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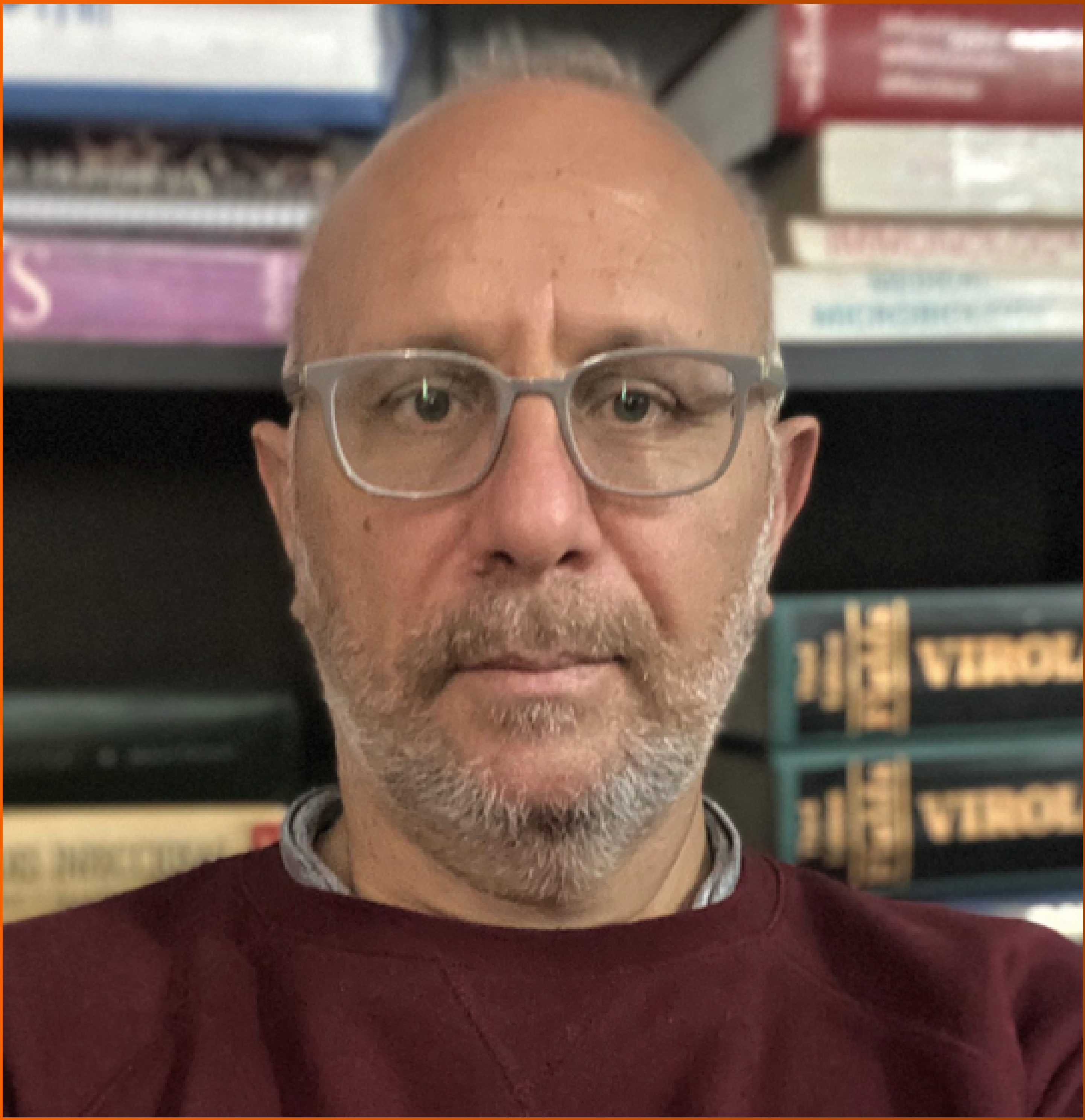

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OPINION REVIEW

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

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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.

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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.

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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 on the 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%), slaughters (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 minimalized 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.

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