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Source / Izvornik: **World Journal of Hepatology, 2021, 13, 723 - 730**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.4254/wjh.v13.i7.723>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:185891>

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Download date / Datum preuzimanja: **2024-08-28**



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Hepatitis E virus in professionally exposed: A reason for concern?

Anna Mrzljak, Ivan Balen, Ljubo Barbic, Maja Ilic, Tatjana Vilibic-Cavlek

ORCID number: Anna Mrzljak 0000-0001-6270-2305; Ivan Balen 0000-0002-7071-539X; Ljubo Barbic 0000-0002-5170-947X; Maja Ilic 0000-0001-7709-1797; Tatjana Vilibic-Cavlek 0000-0002-1877-5547.

Author contributions: Mrzljak A and Balen I made contributions to the conception and design of the study, drafted, and revised the manuscript critically; Vilibic-Cavlek T, Barbic Lj and Ilic M collected data, drafted and wrote the manuscript; All authors read and approved the final manuscript.

Conflict-of-interest statement: All authors have nothing to declare.

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Manuscript source: Invited manuscript

Specialty type: Virology

Anna Mrzljak, Department of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Zagreb 10000, Croatia

Anna Mrzljak, Tatjana Vilibic-Cavlek, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Ivan Balen, Department of Gastroenterology and Endocrinology, General Hospital "Dr. Josip Bencevic", Slavonski Brod 35000, Croatia

Ljubo Barbic, Faculty of Veterinary Medicine, University of Zagreb, Zagreb 10000, Croatia

Maja Ilic, Department of Epidemiology, Croatian Institute of Public Health, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Tatjana Vilibic-Cavlek, Department of Virology, Croatian Institute of Public Health, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Corresponding author: Anna Mrzljak, FEBGH, MD, Associate Professor, Department of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Kispaticeva 12, Zagreb 10000, Croatia. anna.mrzljak@gmail.com

Abstract

The zoonotic risk of hepatitis E virus (HEV) is well established. The HEV seroprevalence rates vary according to geographical region, assays used, and study cohorts. HEV infection is still underdiagnosed, implying the need to evaluate the disease's burden in the general population and specific risk groups, such as professionally exposed. Close contact with various animal reservoirs such as pigs, rabbits, sheep, dogs, wild boars, and deer has been associated with higher anti-HEV seroprevalence as a part of occupational exposure. While exact transmission routes remain to be determined, some general preventive measures such as proper hand hygiene, the usage of personal protective equipment, and the thermal processing of food before consumption should be followed. A "One-Health" multisectoral approach should be implemented to achieve optimal health and well-being outcomes, recognizing the interconnections between humans, animals, plants, and their shared environment, in which a vaccine against the zoonotic genotypes 3 and 4 and swine vaccination should be considered as a possible public health measure. This opinion review comprehensively addresses the HEV burden of professional exposure for butchers, slaughterhouse workers, veterinarians, farmers, hunters, and forestry workers delineates the current limits of protective work measures, and tackles future directions.

Country/Territory of origin: Croatia

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 14, 2021

Peer-review started: March 14, 2021

First decision: March 29, 2021

Revised: March 31, 2021

Accepted: June 25, 2021

Article in press: June 25, 2021

Published online: July 27, 2021

P-Reviewer: Jackson K, Škrlec I

S-Editor: Liu M

L-Editor: Filipodia

P-Editor: Wang LL



Key Words: Hepatitis E virus; Zoonotic infection; Occupational disease; Veterinarians; Farmers; Butchers; Slaughterhouse workers; Forestry workers; Hunters

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Core Tip: The zoonotic risk of hepatitis E virus (HEV) is well established. Close contact with various animal reservoirs such as pigs, rabbits, sheep, dogs, wild boars, and deer has been associated with higher anti-HEV seroprevalence as a part of occupational exposure. However, precise HEV transmission routes yet need to be determined. This opinion review addresses the HEV burden of professional exposure, delineates the current limits of protective work measures, and tackles future directions.

Citation: Mrzljak A, Balen I, Barbic L, Ilic M, Vilibic-Cavlek T. Hepatitis E virus in professionally exposed: A reason for concern? *World J Hepatol* 2021; 13(7): 723-730

URL: <https://www.wjgnet.com/1948-5182/full/v13/i7/723.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v13.i7.723>

INTRODUCTION

The global burden of hepatitis E virus (HEV) is high, with an estimated 20 million new HEV infection events yearly, 3.3 million symptomatic cases, and 44,000 deaths[1]. HEV RNA genotypes 1 and 2, found only in humans, primarily cause waterborne epidemics in resource-poor regions. Infections are usually self-limiting and not associated with progression to chronic disease. In high-income countries, zoonotic HEV genotypes 3, 4, and 7 circulate in various animal species, and human infections are usually asymptomatic, cause sporadic, or clustered cases of hepatitis[2,3]. In immunocompromised individuals, chronic HEV infection can progress to cirrhosis[3,4].

Besides contaminated water, transmission routes include consuming insufficiently cooked meat and meat products from infected animals (*e.g.*, pork liver), transfusions of infected blood derivatives, solid-organ transplants, and vertical transmission[1,3].

In the last two decades, there has been an increase in autochthonous infections related to the transmission of zoonotic genotypes HEV-3 and HEV-4[5]. Seroprevalence rates in the general population of industrialized countries vary from < 5% to > 50%. Higher rates are observed in the southwest region of France, Poland, and Netherlands, moderate seroprevalence rates from 10% to 30% in the United States, United Kingdom, Belgium, and Germany, and the lowest in Canada, Ireland, Australia, and New Zealand[3,6].

In 1995, the first HEV animal strain was found in sera and stool of swine in Nepal's Kathmandu Valley[7]. Since then, different reservoirs (infected pigs, rabbits, wild boars, and deer) and various zoonotic transmission routes[5] have been associated with professional exposures of those in close contact with the reported HEV reservoirs. Detected HEV sequences in pigs, rabbits, and humans are tightly related[8]; however, it is still unclear whether HEV strains from other animals can cross the species barrier and infect humans. Recently described HEV-7, distributed in dromedary camels from the Middle East[9,10], has been detected in a transplant recipient who consumed camel milk and meat[4]. In addition, a Chinese study showed that viral RNA of HEV-4 could be excreted by cow milk[11], implicating possible HEV transmission through milk or milk products.

Accordingly, professionally exposed workers such as butchers, slaughterhouse workers, veterinarians, farmers, hunters, and forestry workers are considered a risk group for HEV infections. This article addresses the burden of professional exposure to HEV, determines the current situation, delineates the limits, and tackles the future directions.

HEV IN VETERINARIANS AND FARMERS

Among domestic animals, pigs are considered the main reservoir of zoonotic HEV-3 and -4 in industrialized countries. High seroprevalence of HEV IgG antibodies was

detected in pigs in many countries, which implicate a high risk of zoonotic transmission to professionally exposed workers, such as veterinarians and farmers. Indeed, the occupational risk is well known and confirmed by numerous studies and several meta-analyses (Table 1) that investigated the association between direct contact with animals and HEV seroprevalence.

However, when interpreting serological studies, it is important to bear in mind that there are considerable variations in sensitivity and/or specificity between different HEV antibody assays. Thus, it is difficult to compare prevalence estimates using different assays[12], and the lack of a gold standard hampers the interpretability of serological studies[13].

The United States data confirmed that swine veterinarians were 1.51 times more likely to be anti-HEV positive than blood donors[14]. Similarly, studies from Norway and Austria show that swine veterinarians are twice as likely to be HEV seropositive than other veterinarians[15,16]. Other studies from France[17], Germany[18], and Israel[19] support high HEV professional exposure in pig farm workers. In Portugal, in addition to pig farmers, higher HEV seroprevalence was also found in sheep farmers and cheesemakers (29.3%) compared to the general population (16.1%)[20]. In east Africa, Rwandan farmers have higher HEV seroprevalence compared to other professions, with the highest being in high-density pig breeding regions[21].

Studies from China demonstrate high IgG seropositivity in veterinarians (26.7%-43.7%)[22-24] and farmers (34.8%-53.0%)[22-24]. In high-density, pig-farming areas in central China, HEV IgG seroprevalence in swine farm workers rises to 48.35% and increases with age and working years, with all the isolates belong to HEV-4d[25]. Except in swine and sheep farmers, higher seroprevalence was observed in deer (40.2%) and mink farmers (31.8%)[22].

However, despite high HEV seroprevalence rates and zoonotic potential, the awareness of HEV is still inadequate in farmers and veterinarians, who report the lack of knowledge and low perception of the HEV's importance for implementing on-farm risk mitigation strategies[26].

Recent studies additionally highlight risk in small animal practitioners due to high HEV seroprevalence in pet animals. Seroprevalence in dogs in the Netherlands and Germany was 18.52% and 56.6%, respectively[27,28]. The same Dutch study showed that 14.89% of cats had HEV antibodies. Nevertheless, the results of a German study show that pet ownership is inversely associated with infection[29]. On the other hand, American data indicate that having a pet in the home increases odds of HEV seropositivity [odds ratio (OR), 1.19 (95% Confidence interval (CI), 1.01-1.40)][30]. These results are in line with the observation that veterinarians and farm staff exposed to dogs in the southwest of China have significantly higher seroprevalence than the general population[23]. In Finland, veterinarians have almost two times higher HEV seroprevalence (10.2%) than non-veterinarians (5.8%), and surprisingly, among veterinarians, the highest HEV seroprevalence (17.8%) was detected among small animal practitioners[31]. Similar results were confirmed in Estonia, where all antibody-positive veterinarians were small animal practitioners[32]. A high HEV seroprevalence in pet animals highlighted that in addition to generally known occupational exposure in pig farm workers (farmers and veterinarians), small animal practitioners could also be professionally exposed to HEV. High HEV seroprevalence in pet animals raises the question of their role in the HEV epidemiology as a potential risk of HEV transmission from pets to their owners, which needs to be further investigated.

HEV IN BUTCHERS AND SLAUGHTERHOUSE WORKERS

In geographically distinct locations, studies on swine related occupational exposure report a higher HEV seroprevalence in butchers and slaughterhouse workers compared to the general population; for Germany (41.7% *vs* 15.5%)[18], Portugal (29.7% *vs* 19.9%)[33], Republic of Moldova (14.3% *vs* 0)[34], India (75% *vs* 10.71%)[35], and Burkina Faso (76% *vs* 47.8%)[36]. However, the general population in these studies should be interpreted with caution, *e.g.*, a control group of freshman students who drank only filtered water may be misleading[35].

The results of several meta-analyses substantiate higher HEV risk in swine-related professions. A meta-analysis on 28 studies from mainland China showed that those professionally exposed (swine farmers, slaughters, swine vendors, and veterinarians) have a 2.63-fold higher risk for HEV IgG seropositivity than the general population [24]. Additionally, a recent meta-analysis on 32 studies on swine-related occupations (swine farmers, butchers, meat processors, port retailers, and veterinarians) from 16

Table 1 Occupation-related key points from meta-analyses on hepatitis E virus infection

Meta-analysis: Region/Period/No of studies	HEV IgG seroprevalence: occupational/general population	Occupation-related key points
16 countries; 1999-2018; 32 studies[37]	32.85%/21.70%	The anti-HEV IgG PR for all swine workers was 1.52 (95%CI: 1.38-1.76); butchers 1.75 (95%CI: 1.31-2.35), swine farmers 1.51 (95%CI: 1.32-1.74), meat processors 1.46 (95%CI: 1.13-1.89), veterinarians 1.36 (95%CI: 1.15-1.61) and pork retailers 1.19 (95%CI: 1.09-1.29) compared to the general population; The anti-HEV IgG PR for swine workers in Asia was 1.49 (95%CI: 1.35-1.64) and in Europe 1.93 (95%CI: 1.49-2.50)
Mainland China; 2004- 2018; 28 studies[24]	47.4%/27.3%	Anti-HEV IgG positivity: Swine vendors (77.0%), producers (56.0%), swine farmers (53.0%), slaughterers (51.7%) and veterinarians (43.7%); The OR for HEV IgG seropositivity in swine occupational population was 2.63 (95%CI: 1.87-3.70) compared to the general population
Europe; 2003-2015; 73 studies[51]	17%/28% using WT	Seroprevalence rates depend on the serologic assays used; increased with age, were unrelated to gender, varied within countries; Individuals in contact with swine/wild animals had higher seroprevalence rates than the general population, irrespective of assay used ($P < 0.0001$)
Global, non-endemic HEV countries; 1994- 2018; 163 studies[52]	Not calculated	The OR for HEV seropositivity for occupational contact with pigs was 1.95 and for the employment in forestry population 2.49 compared to the general population; Recreational hunting was a non-significant predictor for HEV seropositivity; Contact with pigs (not categorized as occupational), cats or horses was non-significantly associated, contact with dogs was significantly associated with increased odds of HEV IgG seropositivity; The consumption of meat (uncooked liver sausage, rabbit and game meat, liver or organ meats, bacon or ham, and pork) was a significant predictor of HEV IgG seropositivity (median OR = 1.44, range (1.12-2.77))

CI: Confidence interval; HEV: Hepatitis E virus; OR: Odds ratio; PR: Prevalence ratio; WT: Wantai test.

different countries demonstrated that swine workers are 1.52-fold more likely to be HEV IgG seropositive than the general population. Interestingly, the association with the HEV exposure, the prevalence ratio (PR) is higher in Europe (PR = 1.93, 95%CI 1.49-2.50) than in Asia (PR = 1.49, 95%CI 1.35-1.64)[37] (Table 1).

Furthermore, the data show that rabbit slaughterhouse workers have a 6.9-fold increased risk for HEV compared to the general population and that their seropositivity also increases with working years[38].

The precise HEV transmission route among occupationally exposed workers remains to be determined. However, it is possible that increased risk of infection during slaughtering results from manipulation of raw HEV-rich organs and tissues (*i.e.* liver and bile) without direct consumption[18]. In addition, well-known risk factors for anti-HEV IgG seropositivity are the frequency and duration of contact with animals [33,39].

Over the past decades, it has become clear that a collaborative and multisectoral approach across boundaries of animal, human, and environmental health (a One-Health approach) is needed to develop control and achieve optimal health outcomes in a setting of zoonotic diseases. The use of protective equipment and vaccination (when possible) should be an integral part of the prevention of zoonotic infections. The HEV studies on protective equipment in butchers and slaughterhouse workers are scarce with conflicting results. An Indian study showed that slaughterhouse workers are routinely in contact with swine without adequate protective equipment[35]. A South Korean study demonstrated that anti-HEV IgG positive slaughterhouse workers use protective equipment (vinyl gloves, aprons, boots, and disposable protective suits) more often than anti-HEV IgG negative workers, suggesting that the equipment does not prevent the HEV infection or that the equipment is not appropriately used[40]. Although the clinical course of HEV infection in most cases is subclinical, in middle-aged and older men workers with underlying liver disease, the risk of HEV infection should be especially minimized given the frequency of complications in this population group[41]. The authors propose that for workers at continued risk of exposure, strict hygiene measures, personal protective equipment, and a vaccine against the zoonotic genotypes 3 and 4 and swine vaccination should be considered. However, the first and only HEV vaccine produced and licensed in China is not approved for widespread use, even though it shows a good tolerance and the efficacy of 86.8% on the extended follow-up[42,43]. Despite these results, the efficacy in different genotypes of the virus and safety in chronic liver disease and other vulnerable populations remains unclear[43].

HEV IN FORESTRY WORKERS AND HUNTERS

In Europe, hunting and forestry work, particularly woodcutting, are associated with increased HEV seropositivity[17,44-47]. It is a well-known fact that the HEV seroprevalence increases with age, duration, and animal-related activity frequency. This general trend is also confirmed for the forestry workers and hunters[47,48].

However, some studies do not support previous data. Studies from central Germany and Northern Italy showed no differences in anti-HEV IgG antibodies in hunters[49] and forestry workers compared to the general population[50].

A meta-analysis on HEV seroprevalence in Europe conducted on 73 studies shows that individuals in contact with swine/wild animals have significantly higher seroprevalence rates than the general population. It is important to notice that they vary according to geographical region, assays employed, and study cohorts[51].

As wild boars and deer represent important HEV reservoirs, HEV transmission route in hunters may occur during skinning and disemboweling of an infected animal or through contact with its blood or feces[49]. Studies show that hand hygiene immediately after disembowelment reduces the HEV infection risk[48] and that the regular use of protective gloves is associated with an 88% lower HEV seroprevalence [49]. Additionally, a study from Southern France found that wearing work boots by forestry workers is associated with significantly lower HEV seroprevalence (46% without *vs* 28% with boots). Interestingly, no differences were detected for wearing gloves (39% without *vs* 34% with gloves)[17]. Despite conflicting evidence, the authors believe the use of personal protection minimizes the risk of infection.

In conclusion, most of the published studies showed that the risk of HEV infection is higher in forestry workers and hunters than in the general population. However, some studies did not identify hunting activity as an important risk factor for the HEV seropositivity. Close and frequent contact with HEV-infected animals, especially wild boars, represents important risk factors, where the use of personal protection minimizes the risk of infection.

CONCLUSION

Given the high seroprevalence rates observed in swine workers, veterinarians, farmers and hunters, contacts with infected animal reservoirs (mainly pigs, wild boars, deer) have been recognized as risk factors for the transmission of HEV. The list of new animal reservoirs is ever-expanding as new HEV strains are continuously being found in a broad range of hosts. Although the precise HEV transmission route in occupationally exposed workers remains to be determined, occupational exposure plays a significant role.

HEV infection is still an underdiagnosed disease due to the lack of routine diagnosis and surveillance protocols, limiting the knowledge of the data about the HEV burden. Thus, there is a need for a realistic evaluation of HEV disease's burden in humans in general and in specific risk groups, such as professionally exposed.

A better understanding of HEV transmission routes from the infected animals to workers might help develop more specific preventive measures for specific occupational groups that have shown to be associated with the higher risk of acquiring HEV. Until other evidence is found, several protective measures to decrease the risk in occupationally exposed groups should be respected: the proper hand hygiene following contact with animals known to be HEV reservoir, the usage of recommended personal protective equipment, and the proper thermal processing of food before consumption. Although HEV infection is not an economically important pig disease, developing a vaccine against the zoonotic genotypes 3 and 4 and swine vaccination should be considered a possible public health measure. Epidemiologically important pet animals should also be further investigated as a potential additional risk factor for small animal practice veterinarians and pet animal owners.

Further testing of different populations including the general population and professionally exposed persons as well as animals are needed to better understand the epidemiology of hepatitis E.

REFERENCES

- 1 **World Health Organization.** Hepatitis E. [cited 7 March 2021]. [Internet]. Available from: <https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-e>

- 2 **Nimgaonkar I**, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 96-110 [PMID: [29162935](#) DOI: [10.1038/nrgastro.2017.150](#)]
- 3 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines on hepatitis E virus infection. *J Hepatol* 2018; **68**: 1256-1271 [PMID: [29609832](#) DOI: [10.1016/j.jhep.2018.03.005](#)]
- 4 **Lee GH**, Tan BH, Teo EC, Lim SG, Dan YY, Wee A, Aw PP, Zhu Y, Hibberd ML, Tan CK, Purdy MA, Teo CG. Chronic Infection With Camelid Hepatitis E Virus in a Liver Transplant Recipient Who Regularly Consumes Camel Meat and Milk. *Gastroenterology* 2016; **150**: 355-357.e3 [PMID: [26551551](#) DOI: [10.1053/j.gastro.2015.10.048](#)]
- 5 **Kamar N**, Izopet J, Pavio N, Aggarwal R, Labrique A, Wedemeyer H, Dalton HR. Hepatitis E virus infection. *Nat Rev Dis Primers* 2017; **3**: 17086 [PMID: [29154369](#) DOI: [10.1038/nrdp.2017.86](#)]
- 6 **Capai L**, Falchi A, Charrel R. Meta-Analysis of Human IgG anti-HEV Seroprevalence in Industrialized Countries and a Review of Literature. *Viruses* 2019; **11** [PMID: [30669517](#) DOI: [10.3390/v11010084](#)]
- 7 **Clayson ET**, Innis BL, Myint KS, Narupiti S, Vaughn DW, Giri S, Ranabhat P, Shrestha MP. Detection of hepatitis E virus infections among domestic swine in the Kathmandu Valley of Nepal. *Am J Trop Med Hyg* 1995; **53**: 228-232 [PMID: [7573701](#) DOI: [10.4269/ajtmh.1995.53.228](#)]
- 8 **De Schryver A**, De Schrijver K, François G, Hambach R, van Sprundel M, Tabibi R, Colosio C. Hepatitis E virus infection: an emerging occupational risk? *Occup Med (Lond)* 2015; **65**: 667-672 [PMID: [26452392](#) DOI: [10.1093/occmed/kqv154](#)]
- 9 **Woo PC**, Lau SK, Teng JL, Tsang AK, Joseph M, Wong EY, Tang Y, Sivakumar S, Xie J, Bai R, Wernery R, Wernery U, Yuen KY. New hepatitis E virus genotype in camels, the Middle East. *Emerg Infect Dis* 2014; **20**: 1044-1048 [PMID: [24856611](#) DOI: [10.3201/eid2006.140140](#)]
- 10 **Rasche A**, Saqib M, Liljander AM, Bornstein S, Zohaib A, Renneker S, Steinhagen K, Wernery R, Younan M, Gluecks I, Hilali M, Musa BE, Jores J, Wernery U, Drexler JF, Drosten C, Corman VM. Hepatitis E Virus Infection in Dromedaries, North and East Africa, United Arab Emirates, and Pakistan, 1983-2015. *Emerg Infect Dis* 2016; **22**: 1249-1252 [PMID: [27315454](#) DOI: [10.3201/eid2207.160168](#)]
- 11 **Huang F**, Li Y, Yu W, Jing S, Wang J, Long F, He Z, Yang C, Bi Y, Cao W, Liu C, Hua X, Pan Q. Excretion of infectious hepatitis E virus into milk in cows imposes high risks of zoonosis. *Hepatology* 2016; **64**: 350-359 [PMID: [27286751](#) DOI: [10.1002/hep.28668](#)]
- 12 **Sommerkorn FM**, Schauer B, Schreiner T, Fickenscher H, Krumbholz A. Performance of Hepatitis E Virus (HEV)-antibody tests: a comparative analysis based on samples from individuals with direct contact to domestic pigs or wild boar in Germany. *Med Microbiol Immunol* 2017; **206**: 277-286 [PMID: [28397024](#) DOI: [10.1007/s00430-017-0503-4](#)]
- 13 **Norder H**, Karlsson M, Mellgren Å, Konar J, Sandberg E, Lasson A, Castedal M, Magnusius L, Lagging M. Diagnostic Performance of Five Assays for Anti-Hepatitis E Virus IgG and IgM in a Large Cohort Study. *J Clin Microbiol* 2016; **54**: 549-555 [PMID: [26659210](#) DOI: [10.1128/JCM.02343-15](#)]
- 14 **Meng XJ**, Wiseman B, Elvinger F, Guenette DK, Toth TE, Engle RE, Emerson SU, Purcell RH. Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries. *J Clin Microbiol* 2002; **40**: 117-122 [PMID: [11773103](#) DOI: [10.1128/jcm.40.1.117-122.2002](#)]
- 15 **Lange H**, Øverbø J, Borgen K, Dudman S, Hoddevik G, Urdahl AM, Vold L, Sjurseth SK. Hepatitis E in Norway: seroprevalence in humans and swine. *Epidemiol Infect* 2017; **145**: 181-186 [PMID: [27671461](#) DOI: [10.1017/S0950268816002144](#)]
- 16 **Taus K**, Schmoll F, El-Khatib Z, Auer H, Holzmann H, Aberle S, Pekard-Amenitsch S, Monschein S, Sattler T, Steinparzer R, Allerberger F, Schmid D. Occupational swine exposure and Hepatitis E virus, Leptospira, Ascaris suum seropositivity and MRSA colonization in Austrian veterinarians, 2017-2018-A cross-sectional study. *Zoonoses Public Health* 2019; **66**: 842-851 [PMID: [31419070](#) DOI: [10.1111/zph.12633](#)]
- 17 **Chaussade H**, Rigaud E, Allix A, Carpentier A, Touzé A, Delzescaux D, Choutet P, Garcia-Bonnet N, Coursaget P. Hepatitis E virus seroprevalence and risk factors for individuals in working contact with animals. *J Clin Virol* 2013; **58**: 504-508 [PMID: [24084601](#) DOI: [10.1016/j.jcv.2013.08.030](#)]
- 18 **Krumbholz A**, Mohn U, Lange J, Motz M, Wenzel JJ, Jilg W, Walther M, Straube E, Wutzler P, Zell R. Prevalence of hepatitis E virus-specific antibodies in humans with occupational exposure to pigs. *Med Microbiol Immunol* 2012; **201**: 239-244 [PMID: [21773797](#) DOI: [10.1007/s00430-011-0210-5](#)]
- 19 **Shirazi R**, Pozzi P, Wax M, Bar-Or I, Asulin E, Lustig Y, Mendelson E, Ben-Ari Z, Schwartz E, Mor O. Hepatitis E in pigs in Israel: seroprevalence, molecular characterisation and potential impact on humans. *Euro Surveill* 2018; **23** [PMID: [30621824](#) DOI: [10.2807/1560-7917.ES.2018.23.49.1800067](#)]
- 20 **Mesquita JR**, Santos-Ferreira N, Ferreira AS, Albuquerque C, Nóbrega C, Esteves F, Cruz R, Vala H, Nascimento MSJ. Increased risk of hepatitis E virus infection in workers occupationally exposed to sheep. *Transbound Emerg Dis* 2020 [PMID: [32090484](#) DOI: [10.1111/tbed.13524](#)]
- 21 **Twagirumugabe T**, Saguti F, Habarurema S, Gahutu JB, Bergström T, Norder H. Hepatitis A and E virus infections have different epidemiological patterns in Rwanda. *Int J Infect Dis* 2019; **86**: 12-14 [PMID: [31238154](#) DOI: [10.1016/j.ijid.2019.06.019](#)]
- 22 **Kang YH**, Cong W, Zhang XY, Wang CF, Shan XF, Qian AD. Hepatitis E virus seroprevalence among farmers, veterinarians and control subjects in Jilin province, Shandong province and Inner Mongolia Autonomous Region, China. *J Med Virol* 2017; **89**: 872-877 [PMID: [27664799](#) DOI: [10.1093/jm/89.7.872](#)]

- 10.1002/jmv.24693]
- 23 **Zeng MY**, Gao H, Yan XX, Qu WJ, Sun YK, Fu GW, Yan YL. High hepatitis E virus antibody positive rates in dogs and humans exposed to dogs in the south-west of China. *Zoonoses Public Health* 2017; **64**: 684-688 [PMID: [28714127](#) DOI: [10.1111/zph.12377](#)]
 - 24 **Yue N**, Wang Q, Zheng M, Wang D, Duan C, Yu X, Zhang X, Bao C, Jin H. Prevalence of hepatitis E virus infection among people and swine in mainland China: A systematic review and meta-analysis. *Zoonoses Public Health* 2019; **66**: 265-275 [PMID: [30884147](#) DOI: [10.1111/zph.12555](#)]
 - 25 **Shu Y**, Chen Y, Zhou S, Zhang S, Wan Q, Zhu C, Zhang Z, Wu H, Zhan J, Zhang L. Cross-sectional Seroprevalence and Genotype of Hepatitis E Virus in Humans and Swine in a High-density Pig-farming Area in Central China. *Viral Sin* 2019; **34**: 367-376 [PMID: [31264049](#) DOI: [10.1007/s12250-019-00136-x](#)]
 - 26 **Teixeira-Costa C**, Andraud M, Rose N, Salines M. Controlling hepatitis E virus in the pig production sector: Assessment of the technical and behavioural feasibility of on-farm risk mitigation strategies. *Prev Vet Med* 2020; **175**: 104866 [PMID: [31838401](#) DOI: [10.1016/j.prevetmed.2019.104866](#)]
 - 27 **Li Y**, Qu C, Spee B, Zhang R, Penning LC, de Man RA, Peppelenbosch MP, Fieten H, Pan Q. Hepatitis E virus seroprevalence in pets in the Netherlands and the permissiveness of canine liver cells to the infection. *Ir Vet J* 2020; **73**: 6 [PMID: [32266057](#) DOI: [10.1186/s13620-020-00158-y](#)]
 - 28 **Dähnert L**, Conraths FJ, Reimer N, Groschup MH, Eiden M. Molecular and serological surveillance of Hepatitis E virus in wild and domestic carnivores in Brandenburg, Germany. *Transbound Emerg Dis* 2018; **65**: 1377-1380 [PMID: [29655214](#) DOI: [10.1111/tbed.12877](#)]
 - 29 **Wichmann O**, Schimanski S, Koch J, Kohler M, Rothe C, Plentz A, Jilg W, Stark K. Phylogenetic and case-control study on hepatitis E virus infection in Germany. *J Infect Dis* 2008; **198**: 1732-1741 [PMID: [18983248](#) DOI: [10.1086/593211](#)]
 - 30 **Kuniholm MH**, Purcell RH, McQuillan GM, Engle RE, Wasley A, Nelson KE. Epidemiology of hepatitis E virus in the United States: results from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Infect Dis* 2009; **200**: 48-56 [PMID: [19473098](#) DOI: [10.1086/599319](#)]
 - 31 **Kantala T**, Kinnunen PM, Oristo S, Jokelainen P, Vapalahti O, Maunula L. Hepatitis E Virus Antibodies in Finnish Veterinarians. *Zoonoses Public Health* 2017; **64**: 232-238 [PMID: [27621202](#) DOI: [10.1111/zph.12312](#)]
 - 32 **Lassen B**, Janson M, Neare K, Tallo T, Reshetnjak I, Kuznetsova T, Viltrop A, Golovljova I, Jokelainen P. Prevalence of Antibodies Against Hepatitis E Virus in Veterinarians in Estonia. *Vector Borne Zoonotic Dis* 2017; **17**: 773-776 [PMID: [28933680](#) DOI: [10.1089/vbz.2017.2122](#)]
 - 33 **Teixeira J**, Mesquita JR, Pereira SS, Oliveira RM, Abreu-Silva J, Rodrigues A, Myrmet M, Stene-Johansen K, Øverbø J, Gonçalves G, Nascimento MS. Prevalence of hepatitis E virus antibodies in workers occupationally exposed to swine in Portugal. *Med Microbiol Immunol* 2017; **206**: 77-81 [PMID: [27770276](#) DOI: [10.1007/s00430-016-0484-8](#)]
 - 34 **Sajin O**, Spînu C, Pinzaru I, Isac M, Spînu I, Guțu V, Paraschiv A, Suveică L. Seroprevalence and risk assessment of viral hepatitis E infection in a group of exposed persons from Republic of Moldova. *J Infect Dev Ctries* 2019; **13**: 461-464 [PMID: [32053517](#) DOI: [10.3855/jidc.11397](#)]
 - 35 **Bansal M**, Kaur S, Deka D, Singh R, Gill JPS. Seroepidemiology and molecular characterization of hepatitis E virus infection in swine and occupationally exposed workers in Punjab, India. *Zoonoses Public Health* 2017; **64**: 662-672 [PMID: [28449278](#) DOI: [10.1111/zph.12363](#)]
 - 36 **Traoré KA**, Ouoba JB, Huot N, Rogée S, Dumarest M, Traoré AS, Pavio N, Barro N, Roques P. Hepatitis E Virus Exposure is Increased in Pork Butchers from Burkina Faso. *Am J Trop Med Hyg* 2015; **93**: 1356-1359 [PMID: [26438027](#) DOI: [10.4269/ajtmh.15-0321](#)]
 - 37 **Huang X**, Huang Y, Wagner AL, Chen X, Lu Y. Hepatitis E virus infection in swine workers: A meta-analysis. *Zoonoses Public Health* 2019; **66**: 155-163 [PMID: [30548110](#) DOI: [10.1111/zph.12548](#)]
 - 38 **Geng Y**, Zhao C, Geng K, Wang C, Wang X, Liu H, Wang Y. High seroprevalence of hepatitis E virus in rabbit slaughterhouse workers. *Transbound Emerg Dis* 2019; **66**: 1085-1089 [PMID: [30661292](#) DOI: [10.1111/tbed.13130](#)]
 - 39 **Temmam S**, Besnard L, Andriamandimby SF, Foray C, Rasamoelina-Andriamanivo H, Héraud JM, Cardinale E, Dellagi K, Pavio N, Pascalis H, Porphyre V. High prevalence of hepatitis E in humans and pigs and evidence of genotype-3 virus in swine, Madagascar. *Am J Trop Med Hyg* 2013; **88**: 329-338 [PMID: [23208879](#) DOI: [10.4269/ajtmh.2012.12-0615](#)]
 - 40 **Kim BS**, Lim HS, Lee K, Min YS, Yoon YS, Jeong HS. A survey on the status of hepatitis e virus infection among slaughterhouse workers in South Korea. *J Prev Med Public Health* 2015; **48**: 53-61 [PMID: [25652711](#) DOI: [10.3961/jpmph.14.048](#)]
 - 41 **Dalton HR**, Seghatchian J. Hepatitis E virus: Emerging from the shadows in developed countries. *Transfus Apher Sci* 2016; **55**: 271-274 [PMID: [27843081](#) DOI: [10.1016/j.transci.2016.10.016](#)]
 - 42 **Zhu FC**, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Wang H, Yang CL, Jiang HM, Cai JP, Wang YJ, Ai X, Hu YM, Tang Q, Yao X, Yan Q, Xian YL, Wu T, Li YM, Miao J, Ng MH, Shih JW, Xia NS. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010; **376**: 895-902 [PMID: [20728932](#) DOI: [10.1016/S0140-6736\(10\)61030-6](#)]
 - 43 **Murali AR**, Kotwal V, Chawla S. Chronic hepatitis E: A brief review. *World J Hepatol* 2015; **7**: 2194-2201 [PMID: [26380044](#) DOI: [10.4254/wjh.v7.i19.2194](#)]
 - 44 **Montagnaro S**, De Martinis C, Sasso S, Ciarcia R, Damiano S, Auletta L, Iovane V, Zottola T,

- Pagnini U. Viral and Antibody Prevalence of Hepatitis E in European Wild Boars (*Sus scrofa*) and Hunters at Zoonotic Risk in the Latium Region. *J Comp Pathol* 2015; **153**: 1-8 [PMID: 26025105 DOI: 10.1016/j.jcpa.2015.04.006]
- 45 **Dremsek P**, Wenzel JJ, John R, Ziller M, Hofmann J, Groschup MH, Werdermann S, Mohn U, Dorn S, Motz M, Mertens M, Jilg W, Ulrich RG. Seroprevalence study in forestry workers from eastern Germany using novel genotype 3- and rat hepatitis E virus-specific immunoglobulin G ELISAs. *Med Microbiol Immunol* 2012; **201**: 189-200 [PMID: 22179131 DOI: 10.1007/s00430-011-0221-2]
- 46 **Mansuy JM**, Legrand-Abrevanel F, Calot JP, Peron JM, Alric L, Agudo S, Rech H, Destruel F, Izopet J. High prevalence of anti-hepatitis E virus antibodies in blood donors from South West France. *J Med Virol* 2008; **80**: 289-293 [PMID: 18098159 DOI: 10.1002/jmv.21056]
- 47 **Carpentier A**, Chaussade H, Rigaud E, Rodriguez J, Berthault C, Boué F, Tognon M, Touzé A, Garcia-Bonnet N, Choutet P, Coursaget P. High hepatitis E virus seroprevalence in forestry workers and in wild boars in France. *J Clin Microbiol* 2012; **50**: 2888-2893 [PMID: 22718947 DOI: 10.1128/JCM.00989-12]
- 48 **Baumann-Popczyk A**, Popczyk B, Gołab E, Rożej-Bielicka W, Sadkowska-Todys M. A cross-sectional study among Polish hunters: seroprevalence of hepatitis E and the analysis of factors contributing to HEV infections. *Med Microbiol Immunol* 2017; **206**: 367-378 [PMID: 28776194 DOI: 10.1007/s00430-017-0515-0]
- 49 **Schielke A**, Ibrahim V, Czogiel I, Faber M, Schrader C, Dremsek P, Ulrich RG, John R. Hepatitis E virus antibody prevalence in hunters from a district in Central Germany, 2013: a cross-sectional study providing evidence for the benefit of protective gloves during disembowelling of wild boars. *BMC Infect Dis* 2015; **15**: 440 [PMID: 26493830 DOI: 10.1186/s12879-015-1199-y]
- 50 **Monini M**, Ostanello F, Dominicis A, Tagliapietra V, Vaccari G, Rizzoli A, Trombetta CM, Montomoli E, Di Bartolo I. Seroprevalence of Hepatitis E Virus in Forestry Workers from Trentino-Alto Adige Region (Northern Italy). *Pathogens* 2020; **9** [PMID: 32674277 DOI: 10.3390/pathogens9070568]
- 51 **Hartl J**, Otto B, Madden RG, Webb G, Woolson KL, Kriston L, Vettorazzi E, Lohse AW, Dalton HR, Pischke S. Hepatitis E Seroprevalence in Europe: A Meta-Analysis. *Viruses* 2016; **8** [PMID: 27509518 DOI: 10.3390/v8080211]
- 52 **Wilhelm B**, Waddell L, Greig J, Young I. A systematic review and meta-analysis of predictors of human hepatitis E virus exposure in non-endemic countries. *Zoonoses Public Health* 2020; **67**: 391-406 [PMID: 32196945 DOI: 10.1111/zph.12698]



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