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An occupational risk of hepatitis E virus infection in the workers along the meat supply chains in Guangzhou, China

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ABSTRACT

Hepatitis E virus (HEV) causes infections in humans and animals. HEV have been identified in pig farms, markets and swine workers, but studies with parallel observations along the poultry and pork supply chains remains limited. This study aimed to characterize HEV infection risks in workers along the meat supply chain. Two rounds of cross-sectional surveys were performed among swine and poultry workers in pig and poultry farms, slaughterhouses, wholesale and retail live poultry markets, live pig markets and pork markets. Human sera from the workers and the general population were collected and tested for HEV specific IgM/IgG antibodies by commercial indirect-ELISA test kits. Risk factors of HEV seropositivity associated with different occupational settings were identified using logistic regression. 47.0% (156/332) of the swine workers and 40.2% (119/296) of the poultry workers were seropositive, compared to 26.1% (35/134) in the general population. Multivariable analysis showed that human HEV infection risk increased along the pork supply chain, with the highest risk at pig slaughterhouses (adjusted OR = 3.19, 95% CI = 1.49–6.88) and pork markets (adjusted OR = 2.02, 95% CI = 1.04–3.97), but no significant higher risk was observed among poultry workers. Swine occupational exposure is associated with HEV infection, especially in workers in pig slaughterhouses and pork markets. Strengthening control measures in these settings is important for HEV control and long term HEV elimination.

1. Introduction

Hepatitis E virus (HEV) is an enteric RNA virus that proliferates in a wide range of hosts worldwide, including human, pigs, rabbits, wild boars, rats, red deer and birds [1,2]. HEV mostly causes self-limiting hepatitis in human, but may also result in chronic hepatitis among immunocompromised patients [3]. It was estimated that about twenty million HEV infections occurred globally each year, leading to roughly 3.3 million clinical cases with more than 40 thousand related deaths [4]. In addition, HEV infection was also associated with high morbidity and mortality in pregnant women in developing countries. HEV was transmitted to human via fecal-oral and zoonotic routes, the latter of which including consumption of raw pig meat or livers as well as exposure to infected pigs [5,6].

HEV belongs to genus *Orthohepevirus,* including species *Orthohepevirus A*, *Orthohepevirus B* (avian HEV), *Orthohepevirus C* (rat-HEV),

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Orthohepevirus D (bat-HEV) [7,8]. Human Hepatitis E was also known to be caused by *Orthohepevirus* A and *Orthohepevirus* C (rat-HEV) [9,10]. *Orthohepevirus* A includes 8 genotypes (HEV-1 – HEV-8) with natural hosts including human, pigs, rabbits and camels. Genotypes HEV-1, HEV-2, HEV-3 and HEV-4 were mainly found in human, while HEV-3, HEV-4, HEV-5, HEV-6 were mostly found in pigs. HEV-3 and HEV-4 were considered as zoonotic genotypes with capability of transmission from pigs to humans [11]. Avian HEVs were grouped into 5 genotypes (genotypes 1–5) and were mainly found in birds, sharing antigenical and genetical similarity with *Orthohepevirus* A [12]. In 2020, A novel genotype avian HEV was discovered which had a higher sequence similarity with *Orthohepevirus* A, though it has not been detected in humans, there is a potential threat as a zoonotic HEV [13].

In China, HEV seroprevalence among blood donors varies from 25% to 34% [14]. Consumption of pig livers was identified as a risk factor of HEV infection for the general population [15], while pig farmers and rabbit slaughterhouse workers had higher HEV infection risks [16–18]. In Guangdong, a province in Southern China, HEV infection is common among domestic pigs, with an average seroprevalence of 65% (ranging from 35% to 92%) [16]. In an epidemiological investigation of 20 poultry farms, avian-HEV seropositivity in chickens exceeded 70% [19], while two other studies found that seropositivity in farmed wild boars and Sika deer were lower (24.5% and 5.4% respectively) [20,21].

Many studies have reported high prevalence of anti-HEV antibodies in swine slaughterhouse workers and farmers, suggesting occupational risk of HEV infection [22,23]. However, few studies examined occupational infection risk in different settings along the pork and poultry supply chains systematically. A systematic review compared HEV seroprevalence worldwide among swine-related workers in different settings, however large heterogeneity was observed except for swine veterinarian only [24]. This precluded profiling of HEV risks in different settings among swine and poultry workers who have likely not trained with self-protective measures. In this study, we filled this gap by investigating HEV infections among occupational workers along both the pork and poultry meat supply chains. Our aim was to characterize occupational risks of HEV infection in settings with exposure to swine (pig farms, live pig markets, pig slaughterhouses and pork market) and poultry (poultry farms, slaughterhouses, retail and wholesale LPMs), compared to the general populations.

2. Materials and methods

2.1. Study design

The study was carried out during October 2015 to July 2016 in Guangzhou city in Southern China with 2 rounds of serosurveys (Fig. 1). Poultry workers and general population subjects with no occupational and backyard poultry and pig exposure were recruited as reported previously [13]. Swine workers from 8 pig farms, 1 live pig market (including 12 trading stalls and 12 transportation vehicles), 2 pig slaughterhouses and 6 pork markets (including 2 trading stalls per retail stall) were recruited in person during study visits. Pig offal are popular food in China and were hence separately processed and handled in the pig slaughterhouses and pork markets. The inclusion criteria were: 1) had been working or living in settings with swine exposure (swine farm, live pig market, pig slaughterhouse or pork market) for more than 10 weeks, and exposed to pigs for more than 5 h a week; 2) age ≥ 16 years. We excluded subjects who are: 1) Immunocompromised or suffering from acute respiratory tract infection and in pregnancy; and 2) suffering from immunosuppressive or immunodeficiency disease (including HIV infection) or receiving immunosuppressive therapy. 3–5 mL blood sample was collected from each participant. During the visits, we also carried out face-to-face interviews by trained personnel to collect information on demographics, exposure history to pigs, and other related information (see Supplementary Appendix 2 for the questionnaire).

The protocol of blood sampling and face-to-face interview were approved by the ethics committee of School of Public Health, Sun Yat-Sen University (No. 2014–018). Written informed consent was obtained prior to blood sample collection and interviews.

2.2. Laboratory analysis

Commercially available HEV ELISA testing kits were used for the detection of HEV specific IgM (with specificity 98.40% and sensitivity 97.10%) and IgG (with specificity 99.90% and sensitivity 99.08%) antibodies (Wantai BioPharm, Beijing, China). All experimental operations and laboratory procedures were carried out as instructed by the manufacturer. The results of the ELISA tests were present as ratios (s/co), and the interpretations were made in accordance with the instructions.

2.3. Statistical analysis

Survey data were managed using EpiData 3.1 software (http://epidata.dk/). Data were entered twice independently, and logical check

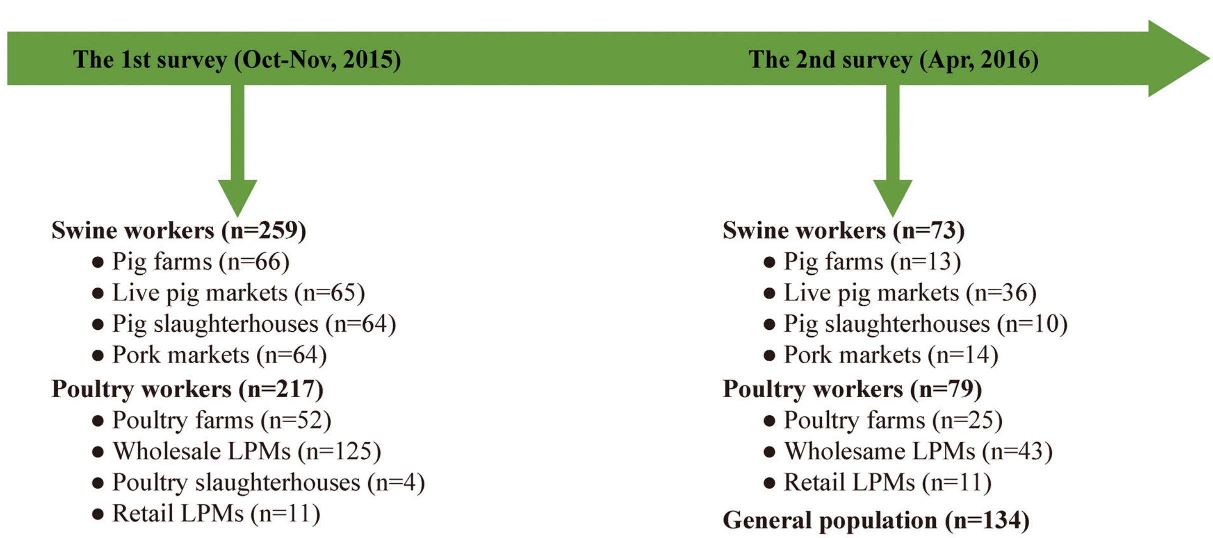

Fig. 1. Timeline of sample collection from poultry and swine workers, and the general population, 2015–16.

were performed using structured query language to ensure accuracy. Survey and laboratory data were subsequently merged into a master dataset, linked by individual study participant numbers. HEV serological results were first studied as dichotomous outcomes using two-sided Chi-square tests or the Fisher's exact test. Multivariable logistic regression analyses were performed to identify risk factors associated with previous HEV infection, accounting for confounders such as age. The analysis included data from the general population, using age as a proxy of natural HEV infection from human, to allow estimation of the additional HEV infection risks from swine and poultry. Data analyses were performed using SPSS software version 20.0 (IBM, Chicago, USA) and R version 4.0.4 (R Development Core Team).

3. Results

Serum samples were collected from 332 swine workers, 296 poultry workers and 134 subjects from the general population, with HEV seropositivity of 47.0% (95% confidence interval [CI] 41.6–52.4%), 40.2% (95% CI 34.6–45.8%) and 26.1% (95% CI 18.7–33.6%) respectively (Tables 1 & 2). There were significantly higher HEV seropositivity in swine and poultry workers, compared to the general population (OR = 2.5, 95% CI 1.6–3.9 and 1.9, 95% CI 1.2–3.0 respectively), however the difference between swine and poultry workers was not significant (*p*-value = 0.091). (Table 2).

Among the HEV-seropositive samples, 16 out of 275 (5.8%) and 1 out of 35 (2.9%) were IgM positivity among occupational workers and the general population respectively (supplementary appendix 1). The proportions of recent HEV infections were similar (p-value = 0.704).

In our serosurveys among swine workers, slaughterhouse workers had the highest HEV seropositivity (60.8%, 95% CI 49.7–71.9%). In the multivariable analysis, anti-HEV IgG/IgM seropositivity was associated with age (adjusted OR [aOR] = 1.04, 95% CI = 1.02–1.06) but not with duration of pig exposure (aOR = 1.01, 95% CI = 0.98–1.05), with significantly higher risks in pig slaughterhouse workers (aOR = 3.19, 95% CI = 1.49–6.88) and pork markets (aOR = 2.02, 95% CI = 1.04–3.97) (Table 3). No significant sex difference was observed (*p*-value = 0.163).

Among poultry workers, slaughterhouse workers had the highest HEV seropositivity (75.0%, 95% CI 32.6–100.0%) (Table 4). In the multivariable analysis, while HEV seropositivity was significantly associated with age (aOR = 1.04, 95% CI = 1.02–1.06), the risk did not increase significantly over duration of exposure (*p*-value = 0.664) or by workplace (p-value = 0.343). Irrespective of workplace, HEV seropositivity among poultry works was not significantly higher (aOR = 1.52, 95% CI = 0.88–2.65) than that of the general population. No significant sex difference was observed (p-value = 0.466, Table 4). In both swine and poultry workers, there were weak correlations between age and duration of exposure (Pearson correlation coefficients = 0.27 and 0.14, respectively).

Table 1
Characteristics of the swine and poultry workers and the general population who have participated in the serological surveys.

Characteristics	N	%
Swine workers		
Age, y, median (range)	332	42 (16–66)
Gender		
Male	243	73.2
Female	89	26.8
Type of workplace		
Pig farms	79	23.8
Live pig markets	101	30.4
Pig slaughterhouses	74	22.3
Pork markets	78	23.5
Poultry workers		
Age, y, median (range)	296	44 (16–73)
Gender		
Male	207	69.9
Female	89	30.1
Type of workplace		
Poultry farms	77	26.0
Wholesale LPMs	168	56.8
Poultry slaughterhouses	4	1.4
Retail LPMs	47	15.9
General population		
Age, y, median (range)	134	37 (17–66)
Gender		
Male	92	68.7
Female	42	31.3

Abbreviations: CI, confidence interval; LPMs: live poultry markets.

Table 2
HEV seroprevalence in the study populations.

Population	N	Seropositive, n	(%)	(95% CI)	OR (95% CI)
General populations	134	35	(26.1)	(18.7–33.6)	Reference
Occupational workers					
Swine workers	332	156	(47.0)	(41.6–52.4)	2.5 (1.6–3.9)
Poultry workers	296	119	(40.2)	(34.6–45.8)	1.9 (1.2–3.0)

Abbreviations: CI, confidence interval; OR: odds ratio.

4. Discussion

There is a low awareness of zoonotic HEV transmission, though HEV is recognized as a good sentinel pathogen to evaluate transmission risk of other zoonotic pathogens at the animal-human interface [25–27]. Human can be infected naturally with genotypes HEV-1, HEV-2, HEV-3, HEV-4 [28], while pig was one of the most common natural reservoirs of HEV genotypes HEV-3, HEV-4 [8]. These genotypes have been identified in pig farms, markets and swine workers, but studies with parallel observations along the poultry and pork supply chains are limited. In our study, we collected samples along the meat supply chain, from pig farms, live pig markets, slaughterhouses to pork markets, and from poultry farms, slaughterhouses to wholesale and retail LPMs, to characterize virus dissemination in these settings. Our study also included controls from the general population which allowed us to highlight additional HEV risk associated with animal exposure.

The seroprevalence of HEV-specific IgG/IgM among the general population were around 20–30% in China [14,29–31]. In this study, the HEV specific IgG/IgM in the general population without occupational animal exposure was 26.1%, similar to the above studies and also a previous serosurvey in blood donors with seroprevalence of 25.8% in Guangzhou [31].

Occupational risk of HEV infection was mainly reported at pig farms, but there were inconsistent results on how pig exposure may impact occupational risk of HEV. European countries such as Portugal, United Kingdom and Sweden found that pig exposure was not a significant occupational risk factor for HEV infections [32], while other studies found that animal exposures were associated with occupational workers infected with HEV [17,24,33]. There was large heterogeneity by location and occupation which hindered comparison of risk by settings [24]. Our study systematically collected samples along the pork and poultry supply chain which allowed identification of sites with elevated risk of HEV transmission. Highest risk of HEV seropositivity was identified in pig slaughterhouses (aOR = 3.19) and pork markets (aOR = 2.02), after accounting for important confounders such as age as a proxy of natural HEV exposure in the general population. Interestingly, a meta-analysis also identified similarly higher risk of HEV seropositivity among swine workers (prevalence ratio = 1.52) compared to the general population, however our study highlighted additional risk for swine workers in slaughterhouse and pork markets [24]. Possible reasons included that

Table 3
Seroprevalence and risk of HEV infections among swine workers along the pork supply chains.

Variable	N	Seropositive, n (%)	(95% CI)	aOR* (95% CI)	*p* value
Sex					0.163
Female	89	36 (40.4)	(30.0–50.6)	Reference	
Male	243	120 (49.4)	(43.1–55.7)	1.37 (0.88–2.14)	
Age group (y)					
<35	91	27 (29.7)	(20.7–39.4)		
35–44	112	54 (48.2)	(39.3–57.4)		
45–54	101	58 (57.4)	(47.1–67.3)		
≥55	28	17 (60.7)	(42.9–78.6)		
Age# (y)				1.04 (1.02–1.06)	<0.001
Type of workplace*					0.027
General populations	134	35 (26.1)	(18.7–33.6)	Reference	
Pig farms	79	36 (45.6)	(34.6–56.6)	1.86 (0.96–3.61)	
Live pig markets	101	40 (39.6)	(30.1–49.1)	1.38 (0.72–2.64)	
Pig slaughterhouses	74	45 (60.8)	(49.7–71.9)	3.19 (1.49–6.88)	
Pork markets	78	35 (44.9)	(33.8–55.9)	2.02 (1.04–3.97)	
Period of duration of exposure to pigs (y)					
No occupational exposure	134	35 (26.1)	(18.7–33.6)		
<3	72	25 (34.7)	(23.7–45.7)		
3–9	166	78 (47.0)	(39.4–54.6)		
≥10	94	53 (56.4)	(46.4–66.4)		
Duration of exposure to pigs# (y)				1.01 (0.98–1.05)	0.489

Abbreviations: CI, confidence interval; aOR: adjusted odd ratio.
* including the general population ($n = 134$).
\# non-linear relation was tested in a general additive model. Age effect and duration of exposure were found to be linear (both effective degrees of freedom = 1).

Table 4
Seroprevalence and risk of HEV infections among poultry workers along the poultry supply chains.

Variable	N	Seropositive, n (%)	(95% CI)	aOR* (95% CI)	p value
Sex					0.466
Female	89	36 (40.4)	(30.3–50.6)	Reference	
Male	207	83 (40.1)	(33.4–46.8)	1.18 (0.76–1.86)	
Age group (y)					
<35	78	17 (21.8)	(13.4–31.0)		
35–44	82	32 (39.0)	(28.2–50.0)		
45–54	118	61 (51.7)	(43.1–60.9)		
≥55	18	9 (50.0)	(26.3–73.7)		
Age# (y)				1.04 (1.02–1.06)	<0.001
Type of workplace*					0.343
General populations	134	35 (26.1)	(18.7–33.6)	Reference	
Poultry farms	77	32 (41.6)	(29.9–53.2)	1.36 (0.68–2.70)	
Wholesale LPMs	168	65 (38.7)	(31.5–46.4)	1.54 (0.85–2.80)	
Poultry slaughterhouses	4	3 (75.0)	(25.0–100.0)	7.09 (0.80–152.55)	
Retail LPMs	47	19 (40.4)	(27.7–55.3)	1.59 (0.73–3.40)	
Period of duration of exposure to poultry (y)					
No occupational exposure	134	35 (26.1)	(18.1–33.6)		
<3	96	43 (44.8)	(34.8–54.7)		
3–9	126	40 (31.7)	(23.6–39.9)		
≥10	74	36 (48.6)	(37.3–60.0)		
Duration of exposure to poultry# (y)				1.01 (0.97–1.05)	0.664

Abbreviations: CI, confidence interval; LPMs: live poultry markets; aOR: adjusted odds ratio.
* including the general population (n = 134).
\# non-linear relation was tested in a general additive model. Age effect was found to be nearly linear (effective degree of freedom = 1.68 which is close to 1) and the effect of duration of exposure was not statistically significant ($p = 0.405$). A linear term was used in the final model for better interpretability and to avoid identifiability problem between type of work place and duration of exposure.

the main sites of HEV proliferation were in livers and feces, followed by other organs such as kidney and heart [34]. Pig offal including liver are consumed in China and in Asia, hence swine slaughterhouse and pork market workers had an even higher exposure comparing to other swine workers, and HEV RNA seropositivity rates reached up to 64.7% in Guangdong [16]. This indicated risk-based preventive measures are needed with the most stringent measures applicable to slaughterhouses and pork markets.

In contrast, we found that poultry workers did not have a significantly higher risk of HEV seropositivity than the general population taking into account confounding factor of age, though three out of four poultry slaughterhouse workers were HEV seropositive. Currently, no study has confirmed that avian HEV is zoonotic, though a novel avian HEV was reported in 2020 which had higher sequence identities and shared some specific amino acid sites with *Orthohepevirus* A HEV strains, hence we could not rule out the possibility of cross-species transmission. [13,19,35,36]. Our results did not identify significant risk of HEV infection among poultry workers after accounting for age, indicating low spillover risk of avian HEV to human. In the future, studies should analyze the evolution and genome of avian HEV and monitor potential avian HEV spillover events.

The ongoing SARS-CoV-2 pandemic illustrated that the human-animal-environment interfaces would be the forefront to defense against emerging and zoonotic pathogens [37,38]. Occupational workers with frequent animal exposure had a higher risk of zoonotic pathogen spillover [17,39]. There has been increasing awareness on the interactions between human health, animal health and the environment, and a One Health approach allows better monitoring of potential zoonotic pathogens [40]. Currently, there is no routine HEV surveillance in the hospitals in China, but only monitoring of patients with liver disease. Active surveillance at the human-animal-environment interface has the potential to improve substantially the detection capacity to emerging zoonotic infections.

Our results showed that after accounting for age, longer exposure to pigs was not associated with a higher risk of HEV infections. This suggested prior training on the use of personal preventive measures is likely crucial, and these measures should be incorporated in the daily work routine to maintain long-term compliance.

A safe and highly efficacious vaccine for hepatitis E has been licensed by in China for nearly a decade [41]. However, HEV vaccination was not promoted among occupational workers as a public health intervention, probably due to the self-limiting nature of HEV infection. The zoonotic risk of HEV should not be neglected for achieving the World Health Organization target of viral hepatitis elimination by 2030 [42,43].

Our study had some limitations. First, we did not carry out HEV pathogen detection for the study participants and hence could not differentiate the species and genotype of *Orthohepatitis* which infected swine and poultry workers. Human infections with avian HEV (*Orthohepatitis* B) were not reported, but it is prudent to monitor potential animal-to-human transmission of *Orthohepatitis* A at the animal-human interface. In our analysis, we adjusted for the age effect as a proxy of exposure to HEV transmission in human, to estimate the additional animal-to-human transmission risk of HEV. Second, HEV seroprevalence of in poultry workers may be underestimated. There is an approximately 40% amino-acid sequence similarity between human/swine HEV and avian HEV (supplementary appendix 3), indicating some serum cross-reactivity. Third, the sample size was limited to detect differences in HEV infection across all specific settings, though we identified pig slaughterhouses as the setting for highest risk of zoonotic HEV transmission, among several other settings with elevated risks. Fourth, we did not collect data on HEV vaccination status of the study subjects. Because HEV vaccine is not covered in the Expanded Program on Immunization, and only about 50,000 HEV vaccines were issued per year by National Institutes for Food and Drug Control in China (https://bio.nifdc.org.cn/pqf/search.do). This translated to a $< 0.05\%$ HEV vaccine uptake in China and hence HEV vaccination status should have limited impact on our results and conclusions.

Overall, our findings revealed that Chinese swine workers have increased risk to Hepatitis E virus infection compared to the general population, with highest risks at pig slaughterhouses and pork markets. HEV vaccination to workers with frequent exposure to swine would reduce cross-species HEV transmission in China and probably in Asia with similar pork and offal consumption.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2022.100376.

References

[1] V. Doceul, E. Bagdassarian, A. Demange, N. Pavio, Zoonotic hepatitis E virus: classification, animal reservoirs and transmission routes, Viruses 8 (10) (2016) 270.
[2] G. Reuter, A. Boros, P. Pankovics, Review of hepatitis E virus in rats: evident risk of species Orthohepevirus C to human zoonotic infection and disease, Viruses 12 (10) (2020) 1148.
[3] H. Sooryanarain, X.J. Meng, Swine hepatitis E virus: cross-species infection, pork safety and chronic infection, Virus Res. 284 (2020), 197985.
[4] S.K. Asrani, H. Devarbhavi, J. Eaton, P.S. Kamath, Burden of liver diseases in the world, J. Hepatol. 70 (1) (2019) 151–171.
[5] V. Thakur, R.K. Ratho, S. Kumar, S.K. Saxena, I. Bora, P. Thakur, Viral hepatitis E and chronicity: a growing public health concern, Front. Microbiol. 11 (2020), 577339.
[6] S.R. Pallerla, D. Harms, R. Johne, D. Todt, E. Steinmann, M. Schemmerer, J. J. Wenzel, J. Hofmann, J.W.K. Shih, H. Wedemeyer, C.T. Bock, T.P. Velavan, Hepatitis E virus infection: circulation, molecular epidemiology, and impact on global health, Pathogens 9 (10) (2020) 856.
[7] D.B. Smith, J. Izopet, F. Nicot, P. Simmonds, S. Jameel, X.J. Meng, H. Norder, H. Okamoto, W.H.M. van der Poel, G. Reuter, M.A. Purdy, Update: proposed reference sequences for subtypes of hepatitis E virus (species Orthohepevirus a), J. Gen. Virol. 101 (7) (2020) 692–698.
[8] S.P. Kenney, The current host range of hepatitis E viruses, Viruses 11 (2019) 452.
[9] S. Sridhar, C.C. Yip, S. Wu, N.F. Chew, K.H. Leung, J.F. Chan, P.S. Zhao, W. M. Chan, R.W. Poon, H.W. Tsoi, J.P. Cai, H.S. Chan, A.W. Leung, C.W. Tse, J.S. Zee, O.T. Tsang, V.C. Cheng, S.K. Lau, P.C. Woo, D.N. Tsang, K.Y. Yuen, Transmission of rat hepatitis E virus infection to humans in Hong Kong: a clinical and epidemiological analysis, Hepatology 73 (1) (2020) 10–22.
[10] J.B. Geng, M.R. Wang, J. Wang, L. Wang, Z.G. Yang, Y. Cheng, F. Qiao, M. Wang, Y. Dong, Y.H. Sui, C.L. He, L. Gao, Genetic characteristics and pathogenicity of hepatitis E virus isolated from patients in eastern China, genotype 4 HEV can result in acute liver failure, Int. J. Infect. Dis. 15 (2011) S67.
[11] X.J. Meng, Expanding host range and cross-species infection of hepatitis E virus, PLoS Pathog. 12 (8) (2016), e1005695.
[12] P. Sun, S.L. Lin, S.H. He, E.M. Zhou, Q. Zhao, Avian hepatitis E virus: with the trend of genotypes and host expansion, Front. Microbiol. 10 (2019) 1696.
[13] Q. Su, Z.H. Zhang, Y.W. Zhang, Z.Z. Cui, S. Chang, P. Zhao, Complete genome analysis of avian hepatitis E virus from chicken with hepatic rupture hemorrhage syndrome, Vet. Microbiol. 242 (2020).
[14] L.M. Zhang, S.X. Jiao, Z.S. Yang, L. Xu, L. Liu, Q.X. Feng, X. Zhang, Y. Hou, S.Y. He, J. Saldanha, S. Wang, B. Wang, Prevalence of hepatitis E virus infection among blood donors in mainland China: a meta-analysis, Transfusion 57 (2) (2017) 248–257.
[15] W.J. Yin, Y.L. Han, H.L. Xin, W.L. Liu, Q. Song, Z.Z. Li, S.L. Gao, F.C. Jiang, J. Y. Cao, S.L. Bi, H.T. Liu, Hepatitis E outbreak in a mechanical factory in Qingdao City, China, Int. J. Infect. Dis. 86 (2019) 191–196.
[16] H. Liang, S. Su, S. Deng, H. Gu, F. Ji, L. Wang, C. Liang, H. Wang, G. Zhang, The prevalence of hepatitis E virus infections among swine, swine farmers and the general population in Guangdong Province, China, PLoS One 9 (2) (2014), e88106.
[17] Y.S. Geng, C.Y. Zhao, K.J. Geng, C.Y. Wang, X.P. Wang, H. Liu, Y.C. Wang, High seroprevalence of hepatitis E virus in rabbit slaughterhouse workers, Transbound. Emerg. Dis. 66 (2) (2019) 1085–1089.
[18] A. Krumbholz, U. Mohn, J. Lange, M. Motz, J.J. Wenzel, W. Jilg, M. Walther, E. Straube, P. Wutzler, R. Zell, Prevalence of hepatitis E virus-specific antibodies in humans with occupational exposure to pigs, Med. Microbiol. Immunol. 201 (2) (2012) 239–244.
[19] Q. Su, Y.W. Zhang, Y. Li, Z.Z. Cui, S. Chang, P. Zhao, Epidemiological investigation of the novel genotype avian hepatitis E virus and co-infected immunosuppressive viruses in farms with hepatic rupture haemorrhage syndrome, recently emerged in China, Transbound. Emerg. Dis. 66 (2) (2019) 776–784.
[20] X.X. Zhang, S.Y. Qin, Y. Zhang, Q.F. Meng, J. Jiang, G.L. Yang, Q. Zhao, X.Q. Zhu, First report of hepatitis E virus infection in sika deer in China, Biomed. Res. Int. 2015 (2015), 502846.
[21] Q.L. Liang, L.B. Nie, Y. Zou, J.L. Hou, X.Q. Chen, M.J. Bai, Y.H. Gao, G.X. Hu, X. Q. Zhu, Serological evidence of hepatitis E virus and influenza a virus infection in farmed wild boars in China, Acta Trop. 192 (2019) 87–90.
[22] J. Teixeira, S. Pereira, R.M.S. Oliveira, J. Abreu-Silva, J.R. Mesquita, A. Rodrigues, M.S.J. Nascimento, Occupational exposure to hepatitis E virus (HEV) in Portuguese swine workers, J. Clin. Virol. 82 (2016) S76–S77.
[23] A. Ivanova, V. Tefanova, I. Reshetnjak, T. Kuznetsova, J. Geller, A. Lundkvist, M. Janson, K. Neare, K. Velstrom, P. Jokelainen, B. Lassen, P. Hutt, T. Saar, A. Viltrop, I. Golovljova, Hepatitis E virus in domestic pigs, wild boars, pig farm workers, and hunters in Estonia, Food. Environ. Virol. 7 (4) (2015) 403–412.

[24] X.Y. Huang, Y. Huang, A.L. Wagner, X.X. Chen, Y.H. Lu, Hepatitis E virus infection in swine workers: a meta-analysis, Zoonoses. Public. Hlth. 66 (1) (2019) 155–163.
[25] Lancet_Gastroenterology_&_Hepatology, Hepatitis E: a neglected virus, Lancet. Gastroenterol. Hepatol. 1 (4) (2016) 261.
[26] A.S. Azman, I. Ciglenecki, J.F. Wamala, J. Lynch, R. Aggarwal, M. Rahman, S. Wong, M. Serafini, A.M. Moussa, H.R. Dalton, A. Shrestha, R. Pant, R. Peck, E. S. Gurley, Hepatitis E should be considered a neglected tropical disease, PLoS. Neglect. Trop. Dis 13 (7) (2019), e0007453.
[27] A.C. Mulder, A. Kroneman, E. Franz, H. Vennema, A.D. Tulen, J. Takkinen, A. Hofhuis, C. Adlhoch, S. Aberle, L. Subissi, V. Suin, S. Midgley, T. Kuznetsova, J. Izopet, N. Pavio, C. Baechlein, S.A. Baylisa, V.M. Corman, M. Fabera, R. Johne, C. Kamp, J.J. Wenzel, S. Coughlan, I. Di Bartolo, R. Bruni, A.R. Ciccaglionea, A. R. Garbuglia, E. Suffredini, I. Boxman, B. Hogema, W. van der Poel, H. Zaaijera, R. de Sousaa, B. Velebit, A. Avellona, M. Buti, R. Girones, J. Quer, F. Widen, H. Norder, K. Nystrom, C. Bachofen, R. Sahli, S. Ijaza, S. Treagus, M. Kulka, V. Rizzi, Hevnet, HEVnet: a one health, collaborative, interdisciplinary network and sequence data repository for enhanced hepatitis E virus molecular typing, characterisation and epidemiological investigations, Eurosurveillance 24 (10) (2019) 42–47.
[28] P.P. Primadharsini, S. Nagashima, H. Okamoto, Genetic variability and evolution of hepatitis E virus, Viruses 11 (2019) 456.
[29] F.R. Ren, C.Y. Zhao, L. Wang, Z.Y. Wang, X.Y. Gong, M.L. Song, H. Zhuang, Y. Huang, H. Shan, J.X. Wang, Q. Liu, P. Ness, K.E. Nelson, Y.C. Wang, Hepatitis E virus seroprevalence and molecular study among blood donors in China, Transfusion 54 (3) (2014) 910–917.
[30] D.-M. Nie, X. Zheng, X.-X. Xu, J.-F. Zeng, X.-L. Ye, P. Du, Epidemiological investigation of hepatitis E virus infection in blood donors in Shenzhen, J. Trop. Med. 14 (10) (2014), 1336–1338+1342 (In Chinese).
[31] Q.-Z. You, J.-T. Huang, R. Xu, M. Wang, Q. Liao, Z.-G. Shan, X. Rong, Y.-S. Fu, Epidemiological survey of hepatitis E virus infection in voluntary blood donors in Guangzhou, Chinese J. Zoonoses 35 (04) (2019) 363–368.
[32] J. Teixeira, S.S. Pereira, R.M.S. Oliveira, J. Abreu-Silva, J.R. Mesquita, A. Rodrigues, M.S.J. Nascimento, Is hepatitis E virus infection in swine slaughterhouse workers an occupational risk in Portugal? J. Hepatol. 64 (2016) S460.
[33] J.R. Mesquita, N. Santos-Ferreira, A.S. Ferreira, C. Albuquerque, C. Nobrega, F. Esteves, R. Cruz, H. Vala, M.S.J. Nascimento, Increased risk of hepatitis E virus infection in workers occupationally exposed to sheep, Transbound. Emerg. Dis. 67 (5) (2020) 1918–1921.
[34] N. García, M. Hernández, M. Gutierrez-Boada, A. Valero, D. Rodríguez-Lázaro, Occurrence of hepatitis E virus in pigs and pork cuts and organs at the time of slaughter, Spain, 2017, Front. Microbiol. 10 (2020) 2990.
[35] Q. Su, Y. Li, Y.W. Zhang, Z.H. Zhang, F.F. Meng, Z.Z. Cui, S. Chang, P. Zhao, Characterization of the novel genotype avian hepatitis E viruses from outbreaks of hepatic rupture haemorrhage syndrome in different geographical regions of China, Transbound. Emerg. Dis. 65 (6) (2018) 2017–2026.
[36] Q. Su, Y. Li, F.F. Meng, Z.Z. Cui, S. Chang, P. Zhao, Hepatic rupture hemorrhage syndrome in chickens caused by a novel genotype avian hepatitis E virus, Vet. Microbiol. 222 (2018) 91–97.
[37] A.M. Marty, M.K. Jones, The novel coronavirus (SARS-CoV-2) is a one health issue, One Health 9 (2020), 100123.
[38] P. Zhou, Z.-L. Shi, SARS-CoV-2 spillover events, Science 371 (6525) (2021) 120–122.
[39] J.Y. Wu, E.H. Lau, J. Yuan, M.L. Lu, C.J. Xie, K.B. Li, X.W. Ma, J.D. Chen, Y.H. Liu, L. Cao, M.X. Li, B. Di, Y.F. Liu, J.Y. Lu, T.G. Li, X.C. Xiao, D.H. Wang, Z.C. Yang, J. H. Lu, Transmission risk of avian influenza virus along poultry supply chains in Guangdong, China, J. Inf. Secur. 79 (1) (2019) 43–48.
[40] M.J. Ma, G.L. Wang, B.D. Anderson, Z.Q. Bi, B. Lu, X.J. Wang, C.X. Wang, S. H. Chen, Y.H. Qian, S.X. Song, M. Li, J.A. Lednicky, T. Zhao, M.N. Wu, W.C. Cao, G. C. Gray, Evidence for cross-species influenza a virus transmission within swine farms, China: a one health, prospective cohort study, Clin. Infect. Dis. 66 (4) (2018) 533–540.
[41] I. Ciglenecki, Hepatitis E: urgent action needed, Lancet. Gastroenterol. Hepatol. 2 (3) (2017) 154.
[42] R. Brierley, Elimination of viral hepatitis by 2030: ambitious, but achievable, lancet, Gastroenterol. Hepatol. 4 (2019) 88–89.
[43] M. Najmi, Hepatitis elimination by 2030: Progress and challenges, World J. Gastroenterol. 24 (2018) 4959–4961.