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Quantitative risk assessment of hepatitis E virus: Modelling the occurrence of viraemic pigs and the presence of the virus in organs of food safety interest

Matteo Crotta[a,*], Antonio Lavazza[b], Ana Mateus[a], Javier Guitian[a]

[a] Veterinary Epidemiology, Economics and Public Health Group, The Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield AL9 7TA, UK
[b] Istituto Zooprofilattico Sperimentale della Lombardia e dell' Emilia, Brescia, Italy

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ABSTRACT

Hepatitis E virus (HEV) is a zoonotic pathogen with consumption of pork and derived products identified in different countries as a risk factor for human exposure to HEV. Great efforts have been made to understand the dynamics of virus transmission within domestic swine populations through modelling. However, from a food safety prospective, it is critical to integrate the parameters involved in the transmission dynamics with those governing the actual presence of HEV in the bloodstream, the liver, gallbladder or faeces. To date, several aspects related to the pathogenesis of the disease are still unknown or characterized by significant levels of uncertainty, making this conjunction challenging. We used published serological data obtained from pigs in a farrow-to-finish farm to implement an Immune-Susceptible-Infected-Recovered (MSIR) model reproducing the on-farm dynamics that lead to the occurrence of viraemic pigs at slaughter. Expert opinion on the length of time infectious HEV can be detected in liver, gallbladder/bile and faeces after recovery from viraemic status were used to inform a stochastic model aimed at estimating the expected proportion of viraemic pigs, pigs with infectious HEV in liver, gallbladder/bile and faeces entering the slaughterhouse. To simulate the potential effect of on-farm mitigation strategies, we estimated the changes in outcomes of interest as a function of variations in the baseline transmission parameters. The model predicted a proportion of viraemic pigs entering the slaughterhouse of 13.8% while the proportions of, and ranged from 13.8% to 94.4%, 13.8% to 94.7% and from 25.3% to 30.8% respectively, due to the uncertainty surrounding the experts' opinions. Variations in MSIR model's parameters alert of the need to carefully consider in the application of mitigation strategies aimed at delaying the decay of maternal immunity or the peak of the within herd transmission. When the rate of decay of maternal immunity and the transmission rate were decreased between 80% and 5% and 40% and 5% from the baseline values respectively, adverse effects on were observed. The model highlights the relevance of specific aspects in the pathogenesis of the disease from a food safety prospective and it was developed to be easily reproducible and updatable as soon as accurate data becomes available. As presented, the model can be directly connected to existing or future pig-related models to estimate the significance of the identified parameters on the risk of human exposure to HEV through consumption of pork products.

1. Introduction

The European Food Safety Authority (EFSA) recognises hepatitis E as an emerging public health concern in Europe with a complex epidemiology that includes foodborne transmission (EFSA, 2011).Hepatitis E virus (HEV) is a non-enveloped positive-stranded RNA virus; four different genotypes, each including several subtypes, have been identified so far and linked to specific geographical distributions and host ranges (Lu et al., 2006). Genotypes G1 and G2 have been isolated only in humans and are associated with epidemics in Asia, Africa and Central America (Aggarwal and Naik, 2009) whereas G3 and G4 are zoonotic and circulate in humans and several animals, particularly pigs and other mammalian species (Aggarwal and Naik, 2009; Meng, 2011; Tei et al., 2003; Li et al., 2005). Hepatitis E is usually a mild, self-limiting infection but some cases may develop into a fulminant form with reported mortality rates ranging from 1 to 4% and up to 25% in pregnant woman (Purcell and Emerson, 2008).

A high seroprevalence of zoonotic HEV is reported in pig populations of industrialized countries (Berto et al., 2012a; Caruso et al., 2016; Crossan et al., 2015; Rose et al., 2011; Breum et al., 2010) and HEV

* Corresponding author.
E-mail address: mcrotta4@rvc.ac.uk (M. Crotta).

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RNA has been isolated from processed pork products, especially those containing liver (Berto et al., 2012b,2013; Pavio et al., 2014). A recent case-control study associated the consumption of processed pork products with indigenous HEV infection (Said et al., 2014) in England and Wales and several studies indicated meat products as a source of infection in humans (Colson et al., 2010; Takahashi et al., 2003,2004). This evidence and the ubiquitous nature of the virus in animals -particularly in domestic pigs- raises public health concern for zoonotic infection through direct contact with infected animals or through the consumption of animal meats.

With particular reference to the risk of infection through consumption of meat products, the likely impact of HEV on food safety can be quantified adopting a probabilistic approach and estimating the probability of exposure to the virus through consumption of pork products. Recently, two quantitative risk assessment (QRA) have been published, both aimed at estimating the probability of human exposure to HEV through consumption of pork liver and liver sausages in Switzerland (Sarno et al., 2016; Müller et al., 2017). These models considered the food products rather than individual pigs as the starting point, therefore, the farm level dynamics describing the infectious status of the animals entering the slaughterhouse and the events occurring at processing stage were not explored.

Understanding the role of the dynamics leading to viraemic pigs at slaughter is critical because the presence of HEV in bloodstream is considered as the plausible vehicle for the zoonotic transmission of the virus in humans (Bouwknegt et al., 2009). Moreover, in prospective of future implementation of comprehensive 'farm-to-fork' QRA, it is important to identify the key biological parameters governing the presence of HEV not only in pigs' meat but also in the key offal of major interest as food products (i.e. liver) or as potential source of cross-contamination at slaughter (i.e. faeces, intestine or bile).

In recent years, several studies explored and implemented mathematical models to estimate the transmission parameters of HEV within different domestic swine populations in different countries (Berto et al., 2012a; Andraud et al., 2013; Backer et al., 2012; Satou and Nishiura, 2007). These studies were based on field data and represent a valuable contribution for the understanding of HEV in-field transmission dynamics and the role of factors influencing the probability of infection (e.g. environmental contamination, maternal immunity). However, these models were parameterized using longitudinal data obtained from faecal or serological samples but the actual presence of the virus in the bloodstream and in key organs of food safety interest were not considered. Furthermore, pathogenesis of hepatitis E is still poorly understood (Liu, 2016; Lhomme et al., 2016; Howard et al., 2008), and predicting the presence of the virus in the internal organs over time is challenging given the scarcity of data from dedicated experimental studies.

Following these considerations, the objectives of this study were to: (i) implement a baseline model reproducing the dynamics of HEV infection in a closed population of naturally infected pigs in a farrow-to-finish farm; (ii) estimate the expected proportion of pigs entering the slaughterhouse with infected livers, gallbladder/bile, and excreting virus in faeces and, (iii) quantify the effect of the uncertainty and data gaps in the parameters underlying those estimations.

2. Material and methods

2.1. Baseline model

Data reported from the longitudinal study conducted by de Deus et al. (2008) were used to estimate the parameters of a compartmental model describing the viraemic status of a closed population of pigs over time.

This study was identified as a part of a literature screening conducted in February 2017 on studies reporting longitudinal data on HEV infection preferably in naturally infected swine herds. The PubMed search engine of the MEDLINE database was used with the query: "(Hepatitis E[Title] AND Longitudinal[Title] AND Pigs[title] OR Hepatitis E[Title] AND Naturally infected[Title] AND Pigs[*title*])" and six items were found. Amongst the candidate studies, de Deus et al. (2008), was considered as the most easily reproducible to implement the baseline model to be used for the purpose of this work.

Table 1
Observed number of pigs with evidence of maternal derived immunity (M) and viraemia (V) in time as reported by de Deus et al. (2008).

Sampling week	Sample size	M ($HEV\ IgG^+$)	I (HEV_V^+)
1	42	23	3
3	43	15	3
6	41	9	1
9	36	5	4
12	30	Na	7
15	26	Na	11
18	21	Na	5
22	16	Na	2

In that study, 45 piglets from 19 sows from the same weekly farrowing batch were randomly selected and serially bled at 1, 3, 6, 9, 12, 15, 18 and 22 weeks of age. Serum samples were tested for specific anti-HEV antibodies by ELISA and the presence of HEV RNA was assessed by means of a semi-nested RT-PCR.

As the authors reported the proportion of piglets showing evidence of maternal immunity, an MSIR model (an extension of the Susceptible-Infectious-Recovered (SIR) model that includes the M class for maternally-derived immunity) was used to describe the transition of the population among the compartments in time. The observed number of immune and viraemic pigs in the original study are reported in Table 1.

The model is described by the set of ordinary differential equations:

$$\frac{dM}{dT} = -\delta M$$

$$\frac{dNv}{dT} = \delta M - \beta NvV$$

$$\frac{dV}{dT} = \beta NvV - \gamma V$$

$$\frac{dR}{dT} = \gamma V$$

Where: δ is the decay rate of the population with maternal immunity (M), β is the transition rate from Not-viraemic (Nv) to viraemic (V) and γ represents the recovery rate from the viraemic status.

The 45 monitored piglets were sampled from a number of sows representing 8% of the total sow population (total number of sows in the farm = 240). The hypergeometric process was used to estimate at each ith sampling time the most likely number of seropositive or infected animals if the same proportion of piglets were sampled from the overall sow population.

The estimated proportions of seropositive and infected pigs at each sampling point were used to estimate the rates of decay of animals with maternal immunity (δ), of infection (β) and of recovery (γ). The system of differential equations was first informed by tentative values for the unknown parameters and the reduced gradient algorithm (GRG) for nonlinear problems was then used to estimate the set of parameters that minimizes the residuals from observed and predicted values. A convergence tolerance of 0.0001 was selected as the acceptable relative change in the absolute value of the target (difference in residuals) indicating the objective function value is changing very slowly as algorithm progresses from point to point.

The parameterized system of differential equations allows to estimate the number of immune, not-viraemic, infected and recovered animals at any point in time, therefore, it was used to obtain the proportions of interest at the day of depopulation (*dpDay*) when animals