Chapter 10
Hepatitis E Virus

Vasileios Papatsiros

Abstract Hepatitis E virus (HEV) is taxonomically classified within *Hepeviridae* family and *Orthohepevirus* genus. Genotypes HEV-1 and HEV-2 infect human, while genotypes HEV-3 and HEV-4 are zoonotic viruses that infect humans, domestic pigs and other animal species (e.g. wild boar, deer). The main route of trans-species transmission is the direct contact with infected animals, as well as via the consumption of HEV-contaminated food products or via the faecal–oral route through drinking of contaminated water. HEV-3 has been detected in pigs around the world (South and North America, Europe, Africa, Asia, and Oceania). HEV-4 has mainly reported in domestic pigs and humans in Asia. Domestic pigs, wild boar, and various species of deer reported to play important role in zoonotic transmission of HEV-3 and HEV-4 from animals to humans. The most important reservoirs of the HEV genotypes are domestic pigs and the most HEV infections in humans are foodborne due mainly to consumption of undercooked meat or meat products (e.g. sausages). The main route of natural HEV transmission in pigs is via the faecal–oral. However, the HEV infection in pig is usually asymptomatic, with low impact on health status. Future studies focus on preventive measures to eliminate the appearance and persistence of HEV in pig farms (including biosecurity and vaccination) are required. Moreover, more studies are needed to investigate deeply the role of wildlife in the epidemiology of HEV infection.

Keywords Hepatitis E virus · HEV · Pig · Human · Pork · Epidemiology · Pathogenesis

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10.1 Prologue

Hepatitis E virus (HEV) is the causative agent of hepatitis E and it is classified into family *Hepeviridae*, which is divided in two genera: *Orthohepevirus* and *Piscihepevirus* (Smith et al. 2014). The genus *Piscihepevirus* includes only *Piscihepevirus A* (cutthroat trout virus), while the genus *Orthohepevirus* is divided in four species (Khuroo et al. 2016; Purdy et al. 2017):

(a) *Orthohepevirus A*, including isolates from such humans, domestic pigs, wild boars, deer, mongoose, rabbits, and camels—Fig. 10.1). Moreover, *Orthohepevirus A* has eight genotypes, five members of them are found to infect humans (Johne et al. 2014).
(b) *Orthohepevirus B*, including three avian isolates (HEV-1, HEV-2, and HEV-3),
(c) *Orthohepevirus C,* including isolates from rats, greater bandicoot, Asian musk shrews, mink, and ferrets, and
(d) *Orthohepevirus D*, including isolates from bats

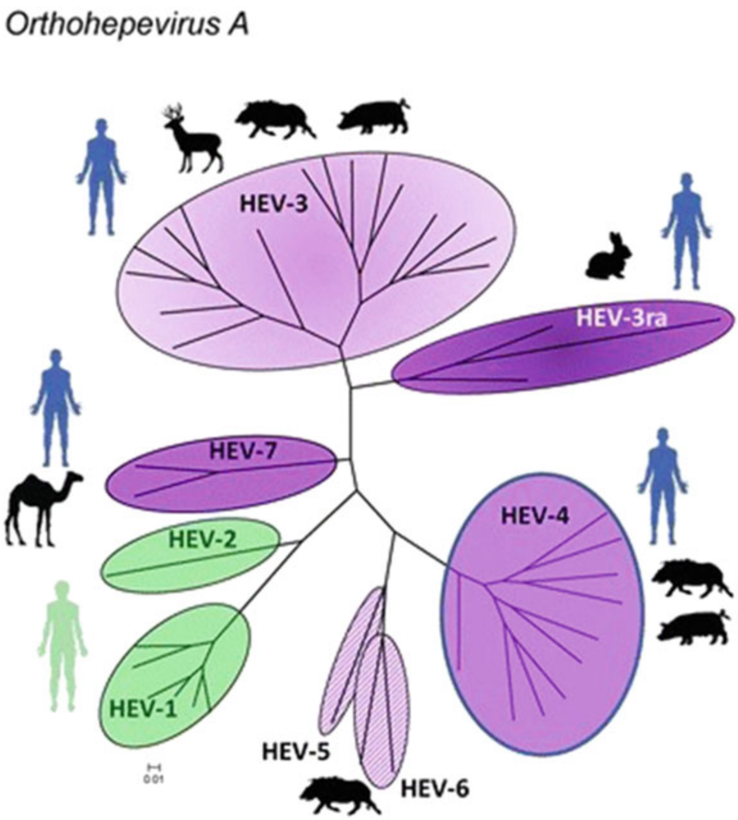

Fig. 10.1 Phylogenetic tree of HEV sequences within the species Orthohepevirus A (adopted from Pavio et al. 2017 and Smith et al. 2016)

HEV is a relatively stable virus, surviving in the gastrointestinal tract environment due to its resistance to gastric secretions and bile salts (Emerson and Purcell 2001). It is a small non-enveloped virus (27–33 nm in diameter) and icosahedral shaped sphere with shaped bumps visible on its surface (Balayan 1997). Its genome consists a single-stranded, positive-sense RNA molecule about 7.5 kilobases (kb) in length, which contains three open reading frames (ORF) (Tam et al. 1991). Based on ORF2 nucleotide sequence analysis, four major genotypes (HEV-1, HEV-2, HEV-3, and HEV-4) have been defined in mammals (Schlauder and Mushahwar 2001).

HEV genotypes 1 and 2 (HEV-1, HEV-2) are reported in humans (Kamar et al. 2017), while HEV genotypes 3 and 4 (HEV-3, HEV-4) are zoonotic viruses, infecting both humans and animals. The main route of trans-species transmission is the direct contact with infected animals, as well as via the consumption of HEV-contaminated food products or via the faecal–oral route through drinking of contaminated water (Colson et al. 2010; Dremsek et al. 2012; Chaussade et al. 2013; Riveiro-Barciela et al. 2015; Guillois et al. 2016). In rabbit species a separate genotype HEV-3 (HEV-3ra) was reported, which also includes a closely related human isolate (Pavio et al. 2017). Furthermore, HEV genotypes 5 and 6 (HEV-5, HEV-6) have been reported in wild boars (Takahashi et al. 2011), while HEV genotypes 7 and 8 (HEV-7, HEV-8) were found in camels (Woo et al. 2016; Lee et al. 2016).

Studies reported the isolation of HEV from various wild and domestic animals, such as domestic pigs, cattle, chickens, sheep, goats, and rodents (Favorov et al. 2000; Meng 2000).

10.2 Epidemiology

10.2.1 Geographic Distribution

The geographical distribution of terrestrial animal reservoirs of HEV is summarized in Fig. 10.2. Pigs, wild boar, and various species of deer are involved in zoonotic transmission of HEV-3 and HEV-4 to humans. However, the role of mongooses, rats, and rabbits in causing human hepatitis E is unclear. Domestic pigs are the most important reservoirs of the HEV genotypes that are capable of infecting humans. In 1997, HEV-3 was first isolated from pigs in USA (Meng et al. 1997) and since then many studies reported high prevalence of HEV (seroprevalences were estimated between 5 and 100%) in pig herds worldwide (de la Caridad Montalvo Villalba et al. 2013; Owolodun et al. 2014; Aniță et al. 2014; Burri et al. 2014; Liu et al. 2015; Merino-Ramos et al. 2016; Thiry et al. 2017a, b), including countries from five continents:

(a) Asia (China, India, Indonesia, Japan, Korea, Mongolia, Philippines, Taiwan, Thailand, and Vietnam),

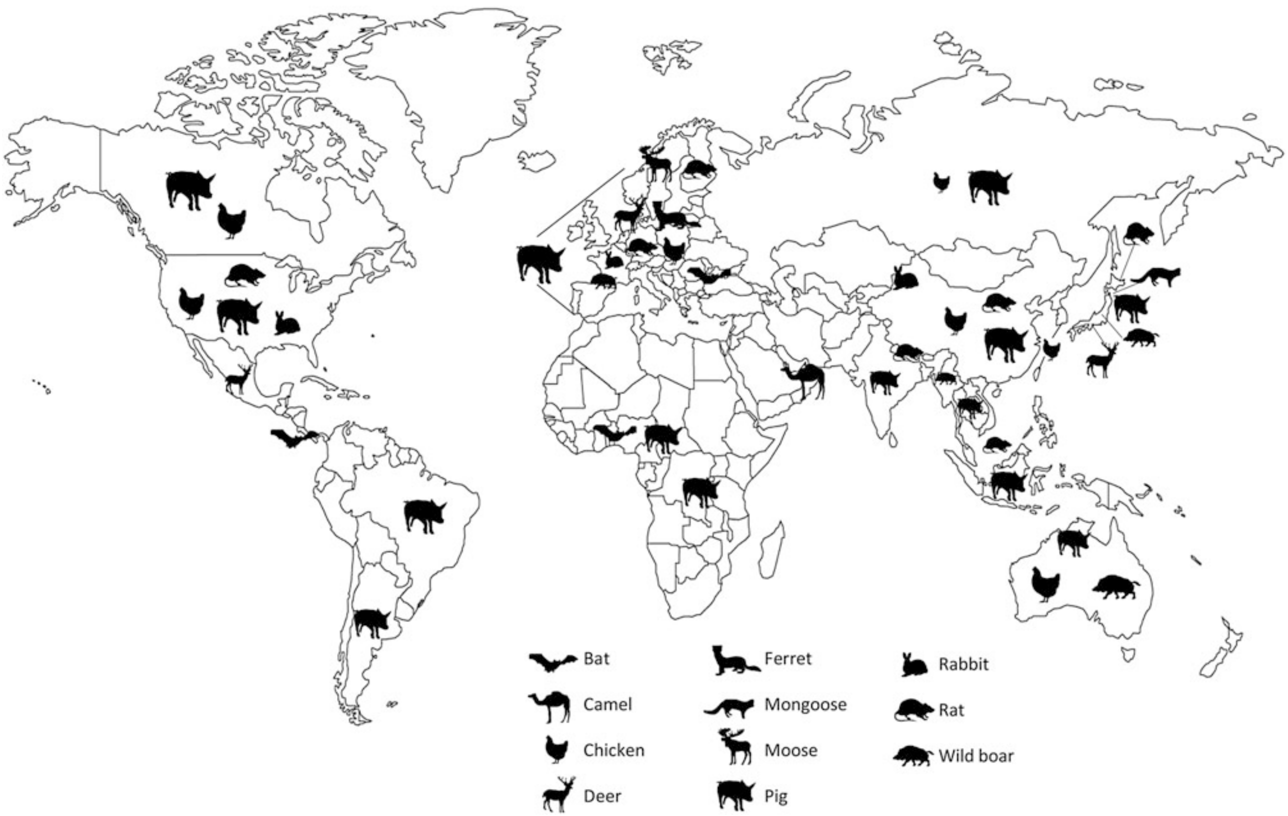

Fig. 10.2 Geographical distribution of HEV3 and HEV4, and novel HEV-like viruses in terrestrial animals (adopted from Sridhar et al. 2015)

(b) South and North America (Argentina, Bolivia, Brazil, Cuba, and Mexico/Canada),
(c) Africa (Cameroon, Democratic Republic of Congo, Nigeria, and Madagascar),
(d) Europe (Belgium, Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Romania, Spain, Sweden, Switzerland, and the United Kingdom), and
(e) Oceania (Australia, New Caledonia, and New Zeeland).

HEV-3 has been detected in pigs from all aforementioned continents, whereas HEV-4 has mainly been reported in pigs and humans in Asia and recently also in Europe (Hsieh et al. 1999; Schlauder and Mushahwar 2001; Cooper et al. 2005; Thiry et al. 2017a, b; Salines et al. 2017; Pavio et al. 2017).

10.2.2 Transmission of HEV to Humans

Mainly reservoirs for genotypes HEV-3 and HEV-4 are domestic pigs and wildlife (wild boars, sika deer) (Pavio et al. 2015). HEV is transmitted primarily in humans via the faecal–oral route (Purcell and Emerson 2001). Human infections are due mainly to consumption of undercooked meat or meat products (e.g. sausages), direct contact with infected animals, drinking contaminated water and environmental contamination by animal manure run-off (Khuroo et al. 2016).

10.2.2.1 Public Health

HEV is the main causative agent of hepatitis E, which is usually an asymptomatic human liver disease. However, hepatitis E is possible to induce a self-limited acute hepatitis in humans, especially in developing countries, which are characterized by problems of access to water, poor sanitation, and high population density (Purcell and Emerson 2000; Worm et al. 2002; Perez-Gracia and Rodriguez-Iglesias 2003). The genotypes HEV-1, HEV-2, HEV-3, and HEV-4 are frequently associated with clinical cases of acute hepatitis or liver failure, as well as neurological problems. Moreover, human infections from genotypes 1 and 2 (HEV-1, HEV-2) are more associated with high mortality rates in pregnant women and pancreatitis incidence (Lhomme et al. 2012, 2016). During last decade, the reported HEV infections are increasing dramatically, due to more frequent and novel application of diagnostic methods (Aspinall et al. 2015).

Generally, hepatitis E due to HEV-3 and HEV-4 infection is an important zoonosis around the world (Wu et al. 2002; Smith et al. 2014). Sporadic cases of acute and chronic hepatitis E in humans due to HEV-3 infection were reported in non-endemic regions of industrialized countries, where the pig was the major source of infection (Smith et al. 2014). Epidemic forms of hepatitis E were associated with infection via drinking of contaminated water in developing countries with poor sanitary conditions, as the contamination of water supplies with human faeces remain a common route of HEV spread in these countries (Kamar et al. 2017). Sporadic forms of hepatitis E have been reported between epidemics of disease in these areas or in humans–patients with previous travelling to endemic areas or in humans–patients from industrialized countries, without travelling abroad (autochthonous hepatitis) (Perez-Gracia et al. 2004). Sporadic cases of hepatitis E were associated with the consumption of raw or undercooked meat products (e.g. liver, sausage) from pig or deer (Meng 2011). Large outbreaks of HEV frequently occur in many tropical and subtropical low-income regions, whereas sporadic HEV infections are seen in humans in industrialized countries. HEV sequences isolated from domestic pigs, wild boar, or deer were reported to be closely related to human HEV sequences in many countries worldwide (Meng 2011).

During last years, human HEV-3 infections have been dramatically increasing and the zoonotic transmission from pig to human is a common fact, based on the high sequence identity between isolated strains of human cases and contemporary isolated strains in pigs (Adlhoch et al. 2016). Nowadays, hepatitis E is an important public health concern, as about 20 million new HEV-1 and HEV-2 per year are reporting, including 3.4 million acute cases with 70,000 deaths due to acute liver disease (Rein et al. 2012). For example, studies reported a 10–40% seroprevalence rate of anti-HEV antibodies in many areas of Africa and Asia, while about 80% in Egypt (Kamar et al. 2017).

10.2.2.2 Pork and Meat Products

HEV foodborne infections in humans are caused mainly after consumption of undercooked meat or various meat products, such as sausages (Colson et al. 2010; Guillois et al. 2016). The consumption the parboiled flesh or liver from wild boar, deer, and domestic pigs is associated with autochthonous cases and outbreaks of hepatitis E (Khuroo and Khuroo 2008; Miyashita et al. 2012). Many studies reported detection of HEV-specific RNA in meat and meat products (mainly in liver as well as in sausages with and without liver) worldwide (Yazaki et al. 2003; Feagins et al. 2007; Kulkarni and Arankalle 2008; Pavio et al. 2017). Recently, HEV-contaminated cow milk is reported as a new high risk factor for HEV foodborne infection (Huang et al. 2016) (Table 10.1).

Studies reported a seroprevalence between 2 and 15% of slaughtered pigs, while the detection of HEV in samples from sausages or meat products containing pig liver was higher (especially products prepared with raw pork liver), ranging between 16 and 47%, (Pavio et al. 2014; Di Bartolo et al. 2015; Crossan et al. 2015). For example in Europe, favourite products made from raw pig liver (e.g. fresh sausage made called Figatellu), which are traditionally eaten raw, are considered at high risk of containing HEV (Colson et al. 2010; Garbuglia et al. 2015; Matsuda et al. 2003). Except pig livers, liver from wild boar and deer are also considered at high risk of containing HEV (Tei et al. 2003). However, in a recent study reported that the

Table 10.1 Prevalence of HEV RNA-positive pork, wild boar, and deer meat products

Product	Geographic area (continent, country)	References
Pig—liver	Asia (China, India Hong Kong, Japan, and Thailand)	Li et al. (2009) Kulkarni and Arankalle (2008) Chan et al. (2017) Okano et al. (2014) Ishida et al. (2012) Intharasongkroh et al. (2017)
	North – South America (USA, Canada, Brazil, and Mexico)	Gardinali et al. (2012) Mykytczuk et al. (2017) Leblanc et al. (2010) Wilhelm et al. (2014) Cantú-Martínez et al. (2013) Feagins et al. (2007)
	Africa (Cameroon, Burkina Faso)	de Paula et al. (2013) Traoré et al. (2015)
	Western, Central and South Europe (France, the United Kingdom, The Netherlands, Germany, Czech Republic, Italy, Serbia, Spain)	Di Bartolo et al. (2010) Jori et al. (2016) Rose et al. (2011) Wenzel et al. (2011) Milojević et al. (2019) Bouwknegt et al. (2007) Berto et al. (2012a, b)
Pig—meat	Western, Central, and South Europe (The Netherlands, Czech Republic, Switzerland, Italy)	Di Bartolo et al. (2010) Boxman et al. (2019) Moor et al. (2018)
	South-East Asia (Thailand)	Intharasongkroh et al. (2017)
Sausages and other products (e.g. figatelli) containing or without liver	North – South America (Canada, Brazil)	Heldt et al. (2016) Mykytczuk et al. (2017)
	South Africa (Republic of South Africa)	Korsman et al. (2019)
	Western, Central, and South Europe (France, United Kingdom, The Netherlands Germany, Switzerland, Spain, Italy)	Colson et al. (2010) Hennechart-Collette et al. (2019) Pavio et al. (2014) Szabo et al. (2015) Garbuglia et al. (2015) Boxman et al. (2019) Martin-Latil et al. (2016) Di Bartolo et al. (2015) Giannini et al. (2018) Berto et al. (2012a, b)

(continued)

Table 10.1 (continued)

Product	Geographic area (continent, country)	References
Wild boar—liver	Western, Central, South and East Europe (Belgium, France, The Netherlands Germany, Czech Republic, Hungary, Italy, Romania)	Thiry et al. (2017a, b) Kaba et al. (2010) Anheyer-Behmenburg et al. (2017) Schielke et al. (2009) Schielke et al. (2015) Adlhoch et al. (2009) Kubankova et al. (2015) Forgách et al. (2010) Serracca et al. (2015) Montagnaro et al. (2015) Porea et al. (2018)
	East Asia (Japan)	Sato et al. (2011) Matsuda et al. (2003) Motoya et al. (2016) Sonoda et al. (2004)
Wild boar—meat	Central Europe (Germany)	Anheyer-Behmenburg et al. (2017) Schielke et al. (2015)
Wild boar—Sausages without liver	Western and Central Europe (Belgium, Germany)	Szabo et al. (2015) Thiry et al. (2017a, b)
Deer—liver	Western and Central Europe (Belgium, France, The Netherlands, Germany, Hungary)	Szabo et al. (2015) Thiry et al. (2017a, b) Lhomme et al. (2015) Anheyer-Behmenburg et al. (2017) Forgách et al. (2010) Rutjes et al. (2010)
Deer—meat	Central Europe (Germany)	Anheyer-Behmenburg et al. (2017) Schielke et al. (2015)

prevalence and the amount of HEV RNA in liver samples from deer were significantly lower in comparison to samples from domestic pigs and wild boars (Pavio et al. 2017).

10.2.2.3 Direct contact/Vocational exposure

Direct contact exposure is also reported as a possible route of HEV transmission. Moreover, studies in many countries reported that the vocational exposure of professionals in pig farms (e.g. swine veterinarians, farm workers) with pigs, manure, and sewage is an important high risk factor for HEV infections (Perez-Gracia et al. 2007; Bouwknegt et al. 2008a; Rutjes et al. 2009; Pavio et al. 2017). For example, swine veterinarians and workers in pig farms reported to be 2–5 times more under

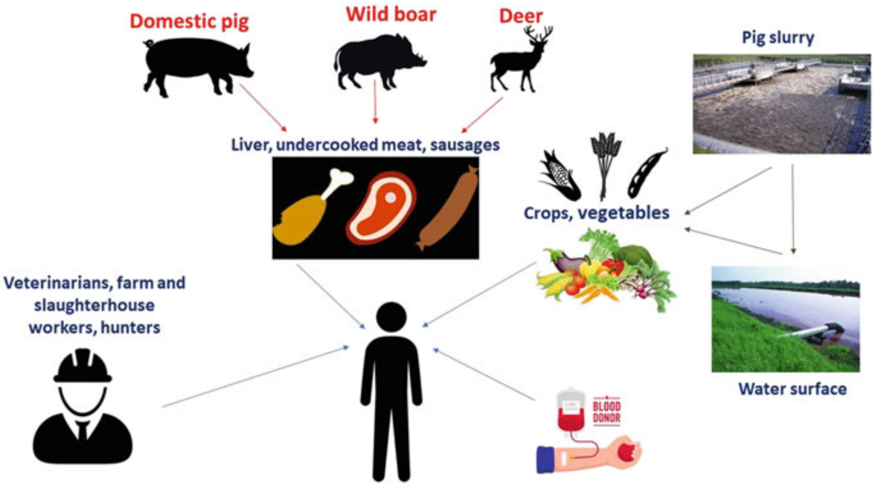

Fig. 10.3 Transmission and exposure routes of HEV infection in humans

the risk to have anti-HEV antibodies in comparison to non-swine veterinarians and the general population (Olsen et al. 2006; Vulcano et al. 2007; Galiana et al. 2008; Bouwknegt et al. 2008b). Moreover, there are reports of HEV transmission due to contact from wildlife to forest workers and hunters, as well as from frequent contact to a pet pig or to pigs at slaughterhouse (Stramer 2014; Juhl et al. 2014; Pavio et al. 2017) (Fig. 10.3).

Recently, HEV transmission from ruminants to farmers (Tritz et al. 2018) and rabbits to humans (slaughterhouse workers) were reported (Geng et al. 2019).

10.2.2.4 Water/Pig Slurry

Hepatitis E is primarily transmitted through the faecal–oral route (Khuroo 1991). Gross faecal contamination of community water supplies has been associated with several outbreaks in developing countries (Khuroo 1980; Naik et al. 1992; Kamar et al. 2017).

The presence of pig manure indicates the potential spread to humans through contact with contaminated crops or in personnel that handle swine manure and spread this waste on agricultural fields (Fernandez-Barredo et al. 2006). Use of pig slurry as pasture can infect agricultural products, such as raspberries, strawberries, and many vegetables used in the salad (Ward et al. 2008; Brassard et al. 2012). Run-off from outdoor pig farms causes contamination of surface water as well as produce receiving surface water (Steyer et al. 2011; Tyrrel and Quinton 2003).

10.2.2.5 Iatrogenic

HEV transmission from blood HEV-infected donors to human by blood transfusion is reported in many studies (Baylis et al. 2012; Hewitt et al. 2014; Gallian et al. 2014; Sauleda et al. 2015; Hogema et al. 2016). Moreover, a case of HEV-7 transmission to human is reported for a liver transplant recipient (Lee et al. 2016).

10.2.3 Transmission of HEV to Pigs

Wild boars are recognized as a potential reservoir of HEV, while HEV is transmitted from them to domestic pigs (Thiry et al. 2016; Schlosser et al. 2015; Jori et al. 2016).

The primary route of natural HEV transmission in pigs is the faecal–oral route, but it may require repeated exposure and high doses of virus (Kasorndorkbua et al. 2004). It is remarkable that the duration of detection of HEV in pig faeces is considerably longer than the duration of HEV viremia (Kasorndorkbua et al. 2004).

Previous studies reported a seroprevalence of HEV in pig between 5% and 100% (Pavio et al. 2017). The prevalence of the virus is depended on the animals age, the kind of tested sample, and the diagnostic method. Usually, HEV infection is detected at an early age after the loss of maternal antibodies. The virus load is high in all ages (weaners, growers, and fatteners), but is reported to be the highest in fatteners. Moreover, the seroprevalence is depended on the production system, as a slightly higher seroprevalence was reported in organic farms compared with conventional and free-range pig farms (Berto et al. 2012a, b). A comprehensive review (Salines et al. 2017) reported that the detection of HEV RNA in pig faeces and serum depends on the pig's age, while the shedding period ranges from 1.5 to 5 months of age (Salines et al. 2017). However, the peak of shedding in faeces happens around 3–4 months of age, whereas the shedding prevalence at slaughter age (around 185 days of age) is possible to be around 6% (Fig. 10.4).

10.3 Pathogenesis

HEV replication occurs mainly in the liver, but the virus can also be detected in other organs, such as small intestine, lymph nodes, and colon (Williams et al. 2001; Ha and Chae 2004). Viraemia is transient (duration of 1–2 weeks), while the peak of viral shedding in faeces occurs 3–8 weeks after weaning (Kantala et al. 2015). The viral shedding in faeces of infected pigs may persist for up to 7 weeks (Pavio et al. 2010). Then it is decreased around 15–18 weeks of age (McCreary et al. 2008), with the appearance of antibodies IgM followed by IgG (seroconversion) (Pavio et al. 2010).

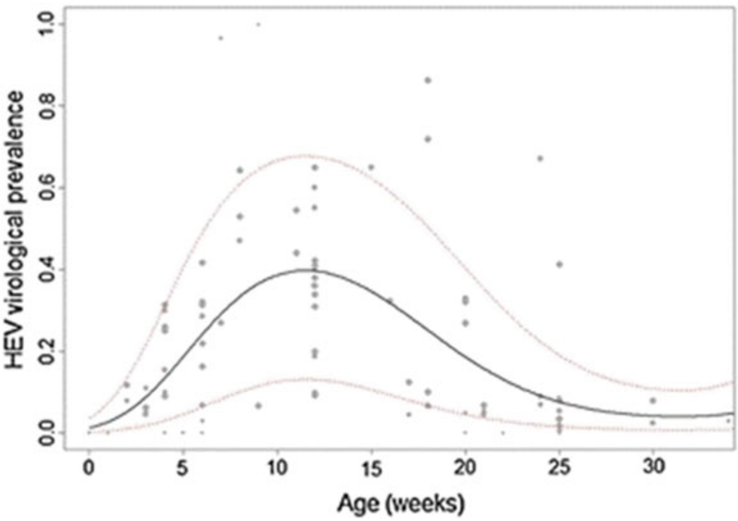

Fig. 10.4 Predicted HEV prevalence in faeces according to animal age (adapted from Salines et al. 2017)

The duration of the immunity acquired after HEV infection is not clear, but re-infection in case of transient decrease of immunity could be possible. A decrease of protection (antibodies or cellular response) over time may happen in older animals and especially in sows (Casas et al. 2011). Many studies reported that the majority of pigs are infected at 8–15 weeks of age, but some of them could be remain positive at slaughter age (de Deus et al. 2008; Meng et al. 1997; Casas et al. 2011). The infection happens at an early age after the loss of maternal antibodies (MAbs), which can be transferred from HEV-Ab positive sows to offspring (Feng et al. 2011). High levels of MAbs are very important for the reduction of prevalence of HEV positive animals (Krog et al. 2019).

10.4 Clinical Signs in Domestic Pig and Wild Boar

HEV infection in pig is usually asymptomatic, without important impact on their health status. HEV replication occurs in the liver and the intestine (Ha and Chae 2004), while it may enhance the clinical performance of disease caused by other porcine viruses, such as porcine reproductive and respiratory syndrome virus (PRRSV) (Salines et al. 2015) or porcine circovirus 2 (PCV2) (Yang et al. 2015; Jäckel et al. 2018). Immune modulatory effects have been reported in cases of PCV2 and HEV co-infection (Jäckel et al. 2018). The aforementioned enhancing activity of the HEV may due to immunosuppressive properties (Cao et al. 2017).

Genotypes HEV-3 and HEV-4 were also reported in wild boars, but without characteristic clinical symptoms in most cases. However, the prevalence of HEV in wild boars is lower than in domestic pigs (Pavio et al. 2017). Furthermore, HEV was detected in species of deer (Neumann et al. 2016; Anheyer-Behmenburg et al. 2017), while other species of animals (e.g. ruminants) are reported to be susceptible to HEV infection (Spahr et al. 2018).

10.5 HEV Monitoring/Prevention

Future studies focus on preventive measures to eliminate the appearance and persistence of HEV in pig farms (including biosecurity and vaccination) are required. Moreover, more studies are needed to investigate deeply the role of wildlife (wild boars, deer, etc.) in the epidemiology of HEV infection.

The prevention of zoonotic HEV infection demands a monitoring system to investigate and prevent the contamination of pork-derived meat products. HEV monitoring activities in the pork production chain are important to be implemented for the following targets:

(a) to maintain a database for the prevalence of HEV and follow-up the prevalence of the different HEV strains;
(b) to investigate in detail the dynamics of HEV infection, as well as their risk factors;
(c) to remove contaminated livers and other high-risk meat products from the food chain;
(d) to inform consumers regarding handling and cooking of high-risk pork-derived meat products (Salines et al. 2017; ANSES 2013).

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Conflict of Interest There is no conflict of interest.

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