR and qRT-PCR assays which targeting the genomic region bridging the RNA polymerase and major capsid protein-coding region (Bányai et al., 2018a; Vinjé, 2015). For RV detection, commercially available EIAs show high specificity and sensitivity (>90%). They are the most widely used assays in clinical and public health laboratories (Bányai et al., 2018a). Upon onset of illness, the viral shedding normally ends within 1 week and can be detected by ELISA until then. RV antigen detection kits like the VIKIA Rota-Adeno antigen test has high sensitivity in detection of RV in infected children (Hung and Chen, 2023; Lagare et al., 2017). However, using RT-PCR increases the duration of detection by several folds. RT-PCR in RV infection is more commonly used for vaccines and epidemiological studies (Crawford et al., 2017). HAVs and HEVs cannot be clinically differentiated from other hepatitis viruses such as hepatitis B, C and hepatitis D due to which serological testing becomes necessary (Anonymous, 2022d; Anonymous, 2022e). Common methods that are used to detect HAV specific antibody are radio immunoassays, immunochemical staining, ELISA, immune blotting, dot blot immunogold filtration techniques. The commercially available diagnostic assays are based on IgM anti HAV EIAs where they detect both IgG and IgM antibodies (Nainan et al., 2006). Detection of HEV is also similar to like that of HAV which is based on detection of specific anti-HEV IgM antibodies in blood (Anonymous, 2022e). Molecular detection methods like RT-PCR are also used to detect the presence of both HAV and HEV in samples of faeces, blood, environmental samples and water. These are more sensitive and accurate than immunoassay for viral antigen detection (Lemon, 1997; Nainan et al., 2006).

4. OTHER DISEASES

Although the most common viral diseases caused by the consumption of contaminated meat are discussed above, there are many other diseases which can result just from direct contact with the infective meat too. The primary source of those diseases has been traced back to meat, and after that those diseases transmit from person-to-person. Few of them are discussed here in this section.

4.1. Coronavirus disease of 2019 (COVID-19)

COVID-19, the recent pandemic that locked the whole world inside, is a disease caused by the novel coronavirus namely SARS- CoV-2 (severe acute respiratory syndrome-coronavirus 2) of the *Coronaviridae* family. Birds, wild animals such as and humans have proven to be hosts for almost all the coronaviruses (Halabowski and Rzymski, 2021). The virus seemed to have originated in bats, however it is suspected that the emergence of COVID-19 in humans has progressed as a zoonotic transmission of the virus from the wet market of Wuhan (Halabowski and Rzymski, 2021; Yuki et al., 2020). Most of the covid patients initially reported were concentrated in and around the wet market of Wuhan. Many exotic and wild animals which included chickens, snakes, civets, rats, giant salamanders etc., and their meat were sold in that market. Cross species transmission is speculated to have happened by direct contact with the contaminated tissues of the animals or by consumption of infected meat. Since mid-June, 2020 there have been series of evidences of re-emerged outbreaks of SARS-CoV-2 linked to salmon contamination in Beijing province of China. SARS-CoV-2 was detected on fresh, frozen foods, as well as the packaging materials. Further this virus was found to remain stable at 4°C refrigerated and -20 and -80 °C freezing temperatures (Han et al., 2021). Minks have been reported to transmit this virus and its variants between live animal and humans in countries such as Denmark, USA, Netherlands and Spain (Koopmans, 2021). After the primary infection, human to human transmission is mostly through droplets or aerosols or contact with contaminated surfaces. Transmission of the virus from the bats to the intermediate host is still undergoing research (Duda-Chodak et al., 2020). The transmission of SARS-CoV-2 from bats to humans although involves an intermediate host but there is doubt regarding which animals act as intermediate hosts (Alanagreh et al., 2020). Pangolins are however highly doubted to have been the intermediate host (Ye et al., 2020). Consumption of bat meat is also suspected to be possible way of transmission. Although COVID 19 primarily causes respiratory infection, studies have also determined presence of virus in the faeces thus raising gastro-intestinal route as a possible entry for the virus (Holshue et al., 2020). Patients of COVID 19 range from asymptomatic to critically ill patients. Symptoms may develop from fever, cough, fatigue, sore throat, runny nose, vomiting nausea, diarrhoea to pneumonia. Critically ill patients might show acute respiratory distress syndrome, heart failure, shock, acute kidney injury (Yuki et al., 2020). Mortality rates are estimated to go as high as 5.7% (Spychalski et al., 2020). Vaccines are being developed in order to combat the spread of COVID-19. The type of vaccines that are being developed includes live attenuated, inactivated, protein or adjuvant, viral vectors and nucleic acids vaccines (Tregoning et al., 2020).

4.2. Middle east respiratory syndrome (MERS)

MERS is a severe respiratory disease caused by the MERS-CoV, another virus of the *Coronaviridae* family. The virus is believed to be originated from zoonotic sources and primary human infections are mainly attributed to direct contact with dromedary camels (*Camelus dromedarius*), which are considered to be the natural hosts for MERS-CoV (Alshukairi et al., 2018). The transmission of this virus through meat can occur by consumption of raw camel meat, particularly the lungs or by contamination of meat with respiratory tissues of an infected carcass in the slaughterhouse (Hemida et al., 2017). After primary infection, the disease is transmitted via person to person. The mortality rate of the disease can be as high as 35%. Clinical signs can vary from mild viz. fever, cough and fatigue to severe, like pneumonia and acute lung injury (Ebrahim et al., 2021). Treatment for MERS is mainly supportive and vaccine candidates against MERS are currently under development and none have been approved for public use as of now (Li et al., 2020). Although epidemics and major outbreaks occur less commonly today, cases are still reported, particularly from the Middle East countries and travelers from those countries.

4.3. Severe acute respiratory syndrome (SARS)

SARS, as the full form says, is also a severe respiratory disease caused by SARS-CoV, yet another virus of the *Coronaviridae*. It was the etiology of the dreaded outbreak which started in 2002 in China, causing 778 deaths out of over 8000 infections (Gong and Bao, 2018). The primary infection is thought to have originated in the wet markets, where meat of civet cats, an important intermediate host of the virus and other game food mammals are sold (Gong and Bao, 2018; Woo et al., 2006). It was speculated and presumed that the civet cats which were for sale were infected by direct contact with horseshoe bats (*Rhinolophus* spp.) (Lytras et al. 2021). The virus is transmitted either by droplet, air or direct contact with the infected individual. The major clinical signs are persistent fever (>38°C), non-productive (dry) cough, myalgia, dyspnoea, chills, malaise and diarrhoea (Hui et al., 2003). Treatment generally consists of respiratory and intensive care support. Despite the non-occurrence of any recent outbreaks, this disease is still a major concern of public health due to its high mortality rate, particularly in regions of the world where consumption of wild animals is a part of the culinary culture.

4.4. Avian influenza

Avian Influenza or bird flu is typically a disease of poultry birds caused by the Avian Influenza virus (AIV) of *Orthomyxoviridae*. AIV has many a times crossed the species barrier to infect humans, thus expressing its zoonotic importance and its serious risk to public health. Countries of eastern Asia reported an epidemic of bird flu caused by the AIV H5N1 strain in poultry in early 2004, in which the virus also infected and killed 54 out of 100 people to which it got transmitted (Webster et al., 2005). In 2013 too, China reported an outbreak of avian influenza in humans, caused by the H7N9 strain. This strain was also responsible with a few fatalities (Chen et al., 2013). Notably, all of the people who were infected were in contact with live poultry or poultry meat a few days before the onset of illness, suggesting that the virus transmits from infected poultry birds or meat to humans. The prominent clinical signs presented are productive cough, hemoptysis, dyspnoea and fatigue. The mortality rate can go up to 50% (Chen et al., 2013; Woo et al., 2006). The treatment mainly includes antiviral therapy (oseltamivir), respiratory and intensive care support. Due to bird flu's high mortality rate in humans and the virus's potential to cause epidemics, people working in the poultry sector and meat processing factories should be extra vigilant so as to prevent any possibilities of transmission of AIV to humans from infected birds. Strict inspection and disinfection measures should be made mandatory in all poultry supply chains to minimize risk (Dai et al. 2022).

5. PREVENTION AND CONTROL

5.1. Noroviral infections

As suggested for any other food (meat) borne diseases, limiting contact with infected people and washing of hands regularly, reduces the chances of transmission of noroviral infection (Anonymous, 2022g). Use of chlorine bleach solution at a concentration of 1000–5000 ppm (1:50–1:10 dilution of household bleach) is recommended for thorough disinfection of contaminated surfaces. Depuration of shellfishes can be practiced to get rid of the viruses from them as a preventive measure, till an extent (Gyawali et al. 2019). As already mentioned, no commercial vaccines are currently available for noroviral infections but some are under clinical phase trials like the NoV VLP vaccine manufactured by Takeda Vaccines, Cambridge, Massachusetts, USA which is under the phase 2 clinical trial (Bányai et al., 2018b).

5.2. Rotaviral infections

As far as rotaviral infections are concerned, RotaTeq and Rotarix (Table 2) which are pentavalent bovine human reassortant vaccine and monovalent human vaccine respectively, have been licenced since 2006 (Bányai et al., 2018b). Globally almost 114 countries have implemented routine infant vaccination against as of January, 2022 (Anonymous, 2022c). Following the strict vaccine protocol for almost a decade in the USA, a steep decline in rotaviral infections were reported in infants (Aliabadi et al., 2015). In another study conducted in USA, reduction in gastroenteritis has been documented in children and adults who were unvaccinated indicating that vaccinating the young infants might be indirectly protecting the children and adults by reducing the chances of transmission (Gastañaduy et al., 2013). Owing to the oral route of administration of RV vaccines, coinfections with other enteric pathogens, illness or malnutrition was thought to influence the performance of this vaccine in developing countries. Therefore, the recommendations for the use of RV vaccines globally were issued in 2009, after conducting few randomized trials in those countries like sub-Saharan Africa (Ghana, Kenya, Mali), Asia (Bangaldesh and Vietnam) (Armah et al., 2010; Zaman et al., 2010). Developing countries shows lower vaccine efficacy (50-64%) compared to developed countries (85-95%) (Bányai et al., 2018b). In 2014, India licensed its first RV vaccine showing 56% efficacy (Rotavac). Serum Institute of India, in 2018 licensed another indigenously manufactured live oral rotavirus vaccine Rotasiil which showed 66% efficacy in a clinical trial conducted in Niger in 2017. The same Rotasiil efficacy with respect to prenatal nutrient supplementation was tested in another trial. Modest increase in immune response was seen with 3 doses of Rotasiil, but not affected by prenatal nutrient supplementation (Isanaka et al., 2021).

5.3. Hepatitis types A and E

Enteric viral hepatitis mainly caused by HAV can be curbed by proper cooking of food, following hygienic practices during preparation and handling of food (Koopmans et al., 2008). Consumption of raw/ minimally cooked shellfish needs to be discouraged for health reasons. Ensuring supply of clean water for irrigation or washing of vegetables can be carried out to reduce contamination at the farm level. Chain of transmission of hepatitis A can be broken by providing proper sanitary facilities for the workers.

6. KEY CHALLENGES

Although vaccines are available currently for some of the meat borne viral diseases, but breaking the transmission cycle must be given paramount importance. In spite of that, preventing the transmission of disease from the source (meat, water, food, etc.) to the host is the first barrier met as a challenge. Failure to comply the GMP, GHP, HACCP rules during meat processing in abattoirs and (or markets) may lead to sporadic outbreaks of meat borne viral diseases. Although depuration is practiced in many countries, but the effectiveness of this technique is still questionable (Koopmans et al., 2008). Immunoprophylactic measures still poses a challenge, as some of those viral diseases do not have approved vaccines at present. The antigenic and genetic diversity of NoV poses a barrier for selection of vaccine candidates. A persistent challenge of oral RV vaccines to reduce morbidity and mortality among vulnerable population in low-income countries compared to high-income countries is the lower efficacy rates of the vaccines, the reason being not clear yet (Church et al., 2019). Maternal antibodies, vitamin (or mineral) deficiencies, coinfections in gastrointestinal tract or any other concurrent infections might be the probable cause (Church et al., 2019). In one study prenatal micronutrient supplementation resulted in nutrient-abundant fetal environment that helped to potentiate the immune system of the infant on birth and improved the performance of the oral vaccines (Albert et al., 2003; Habib et al., 2015). Confirmation and interpretation of positive PCR results is also a diagnostic challenge frequently encountered.

7. CONCLUSION

As per the global population, there is an increase in demand in the meat industry sector. Bacterial and parasitic diseases transmitted by meat still remain the main focus of the general population, but the viral diseases mentioned in this paper, too pose a serious threat to public health, with some of them even having zoonotic significance. Hence, strict measures and importance should be implemented at the animal and meat supply chain levels to ensure prevention of such mentioned viral diseases.

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