



# Estimating the global prevalence of hepatitis E virus in swine and pork products

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## ABSTRACT

Zoonotic transmission of hepatitis E virus (HEV), in particular the genotype (GT) 3 and GT4 strains, constitutes a major one health issue. Swine serves as an important reservoir and the processed pork products essentially contribute to foodborne transmission. This study comprehensively estimated HEV prevalence in domestic pigs, wild boars, and pork products. At global level, we found nearly 60% domestic pigs and 27% wild boars have ever encountered HEV infection based seroprevalence rate. Nearly 13% domestic and 9.5% wild swine are actively infected based on HEV RNA positivity. Importantly, about 10% of commercial pork products are HEV RNA positive, although available data are limited in this respect. Our results indicate the high prevalence rate of HEV infection in pigs and widespread contamination in pork products, although there are substantial variations at regional and country levels. These findings are important for better understanding the global epidemiology and clinical burden of HEV infection in human population related to zoonotic transmission.

## 1. Introduction

Hepatitis E virus (HEV) is a non-enveloped, single-stranded positive-sense RNA virus. It is recognized as the leading cause of acute viral hepatitis. Globally, it is estimated approximately 939 million corresponding to 1 in 8 individuals have ever been infected with HEV [1]. Among the different HEV genotypes (GT) that affect human health, GT3 and GT4 are zoonotic, which have been found in various animal species [2]. Although HEV infection is usually self-limiting or asymptomatic in healthy individuals, GT3 and GT4 HEV infection in organ transplant patients is prone to develop chronic hepatitis [3,4].

Pigs serve as the major reservoir for the zoonotic HEV strains. Anti-HEV antibodies have been widely detected in both domestic pigs and wild boars [5–7]. There are different routes of HEV transmission from pigs to humans, such as direct contact with the animal, indirectly through contaminated environment and the consumption of pork products. However, the contribution of these different transmission routes can vary tremendously among different settings attributing to multi-factors, such as socioeconomic status, farming systems, food chains and life styles. Nevertheless, the widespread consumption of pork

products is inevitably posing a major risk of HEV foodborne transmission in public health. Hepatitis E cases linking to consuming undercooked pork or wild boar meat have been widely reported [8,9].

Globally, the epidemiological feature and clinical burden of HEV infection in human population are distinct among different countries/regions [1]. It is intriguing to postulate whether this is associated with the specific prevalence rate of HEV in local swine population and available pork products. In this study, we aim to estimate the global prevalence of HEV in both domestic pigs and wild boars, as well as pork products in retailers.

## 2. Methods

### 2.1. Data sources, search strategies and study selection

A systematic search was conducted in Medline, Embase, Web of science, Cochrane CENTRAL and Google scholar. Databases were searched for articles in English language from inception until 31 May 2021. Studies were included if they contained epidemiological data about HEV in domestic pig or wild boar. The full search strategies and

*Abbreviations:* HEV, hepatitis E virus; GT, Genotype; 95% CI, 95% confidential interval.

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**Table 1**  
HEV prevalence in domestic swine.

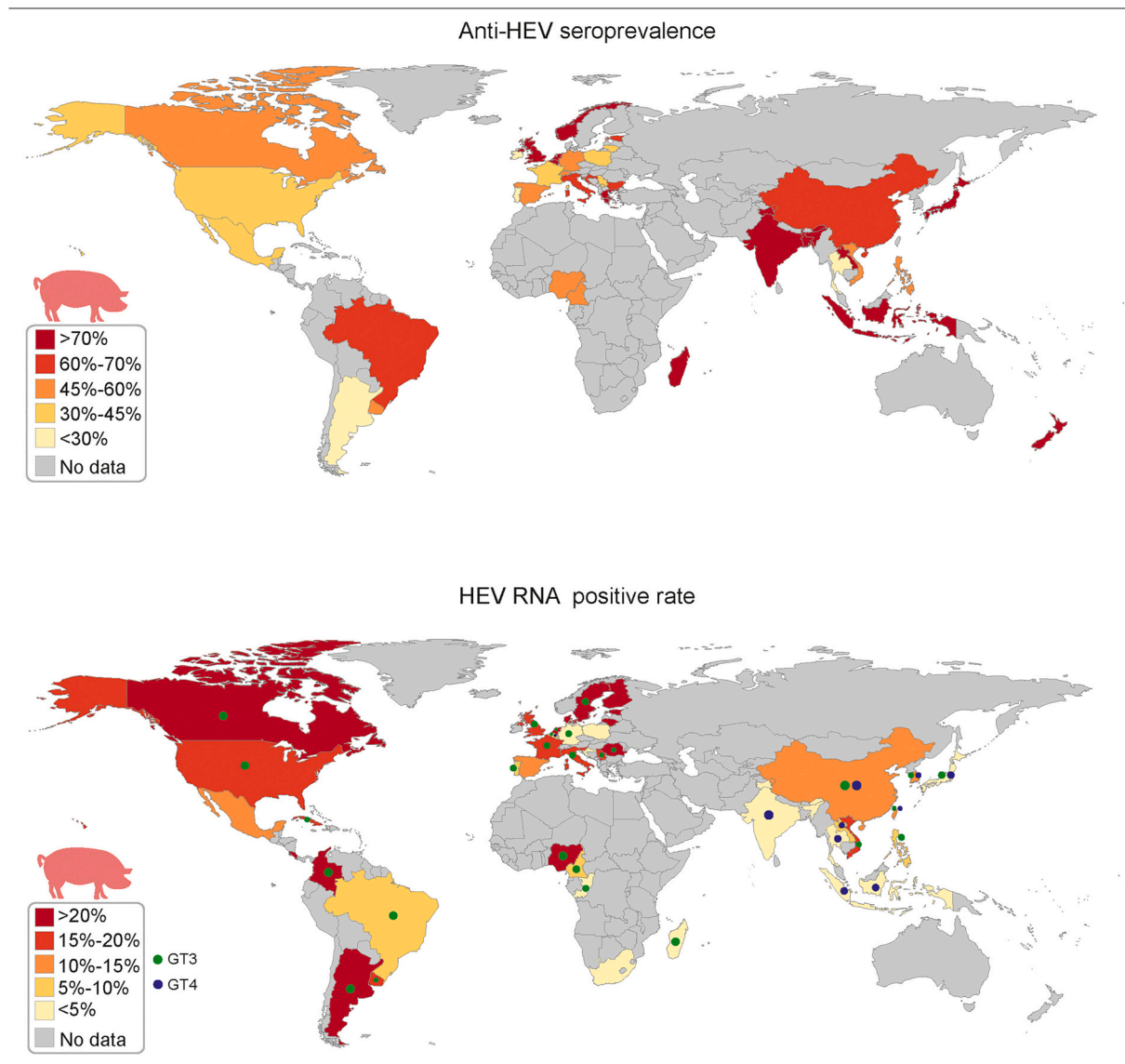
Continent	Country	Anti-HEV antibodies					HEV RNA					Genotype	
		No. of studies	Events	Tested (n)	Prevalence (%)	95% CI	No. of studies	Events	Tested (n)	Prevalence (%)	95% CI		
Asia	Bangladesh	1	82	100	82.00	73.80–88.98	–	–	–	–	–	–	
	China	13	7036	15,461	65.73	46.01–82.99	26	1233	19,493	10.40	7.48–13.74	Major GT4; Minor GT3	
	India	2	297	360	84.02	44.05–100.00	4	30	746	3.35	0.71–7.57	GT4	
	Indonesia	2	224	307	72.99	67.85–77.84	2	3	307	0.93	0.06–2.48	GT4	
	Korea	–	–	–	–	–	5	162	1294	11.13	4.63–19.85	Major GT3; Minor GT4	
	Japan	3	327	442	74.33	39.02–97.42	4	82	869	3.01	0.00–13.24	GT3 + GT4	
	Laos	2	769	899	81.36	26.33–100.00	2	26	455	5.69	0.01–18.78	GT4	
	Philippines	1	155	299	51.84	46.16–57.49	1	22	299	7.36	4.65–10.62	GT3	
	Vietnam	1	300	586	51.19	47.14–55.24	1	148	774	19.12	16.42–21.97	GT3	
	Thailand	1	87	879	9.90	8.01–11.96	1	25	875	2.86	1.85–4.07	GT4	
	Taiwan	–	–	–	–	–	2	82	816	10.17	0.00–43.06	GT3 + GT4	
	Total	26	9277	19,333	67.45	53.50–79.99	48	1813	25,928	8.23	6.21–10.49	–	
	Europe	Belgium	1	307	420	73.10	68.74–77.23	1	8	115	6.96	2.91–12.43	GT3 + GT4
		Bulgaria	4	652	1049	61.69	48.15–74.38	–	–	–	–	–	–
		Croatia	2	524	1484	64.94	8.05–100.00	1	0	469	0.00	0.00–0.37	–
Czech		–	–	–	–	–	–	–	–	–	–	GT3	
Denmark		–	–	–	–	–	1	48	97	49.48	39.53–59.45	–	
Estonia		1	234	380	61.58	56.63–66.41	1	103	449	22.94	19.16–26.95	GT3	
Finland		–	–	–	–	–	1	15	67	22.39	13.11–33.23	GT3	
France		3	1785	7814	38.19	9.19–72.96	6	343	5949	15.60	7.61–25.66	GT3	
Germany		3	1949	3861	54.79	54.92–77.30	1	3	120	2.50	0.31–6.24	GT3	
Greece		1	76	96	79.17	70.41–86.76	–	–	–	–	–	–	
Hungary		–	–	–	–	–	1	52	248	20.97	16.11–26.27	GT3	
Ireland		1	89	330	26.97	22.31–31.90	–	–	–	–	–	–	
Italy		6	2961	5737	66.58	54.92–77.30	8	311	2031	19.20	9.68–30.95	GT3	
Lithuania		1	168	384	43.75	38.82–48.74	1	106	470	22.55	18.88–26.45	–	
Netherlands		2	775	976	75.23	60.91–87.18	2	55	161	38.90	1.20–88.42	GT3	
Norway		1	484	663	73.00	69.55–76.32	–	–	–	–	–	–	
Poland		1	63	143	44.06	35.99–52.28	1	5	146	3.42	0.97–7.11	–	
Portugal		1	4	29	13.79	3.21–29.13	2	44	229	7.94	0.00–40.29	GT3	
Romania		–	–	–	–	–	1	6	19	31.58	12.27–54.50	GT3	
Serbia		2	271	654	41.14	28.63–54.25	1	51	330	15.45	11.74–19.57	GT3	
Slovenia		–	–	–	–	–	2	142	896	15.70	13.36–18.18	GT3	
Spain		5	651	1925	49.66	27.37–72.02	5	64	427	11.77	4.72–21.23	–	
Sweden		–	–	–	–	–	2	150	603	25.40	18.14–33.42	GT3	
Switzerland	2	1281	2199	58.27	56.20–60.33	–	–	–	–	–	–		
UK	2	692	805	79.56	42.36–99.54	5	232	1483	19.31	6.05–37.45	GT3		
Total	39	12,966	28,949	57.46	49.82–64.93	44	1768	14,422	17.19	13.16–21.61	–		
Oceania	New Zealand	1	54	72	75.00	64.28–84.40	–	–	–	–	–	–	
	New Caledonia	–	–	–	–	–	1	6	92	6.52	2.23–12.63	GT3	
	Total	1	54	72	75.00	64.28–84.40	1	6	92	6.52	2.23–12.63	–	
	Canada	1	594	998	59.52	56.45–62.55	2	32	200	22.70	0.00–80.63	GT3	
North America	Costa Rica	–	–	–	–	–	1	19	52	36.54	23.90–50.16	GT3	
	Mexico	3	964	2055	44.98	27.55–63.07	2	28	130	10.40	0.00–56.02	–	
	USA	2	2036	5117	39.73	38.39–41.08	3	366	5256	15.52	3.57–33.50	GT3	
	Cuba	–	–	–	–	–	1	10	53	18.87	9.32–30.65	GT3	
	Total	6	3594	8170	45.06	35.45–54.86	9	455	5691	18.10	8.71–29.84	–	
	Argentina	1	22	97	22.68	14.84–31.59	2	59	189	47.03	0.00–100.0	GT3	
South America	Brazil	5	1021	1542	60.38	37.62–81.01	7	123	1601	7.19	1.86–15.41	GT3	
	Uruguay	1	103	220	46.82	40.25–53.44	1	25	150	16.67	11.09–23.09	GT3	
	Colombia	–	–	–	–	–	1	87	250	34.80	29.01–40.83	GT3	
Africa	Total	7	1146	1859	53.03	33.79–71.81	11	294	2341	15.67	6.75–27.33	–	
	Cameroon	2	286	615	46.50	42.56–50.46	1	8	136	5.88	2.45–10.56	GT3	
	Madagascar	1	178	250	71.20	65.42–76.66	1	3	345	0.87	0.11–2.19	GT3	
	Nigeria	2	204	406	51.76	41.76–61.70	1	69	90	76.67	67.32–84.89	GT3	
	Congo	–	–	–	–	–	1	1	40	2.50	0.00–10.42	GT3	
	South Africa	–	–	–	–	–	1	7	160	4.38	1.66–8.18	–	
	Total	5	668	1271	53.46	43.26–63.52	5	88	771	12.29	0.01–38.70	–	
Overall	Global	84	27,705	59,654	59.33	53.64–64.90	118	4424	49,245	12.71	10.81–14.73	GT3 + GT4	

study selection criteria are provided in the Supplementary file S1-S2.

**2.2. Data extraction, quality assessment and statistical analysis**

Eligible studies were further divided into three study populations: domestic swine, wild boars and market/retailer pork products. Studies were scored according to Joanna Briggs Institute checklist for

prevalence studies [10]. A 95% confidence interval (95% CI) was estimated using Wilson score method, and pooled prevalence rate was calculated by the DerSimonian-Laird random-effects model with Freeman-Tukey double arcsine transformation. Funnel plots and Egger regression test were used to assess potential publication biases. ‘Meta’ package in the R-3.5.3 statistical software was used for meta-analysis as previously described [11,12]. Sensitivity analysis was performed by



**Fig. 1.** Global prevalence of anti-HEV seroprevalence and HEV RNA positivity among domestic swine.

using 'metainf' to investigate the effects of group source and potentially unrepresentative samples. The details of quality assessment and statistical analysis are provided in supplementary S3.

### 3. Results and discussion

By comprehensively searching 5 databases (Supplementary S1–S3), we identified a total of 215 studies met the inclusion criteria, which were processed for analysis of HEV prevalence in domestic pigs, wild boars and pork products (sFig. 1). First, we estimated anti-HEV seroprevalence (indication of ever exposure) and HEV RNA positivity (indication of active infection) in domestic pigs. A total of 84 studies were included to estimate the global anti-HEV seroprevalence, resulting in a pooled rate of 59.33% (37 countries, 95% CI 53.64–64.90,  $I^2 = 99\%$ ; sFig. 2). The highest seroprevalence was found in Oceania (75%, 95% CI 64.28–84.40), but this is only based on one study which likely causes bias in estimation. The second highest seroprevalence rate was found in Asia (67.45%, 95% CI 53.50–79.99,  $I^2 = 100\%$ ), followed by Europe (57.46%, 95% CI 49.82–64.93,  $I^2 = 99\%$ ), Africa (53.46%, 95% CI 43.26–63.52,  $I^2 = 92\%$ ), and South America (53.03%, 95% CI 33.79–71.81,  $I^2 = 99\%$ ) (sFig. 3). Based on 118 studies from 45

countries/territories, the global estimation of HEV RNA positive rate was 12.71% (95% CI 10.81–14.73,  $I^2 = 97\%$ ). The highest rate was found in North America (18.10%, 95% CI 8.71–29.84,  $I^2 = 97\%$ ), followed by Europe (17.19%, 95% CI 13.16–21.61,  $I^2 = 98\%$ ), South America (15.67%, 95% CI 6.75–27.33,  $I^2 = 98\%$ ), Africa (12.29%, 95% CI 0.01–38.70,  $I^2 = 99\%$ ), Asia (8.23%, 95% CI 6.21–10.49,  $I^2 = 97\%$ ), and Oceania (6.52%, 95% CI 2.23–12.63) (sFigs. 4 and 5).

At country level, HEV prevalence in domestic pigs varies substantially, from 9.90% (Thailand, 95% CI 8.01–11.96) to 84.02% (India, 95% CI 44.05–100.00,  $I^2 = 99\%$ ) of anti-HEV seroprevalence, and from 0% (Croatia, 95% CI 0.00–0.37) to 76.67% (Nigeria, 95% CI 67.32–84.89) of HEV RNA positivity (Table 1, Fig. 1). Importantly, we have collected genotyping information of swine HEV. GT3 is universally prevalent across the globe, whereas GT4 is mainly present in Western Pacific region. Interestingly, GT3 and GT4 are co-circulating in countries/territories, such as mainland China, Taiwan, Korea and Japan (Table 1, Fig. 1). This is consistent with clinical observations that both GT3 and GT4 HEV patients have been reported from these regions [13–16]. Although Europe is dominated by GT3, GT4 HEV has been identified in some peculiar cases including chronically infected patients [17]. Here, we found that GT3 and GT4 are also co-circulating in

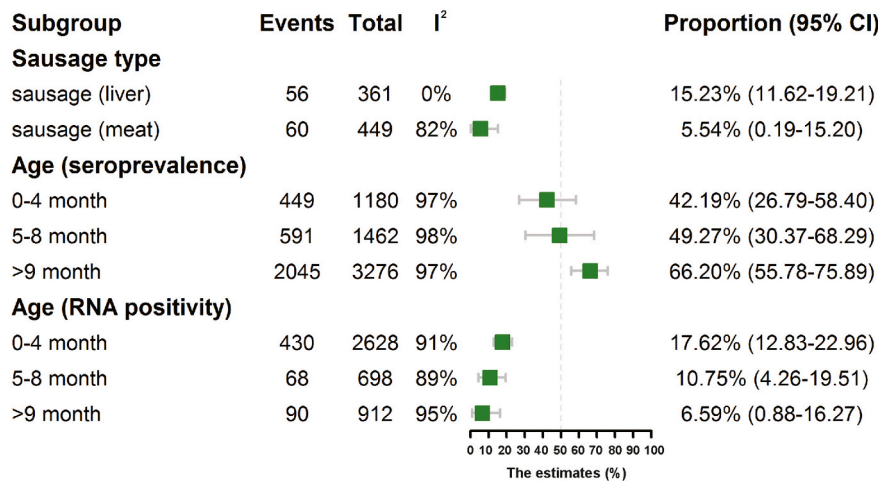


Fig. 2. Subgroup analysis of anti-HEV seroprevalence or HEV RNA positivity.

Table 2  
HEV prevalence in wild boars.

Country	Anti-HEV antibodies					HEV RNA					Genotype
	No. of studies	Events	Tested (n)	Prevalence (%)	95% CI	No. of studies	Events	Tested (n)	Prevalence (%)	95% CI	
China	1	186	758	24.52	21.51–27.67	–	–	–	–	–	–
Korea	1	1041	2736	38.05	36.24–39.88	1	24	1859	1.29	0.82–1.86	Major GT4, minor GT3
Japan	6	262	1139	19.26	10.13–30.37	5	93	2609	3.20	2.51–3.95	Major GT3, minor GT4
Thailand	–	–	–	–	–	1	1	31	3.23	0.00–13.33	GT3
Bulgaria	1	98	240	40.83	34.68–47.13	–	–	–	–	–	–
Croatia	1	311	1000	31.10	28.27–34.01	1	17	150	11.33	6.70–16.95	–
Czech	1	31	366	8.47	5.82–11.56	–	–	–	–	–	–
Estonia	1	81	471	17.20	13.92–20.75	1	13	81	16.05	8.77–24.93	GT3
France	2	160	767	21.07	8.35–37.62	2	15	637	2.35	1.28–3.71	GT3
Germany	1	81	180	45.00	37.78–52.33	4	157	701	22.33	3.34–51.18	GT3
Hungary	–	–	–	–	–	1	8	75	10.67	4.53–18.80	–
Italy	6	560	3416	33.59	15.76–54.21	10	232	1697	13.56	6.57–22.46	GT3
Lithuania	1	178	312	57.05	51.51–62.50	1	86	505	17.03	13.87–20.44	–
Netherlands	1	293	1029	28.47	25.76–31.27	2	8	158	2.67	0.00–14.30	–
Poland	1	90	290	31.03	25.83–36.49	–	–	–	–	–	–
Portugal	–	–	–	–	–	1	24	120	20.00	13.28–27.67	GT3
Romania	–	–	–	–	–	1	9	50	18.00	8.41–30.02	GT3
Slovenia	1	87	288	30.21	25.03–35.65	1	1	288	0.35	0.00–1.49	–
Spain	4	409	1299	41.51	25.30–58.72	2	43	296	14.47	6.48–24.86	–
Sweden	–	–	–	–	–	1	13	159	8.18	4.36–13.00	GT3
Switzerland	1	38	303	12.54	9.03–16.52	–	–	–	–	–	–
Turkey	1	0	93	0	0.00–1.84	–	–	–	–	–	–
EU/ multiples	1	12	104	11.54	6.02–18.47	1	4	104	3.85	0.83–8.58	–
Uruguay	1	31	140	22.14	15.62–29.43	1	13	140	9.29	4.97–14.72	–
Total	33	3949	14,931	26.82	21.69–32.28	37	761	9660	9.45	6.42–12.96	–

domestic pig populations in Belgium (Fig. 1). Thus, the emergence of GT4, which is thought to be more pathogenic, requires more attention from both public health and patient care perspectives.

Next, we performed subgroup analysis of pigs at different developmental stages of their life. As expected, the anti-HEV seroprevalence rate increases over time, from 42.19% (95% CI 26.79–58.40, I<sup>2</sup> = 97%) in 0–4 month old pigs, 49.27% (95% CI 30.37–68.29%, I<sup>2</sup> = 98%) in 5–8 month pigs, to 66.20% (95% CI 55.78–75.89, I<sup>2</sup> = 97%) in over 9 month age pigs. In contrast, the positive rate of HEV RNA showed a reverse pattern, with positive rate of 17.62% (95% CI 12.83–22.96, I<sup>2</sup> = 91%) in pigs of 0–4 month age, 10.75% (95% CI 4.26–19.51, I<sup>2</sup> = 89%) of 5–8 month age, and 6.59% (95% CI 0.86–16.27, I<sup>2</sup> = 95%) over 9 month age (Fig. 2, sFigs. 6 and 7).

Considering the clear differences in husbandry and natural habitat between wild and domesticated pigs, we separately estimated HEV

prevalence in wild boars. Based on data extracted from 33 studies from 19 countries/territories, we estimated that the overall anti-HEV seroprevalence was 26.82% (95% CI 21.69–32.28, I<sup>2</sup> = 98%) (Table 2, sFig. 8). Based on 37 studies from 18 countries/territories, the pooled rate of HEV RNA positivity was 9.45% (95% CI 6.42–12.96, I<sup>2</sup> = 96%) (Table 2, sFig. 9).

Given the important role of foodborne transmission, we collected data on HEV RNA detection rates of pork meat, liver and sausage in retailers. This generated pooled positive rate of 9.5% (95% CI 5.14–14.90, I<sup>2</sup> = 94%), with 13.27% (95% CI 0.99–35.12, I<sup>2</sup> = 98%) in meat, 6.59% (95% CI 1.83–13.49, I<sup>2</sup> = 92%) in liver and 11.70% (95% CI 7.62–16.47, I<sup>2</sup> = 71%) in sausage (sFig. 10). Sausage production represents a very large industry across the globe, particularly in Europe. Sausages are popular in groceries and sold in a variety of species [18]. We thus further compared the HEV positivity between liver sausage and

pork sausage. Notably, we estimated a nearly 3-fold HEV positivity rate of 15.23% (95% CI 11.62–19.21,  $I^2 = 0\%$ ) in liver sausage, compared with 5.54% (95% CI 0.19–15.20,  $I^2 = 82\%$ ) in pork sausage (Fig. 2, sFigs. 11–12).

Finally, we performed sensitivity analysis for HEV prevalence in domestic pigs and wild boars. In this meta-analysis, no significant change was observed by arbitrarily excluding any study from these groups. This low sensitivity supports the reliability of our estimation. However, funnel plot and Egger's test indicate the presence of publication bias ( $p > 0.05$ ) in three analyses, including seroprevalence and HEV RNA prevalence among domestic swine, and RNA prevalence among wild boars, which may potentially compromise the accuracy of prevalence estimation (sFigs. 13–26). Another limitation of our study is that we were unable to estimate HEV prevalence in pork products at regional/country levels and clarify the original place of the products, due to limited data available. Because the current food production and supply chains are diverse and complicated; it has become increasingly important to trace the origin of the contaminated products.

In summary, we found nearly 60% domestic pigs and 27% wild boars have ever encountered HEV infection at global level. Nearly 13% domestic and 9.5% wild swine are experiencing active infection. The risk of potential foodborne transmission is highlighted by our estimation that around 10% commercial pork products are HEV RNA positive. However, there remains gaps of translating these knowledge for better understanding the global epidemiology and clinical burden of HEV infection in human population related to zoonotic transmission. Because HEV zoonosis also involves many other factors, including socioeconomic status, farming style, food production and supply, as well as life styles. Nevertheless, our findings have set a stage for future research to further study the role of swine related HEV zoonosis and to facilitate the development of intervention and prevention strategies.

#### Author contributions

P. L., Z. M. and Q. P.: Project conceptualization. P. L., Y. L. and Y. J.: Data analysis. P. L. and Q. P.: Manuscript writing. Z. M. and Q. P.: supervised the project. All authors reviewed and approved the manuscript.

#### Ethical approval

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

#### Data availability statement

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Appendix.

#### Declaration of Competing Interest

The authors do not have any disclosures to report.

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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.2021.100362>.

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