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Estimating the burden and modeling mitigation strategies of pork-related hepatitis E virus foodborne transmission in representative European countries

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ABSTRACT

Hepatitis E virus (HEV) is an emerging zoonotic pathogen posing global health burden, and the concerns in Europe are tremendously growing. Pigs serve as a main reservoir, contributing to pork-related foodborne transmission. In this study, we aim to specifically simulate this foodborne transmission route and to assess potential interventions. We firstly established a dose-response relationship between the risk of transmission to human and the amount of ingested viruses. We further estimated the incidence of HEV infection specifically attributed to pork-related foodborne transmission in four representative European countries. Finally, we demonstrated a proof-of-concept of mitigating HEV transmission by implementing vaccination in human and pig populations. Our modeling approach bears essential implications for better understanding the transmission of pork-related foodborne HEV and for developing mitigation strategies.

Hepatitis E virus (HEV), a positive-sense single-stranded RNA virus, is a leading cause of acute liver inflammation. It has been estimated that approximately 939 million corresponding to 1 in 8 individuals have ever experienced HEV infection worldwide [1]. Among the eight defined genotypes, HEV genotypes 3 and 4 are zoonotic and primarily circulating in developed countries [2]. Genotype 3 HEV has been isolated from various mammals including human, swine, wild boar, cattle, goat, deer and rabbit, but pigs are recognized as the main reservoir contributing to transmission to humans [3]. HEV has been detected in the liver, gastrointestinal tract, blood, meat and different other organs of pigs. Association of HEV infection with consumption of pork-derived food products has been well-established [4,5], and consuming HEV contaminated food acts as an important rout of transmission.

The concerns of health burdens caused by genotype 3 HEV infection in Europe are tremendously growing [6]. In particular, chronic hepatitis E is frequently reported in Europe, especially in immunocompromised organ transplantation patients [7,8]. Pork-related foodborne transmission is expected to largely contribute to the HEV burden, since consumption of pork-derived food products is common in Europe [9]. Given the lack of sufficient real-world data to define the exact risk and contribution of HEV foodborne transmission, this study aimed to estimate the burden of pork-related HEV foodborne transmission in four representative European countries and the effect of potential mitigation strategies by mathematical modeling.

We first attempted to establish the relationship between the risk of HEV infection in human and the amount of acquired HEV through food consumption. By searching published studies, we collected human cases likely to have acquired HEV infection from a food source. HEV genomic RNA copy numbers of the tested food samples in shops or markets where patients habitually visit were also collected. In total, four studies describing 28 HEV RNA-positive human cases [10–13], reported from 2003 to 2014, matched the inclusion criteria. Food products are derived from the meat or organs of animal reservoirs including pigs [10–12] and deer [13]. By building a logistic dose-response regression model (see details in Supplementary Methods), we estimated the dose-response relation between the risk of transmission to human and the total

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amount of acquired HEV from food (Fig. 1). The probability of infection by oral ingestion of one HEV particle is 2.5×10^{-9} (95% CI 6.8×10^{-10}-1.5×10^{-8}). The estimated orally ingested amount of HEV at which the probability of infection equals 50% is 8.1×10^{6} (95% CI 2.4×10^{6}–2.0×10^{7}) viral genomes. This parameter is essential for estimating pork-derived HEV foodborne infection.

Next, to estimate the contribution of pork-derived foodborne infection, we collected data on HEV incidence from four European countries, Germany, UK, France and the Netherlands. Information on the proportion of pork-derived food contamination with HEV in the food chains were also collected. Technically, we combined the logistic dose-response relationship described above (Fig. 1) and a model of foodborne transmission (Supplementary Methods) for the simulation. The foodborne transmission model describes the process from intake of contaminated pork food to final infection without human-to-human spread. Based on the simulation, the estimated incidence of pork-derived foodborne HEV transmission in the four countries ranges from 1/120784 to 1/2724 (Fig. 2 A-D), from 2001 to 2020. The mean incidence of pork-derived foodborne infection nationwide, based on the non-continuous estimations, is 1/4792 (95%CI 1/559749–1/1679) in Germany, 1/2117 (95% CI 1/366851–1103) in France, 1/29644 (95% CI 1/2693012–1/8028) in UK, and 1/8627 (95% CI 1/1478521–1/4407) in the Netherlands. Correspondingly, the mean number of these HEV cases per year is 17,362 in Germany, 31,648 in France, 2226 in UK, and 1982 in the Netherlands, respectively.

Because HEV incidence has been reported monthly for UK and the Netherlands [14,15], and we thus extracted these data to visualize the incidence trend in these two countries by a polynomial linear regression method. The modeled HEV incidence in UK and the Netherlands showed a similar shape, reaching the summit around 2015 and then gradually decreasing (Fig. 2C and D). We further comparatively simulated the incidence in the four countries with the same levels of pork-derived food contamination with HEV (Fig. 2E). The estimated incidence in France is 1/8069 (95% CI 1/2188–1/732551) (10% contamination), 1/2687 (95% CI 1/243355–1/734) (30%), and 1/1553 (95% CI 1/140265–1/428) (50%), similar to that in Germany but higher than that in the Netherlands and UK.

Our simulation results collectively suggest a substantial burden of pork-related foodborne HEV transmission in Europe. A subsequent question is whether such risk can be prevented through interventions. Effective prevention of HEV transmission likely requires joint efforts from multi-stakeholders. Here, we investigated the potential impact of applying vaccination. A recombinant vaccine, HEV 239, has been licensed in China, which is well-tolerated and effective in the prevention of hepatitis E in the general population [16]. Taking Germany as an example (Supplementary Methods), assuming different vaccination coverage rates (from 10% to 90%) implemented in the general human population, the burden of pork-derived HEV foodborne transmission would be reduced coverage-dependently (Fig. 3A). If targeting at a subpopulation with high frequency of pork-related food consumption, the burden would be reduced by 5.3% (with 10% coverage), 10.0% (20%), 14.9% (30%), 24.3% (50%), 33.6% (70%), and 43.1% (90%), respectively (Fig. 3B).

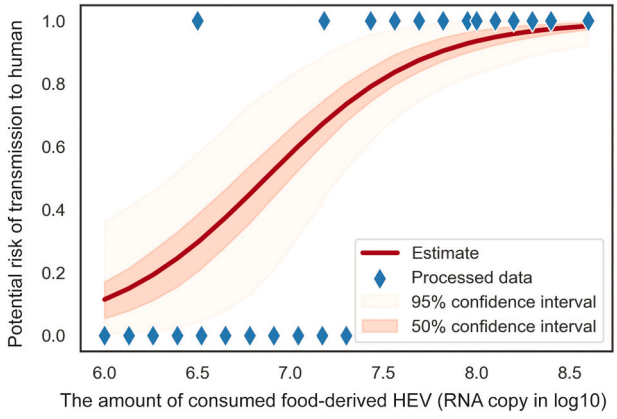

Fig. 1. Logistic dose-dependent relationship between risk of transmission to human and the amount ingested HEV. HEV genomic RNA copy number is indicated by blue diamond. Model fitting is indicated by the curve, and confidence interval by the shade. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Surveillance and interventions throughout the pork production chain are essential for preventing HEV foodborne transmission. A previous study of Switzerland shows that active interventions in food chains is likely to prevent most human cases [17]. However, the current food production and supply chains are diverse, and it has become increasingly difficult to trace the origin of the contaminated products [18]. We believe vaccinating pigs is an alternative option to mitigate the HEV burden in human population, although no approved vaccine is available for preventing HEV infection in pigs. The most important effects of vaccinating pigs are expected to reduce the susceptibility of uninfected animals and the contagiousness of animals once they get infected [19]. Here, we estimated the impact of applying vaccine in pigs on the risk of HEV transmission to humans with the model of Germany (Supplementary Methods). We assumed that the vaccination targets piglets of 10 weeks and is completed in two weeks. We chose this delayed approach of vaccination considering that early vaccination (e.g. for pig of 4 weeks) is likely to be interfered by maternal antibody that produces a strong immunity in newborn piglets.

Because HEV vaccine for pigs is not available currently, we theoretically assumed two vaccination strategies targeting at reduction of the susceptibility of uninfected animals (Fig. 4A) and reduction of the contagiousness of infectious animals (Fig. 4B), respectively. We firstly modeled how viruses circulate in a susceptible pig herd. Based on relationship between human risk and levels of virus ingested (Fig. 1), we then quantitatively estimated the risk of HEV transmission to human when contaminated pork was consumed. In the first scenario (Fig. 4A), a 78% decrease of susceptibility of uninfected animals would result in a 13.7% (95%CI 3.7%–45.9%) reduction of HEV incidence in pigs at slaughterer age, and a 80% (95%CI 40.9%–99.9%) reduction of human cases. In the second scenario (Fig. 4B), a 14% reduction of the contagiousness of infectious animals would lead to a 36% (95%CI 14.5%–68.6%) reduction of HEV incidence in animals at slaughter age, and a 80% (95%CI 72.2%–89.8%) decrease of human cases.

Mapping transmission across the human-animal interface is one of the most important challenges in the control of cross-species infectious diseases in one health. By retrieving published data and examining the drivers of HEV foodborne transmission, we have successfully built a relationship between human risk and the amount of ingested viruses. We observed a dose-dependent effect, meaning that the probability of acquiring infection associates with the quantity of active viral particles ingested orally in a meal. However, due to the complexity of HEV transmission, we did not investigate the role of other transmission routes, such as waterborne, direct contacting with infected animals or blood transfusion. This would require to build additional mathematical models, but the model established in this study could serve as an excellent starting point. Furthermore, we did not consider the differential susceptibility of different human populations, due to the lack of sufficient data in this respect. The collected data on human cases suggest that susceptibility to HEV infection by consuming pork-derived food appears to be independent of age, but is higher in immunocompromised patients even when the viral titer in contaminated pork product is very lower [12].

Although HEV foodborne transmission does not develop a human-to-human spread, the risk of constant dietary exposure in a given population shall not be underestimated. The transmission rate is conditional corresponding to the levels of contaminated food and consumption style. In this study, we only selectively estimated the burden of pork-derived

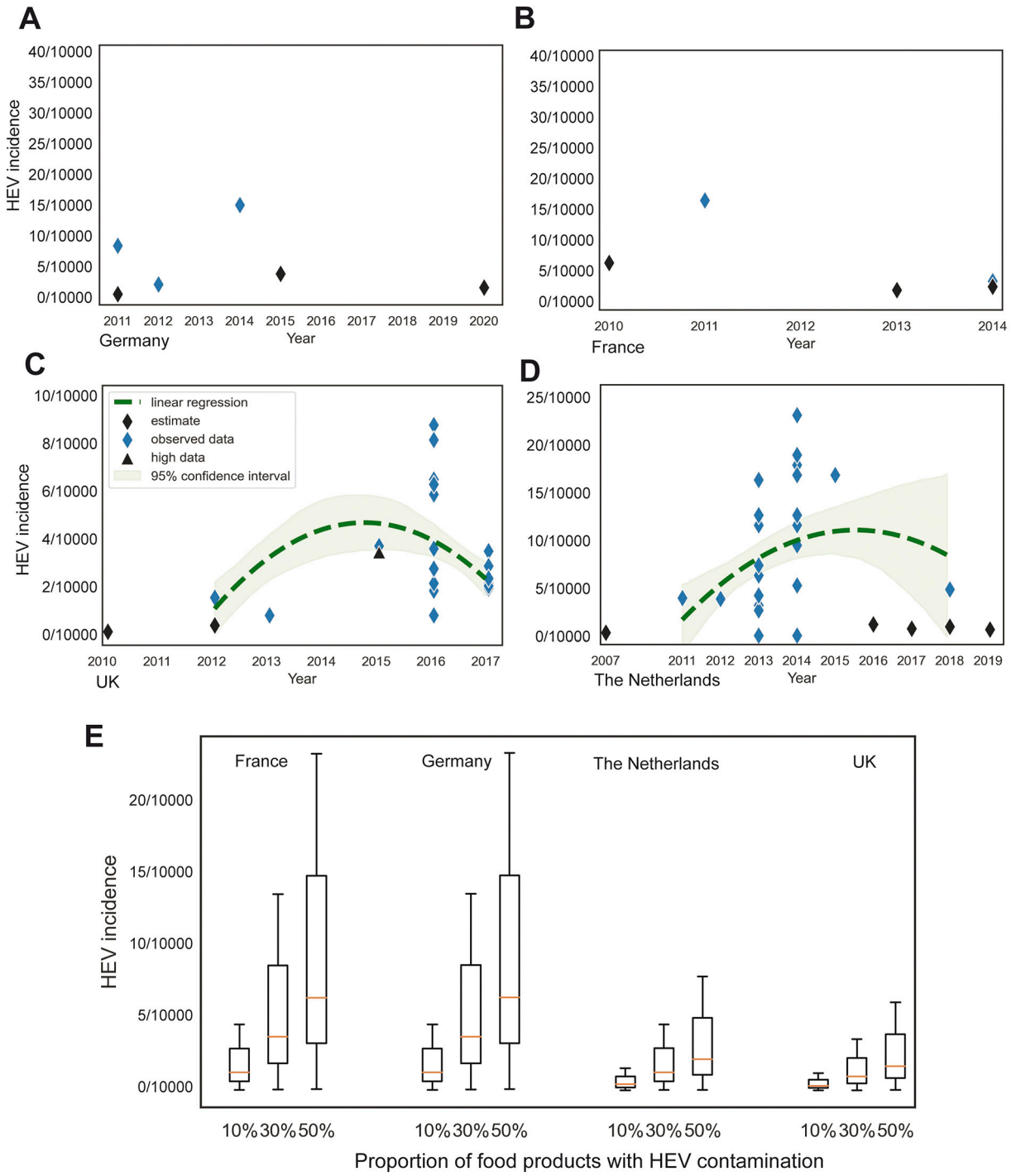

Fig. 2. Estimated HEV incidence of pork-related foodborne infection in four European countries. Estimated incidence (black triangle) in Germany (A), France (B), UK (C), and the Netherlands (D) based on the yearly available data of food contamination with HEV. The reported overall incidence of in each country is indicated by blue diamond. Trends of incidence in UK and the Netherlands were predicted (green curve) by linear regression incorporating monthly HEV incidence data of specific years. (E). Estimated incidence assuming fixed rates (10%, 30% and 50%) of pork-derived food contamination with HEV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

foodborne HEV transmission in four European countries, because of the scarcity of available real-world data required by our mathematical models. But our approach would be applicable for any other countries, if the relevant data become available. Importantly, the estimations by our model appear robust. For example, our estimated mean number of cases of pork-derived foodborne infection in Germany based on estimated incidences in the year of 2011, 2015, and 2020 is 17,945. This is close to the previous estimation (1500 cases) in Switzerland [20], considering the size of its population is around one tenth of Germany.

Given the substantial burden of pork-derived foodborne HEV transmission as estimated, it is essential to develop effective prevention strategies. We hypothetically simulated the applications of vaccine in both human and pig populations, and showed the effectiveness of both approaches. Nevertheless, a major challenge of applying HEV vaccine in general population is the acceptance, although one vaccine has already been licensed in China. Interestingly, we have demonstrated a proof-of-

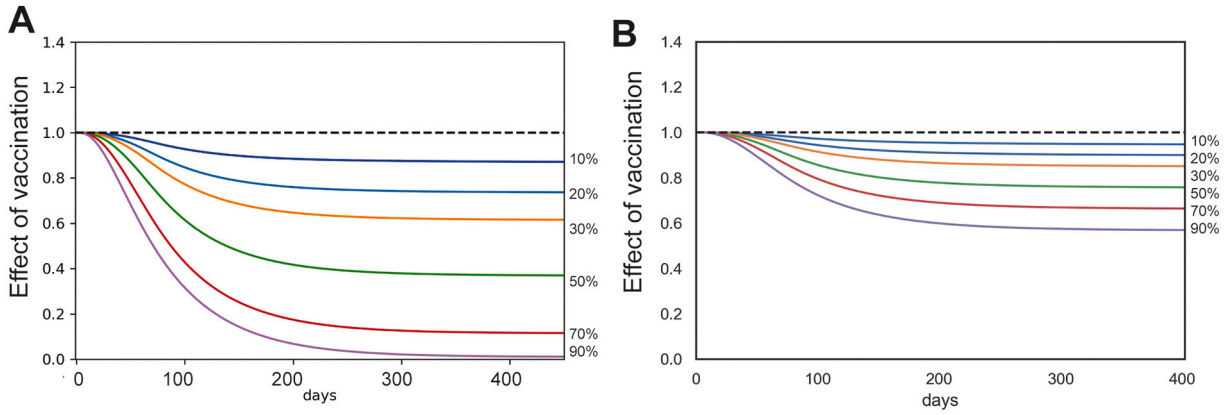

Fig. 3. The impact of vaccinating human population on pork-related foodborne HEV transmission. The licensed HEV vaccine 293 was assumed to be applied in Germany. A three-dose vaccination would be completed in six months, and the corresponding efficacy after one dose (0 month), two doses (one month) and three doses (six months) is 95·5% (95% CI 66·3–99·4%), 100% (95% CI 9.1–100.0%), and 100% (95% CI 72·1–100·0%), respectively. The coverage rate of vaccination assumingly ranges from 10% to 90%. The effects estimated in general population (A) and a subpopulation with high frequency of pork food consumption (B).

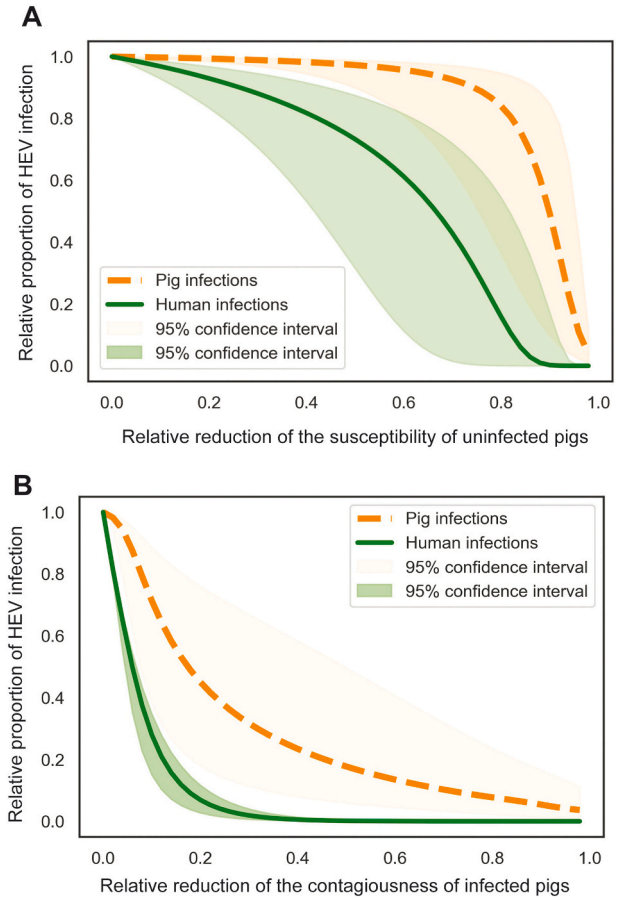

Fig. 4. The impact of vaccinating pigs on pork-related foodborne HEV transmission. (A). The effects of reducing the susceptibility of uninfected animals by vaccination on HEV infections in both pig and human populations were simulated. (B). The effects of reducing the contagiousness of infected animals by vaccination on HEV infections in both pig and human populations.

concept of applying vaccine in high risk population with high frequency of consuming pork products (Fig. 3B). This concept is in line with a large Phase IV clinical trial evaluating the effectiveness in protection of pregnant women by HEV vaccine in Bangladesh (ClinicalTrials.gov Identifier: NCT02759991).

Our results simulating vaccination in pigs quantitatively illustrated the reduction of HEV prevalence in both pig and human populations. However, HEV infection does not affect pig health or the economic performance of swine herds. Thus, it would be a challenge to motivate the development of an HEV vaccine for pugs and the subsequent applications by farmers. Therefore, future studies are required to in-depth evaluate the cost-benefit of vaccinating pigs by incorporating the public health consequences on human population.

In summary, this study has established the relation between the risk of transmission to human and the amount of ingested HEV. We estimated the burden of foodborne HEV infection in four European countries, and demonstrated proof-of-concept of mitigating transmission by implementing vaccination in human and pig populations. Our mathematical modeling approach bears essential implications for better understanding the public health burden and developing mitigation strategies for foodborne HEV as well as many other pathogens.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2021.100350.

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