Une approche de modélisation multi-pathogènes pour comprendre la propagation et la persistance du virus de l'hépatite E dans un élevage de porcs naisseur-engraisseur

Les études de terrain précédemment présentées ont permis de mettre en évidence l'**impact majeur des co-infections immunomodulatrices** des porcs sur la dynamique de l'infection par le HEV, tant en conditions naturelles qu'expérimentales. Toujours à l'échelle individuelle, plusieurs études ont montré le **rôle de l'immunité maternelle** anti-HEV dans les profils d'infection et la transmission du HEV (Andraud *et al.*, 2014; Krog *et al.*, 2019). Au niveau de l'élevage, la **structure de l'élevage, certaines pratiques d'élevage, d'hygiène et de biosécurité** sont reconnues comme ayant aussi une influence sur la dynamique de l'infection par le HEV (Tableau III) (Di Bartolo *et al.*, 2008; Li *et al.*, 2009a; Jinshan *et al.*, 2010; Hinjoy *et al.*, 2013; Rutjes *et al.*, 2014; Walachowski *et al.*, 2014; Lopez-Lopez *et al.*, 2018).

Ainsi, il est essentiel de **prendre en compte tous ces facteurs explicatifs, de manière globale et intégrée**, pour comprendre les modalités de propagation et de persistance du HEV dans un élevage de porcs. Les **approches de modélisation dynamique** apparaissent alors tout à fait pertinentes pour intégrer la dimension liée à la population de porcs et celle relative aux caractéristiques épidémiologiques de l'infection par le HEV chez le porc. Si plusieurs études se sont attachées à décrire et quantifier la transmission du HEV entre les porcs, notamment en conditions expérimentales (Satou et Nishiura, 2007; Bouwknegt *et al.*, 2009; Bouwknegt *et al.*, 2011; Backer *et al.*, 2012; Andraud *et al.*, 2013), elles ne sont pas aisément transposables sur le terrain aux conditions réelles d'élevage, qui associent une population animale dynamique divisée en groupes d'animaux ayant une structure de contact hétérogène à de nombreux facteurs de variation liés à la conduite et aux pratiques d'élevage. **A ce jour, il n'existe pas de modèle prenant en compte la population dynamique d'un élevage et la circulation virale au sein de cet élevage**, seule assurance d'explorer des hypothèses de déterminisme de la propagation et de la persistance du HEV extrapolables à la situation réelle. Dans ce contexte, l'objectif de

l'étude présentée ci-après a été de développer une **approche de modélisation multi-pathogènes** afin de décrire et d'expliquer les conditions de la diffusion et de la persistance du HEV dans un élevage naisseur-engraisseur dans lesquels les porcs sont susceptibles d'être co-infectés par un pathogène intercurrent. Pour ce faire, un **modèle stochastique individu-centré** a été construit en couplant un **modèle de dynamique de population** avec un **modèle épidémiologique multi-pathogènes** représentant la diffusion conjointe et les interactions du HEV et d'un virus immunomodulateur (virus du SDRP, PCV2). Les paramètres du modèle sont principalement dérivés des études expérimentales préalablement conduites (*cf. supra*). Ce modèle a aussi été utilisé pour évaluer l'influence de la structure et de la conduite de l'élevage sur la dynamique du HEV dans l'élevage, ainsi que l'efficacité de stratégies de maîtrise du HEV.

Les résultats de ce travail de modélisation ont été soumis dans le journal *Epidemics* (Salines *et al.*, 2019d) et publiés dans les *Journées Recherche Porcine* (Annexe 4) (Salines *et al.*, 2019e). A l'issue de ce travail, et à la demande du Groupement Technique Vétérinaire (GTV) de Bretagne, un point d'actualité sur le HEV en général et les travaux de l'Anses en particulier a été publié dans un article associé à une communication orale lors de la Journée Vétérinaire Bretonne et dans le Bulletin des GTV (Annexe 5) (Salines *et al.*, 2019b).

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Tackling hepatitis E virus spread and persistence on farrow-to-finish pig farms: insights from a stochastic individual-based multi-pathogen model

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Abstract

Hepatitis E virus (HEV) is a zoonotic agent of which domestic pigs have been recognised as the main reservoir in industrialised countries. The great variability in HEV infection dynamics described on different pig farms may be related to the influence of other pathogens, and in particular viruses affecting pigs' immune response. The objective of this study was to develop a multi-pathogen modelling approach to understand the conditions under which HEV spreads and persists on a farrow-to-finish pig farm taking into account the fact that pigs may be co-infected with an intercurrent pathogen. A stochastic individual-based model was therefore designed that combines a population dynamics model, which enables us to take different batch rearing systems into account, with a multi-pathogen model representing at the same time the dynamics of both HEV and the intercurrent pathogen. Based on experimental and field data, the epidemiological parameters of the HEV model varied according to the pig's immunomodulating virus status. HEV spread and persistence was found to be very difficult to control on a farm with a 20-batch rearing system. Housing sows in smaller groups and eradicating immunomodulating pathogens would dramatically reduce the prevalence of HEV-positive livers at slaughter, which would drop from 3.3% to 1% and 0.2% respectively (p-value < 0.01). It would also decrease the probability of HEV on-farm persistence from 0.6 to 0 and 0.34 respectively (p-value < 0.01) on farms with a 7 batch rearing system. A number of

farming practices, such as limiting cross-fostering, reducing the size of weaning pens and vaccinating pigs against immunomodulating viruses, were also shown to be pivotal factors for decreasing HEV spread and persistence.

Keywords

Hepatitis E virus, farm-level risk factors, multi-pathogen model

1. Introduction

Hepatitis E virus (HEV) is a non-enveloped single-stranded RNA virus usually leading to asymptomatic infections in humans, but which can also cause acute or chronic hepatitis depending, inter alia, on the patient's immunity context (Emerson and Purcell, 2003; Kamar et al., 2011). If genotypes 1 and 2 are exclusively human viruses mainly prevalent in developing countries, genotypes 3 and 4 are shared by humans and other animal species, and are responsible for sporadic human cases in industrialised countries (Dalton et al., 2008; Purcell and Emerson, 2008). HEV-3 is particularly widespread in the swine population (Salines et al., 2017) and a number of autochthonous cases have been linked to the consumption of raw or undercooked pork products, especially those containing a high proportion of liver (Colson et al., 2012; Guillois et al., 2016; Moal et al., 2012; Motte et al., 2012). Hepatitis E is thus recognised as a foodborne zoonosis with domestic pigs being the major reservoir in developed countries (Pavio et al., 2017). The risk of contaminated products entering the food chain is intrinsically related to HEV dynamics in pig herds. However, the epidemiology of HEV in the pig production sector is far from being fully understood. Indeed, prevalence figures from the literature show a high between- and within-survey variability that is only partially explained to date (Salines et al., 2017). This heterogeneity may indicate a broad spectrum of infection dynamics related to farm-specific risk factors. For instance, farm-level observational studies have evidenced that husbandry practices (in terms of hygiene, biosecurity and rearing conditions) may favour HEV spread on farms (Walachowski et al., 2014). Individual risk factors related to piglets' specific characteristics or inherited from their dam have also been sporadically investigated using experimental trials or field studies. The piglet's sex and sow's parity have thus been shown to influence HEV infection dynamics

(Salines et al., 2019b). Andraud et al. (2014) also evidenced that the partial protection conferred by maternally-derived antibodies (MDAs) delayed HEV infection in growing pigs. More recently, Crotta et al. (2018) developed a baseline Quantitative Risk Assessment (QRA) model reproducing the dynamics of HEV infection in a closed population of naturally-infected pigs in a farrow-to-finish pig farm in order to assess the risk of occurrence of viraemic pigs at slaughter. Their model predicted 13.8% of viraemic pigs at slaughter. They also highlighted that a reduction in the maternal immunity coverage would lead to a decrease in the prevalence of viraemic pigs at slaughter (dropping to 12.5%), whereas a 100% passive immunity cover would greatly increase the risk of viraemic pigs (19.8%).

Several studies have been conducted in order to describe and quantify HEV transmission between pigs. For instance, Satou and Nishiura (2007) built a model that took the distribution of time between infection and seroconversion into account to calculate age at infection. They then estimated the basic reproduction ratio from serological data pertaining to Japanese pig farms ($R0 = 4.02$-5.17). Backer et al. (2012) obtained similar R0 values using a Bayesian framework to analyse the prevalence of HEV shedding according to age group from UK data. They also assessed the effectiveness of control measures, including any potential vaccination of pigs against HEV to come, which they found to be more effective when done later rather than earlier in the pig's life. In 2009, Bouwknegt et al. (2009) estimated a higher R0 of 8.8 [4.4-19] through the analysis of serial one-to-one transmission experiments with intravenous inoculation of the initial seeder pig. The same team then developed a dose-response model to assess the contribution of faeces as a source of HEV transmission among pigs (Bouwknegt et al., 2011). They proved that the faecal-oral route of infection was likely but not sufficient to explain the observed transmission, and concluded that other transmission routes may come into play. The hypothesis of environmental transmission was further confirmed by Andraud et al. (2013). An experimental trial was used to investigate HEV transmission factoring in several routes: direct transmission between pen mates, within-pen environmental transmission, and between-pen environmental transmission representing the transfer of faecal material between adjacent pens. They highlighted that the first two modalities were the major routes for HEV transmission and that HEV persistence and accumulation in the environment due to faecal shedding played a major role in viral transmission among pigs.

Immunomodulating swine pathogens such as porcine reproductive and respiratory syndrome virus (PRRSV) or porcine circovirus type 2 (PCV2) are highly prevalent in the pig production

sector, and are known to affect both innate and adaptive pig immune response (Butler et al., 2014; Darwich and Mateu, 2012). Like the chronic hepatitis E cases described in immunocompromised patients (Kamar et al., 2013), they may thus influence HEV infection dynamics. For instance, HEV/PRRSV co-infection has been found to lead to chronic HEV infection both under experimental and natural conditions (Salines et al., 2015; Salines et al., 2019b). Indeed, the authors revealed that PRRSV co-infection delayed, extended and increased HEV shedding, increased HEV transmission among pigs, and increased the risk of HEV-positive livers at slaughter. Co-infection with PCV2 has also been shown to increase direct HEV transmission and delay the time to HEV seroconversion under experimental conditions (Salines et al., 2019a).

Although all these studies have helped disentangle HEV transmission patterns, they did not combine HEV dynamics and population dynamics — the population being- split into animal groups with an extremely heterogeneous contact structure — with numerous external factors linked to the batch rearing system (BRS) and various farming practices. Until now, there was no model integrating both the dynamic population of a farm and HEV circulation on this same farm. To fill this gap, the authors built a stochastic individual-based model to clarify the conditions under which HEV spreads and persists in a farrow-to-finish herd in which pigs may be co-infected with an intercurrent pathogen. This model couples the population dynamics of a farrow-to-finish pig herd, including breeding and growing pigs, with a multi-pathogen model. The latter combines two epidemiological models: the first one represents the dynamics of an immunomodulating virus (hereafter noted IMV, e.g. PRRSV, PCV2) in a simplified way, whereas the second one takes into account detailed epidemiological features of HEV such as passive immunity, environmental compartments and co-infections with the IMV. This kind of model may be used to monitor a wide range of output variables among which the most relevant were selected to summarise the on-farm spread and persistence of HEV and to evaluate the risk of HEV entering the food chain. The impact of the farm's structure and potential control strategies (based on the modification of husbandry practices and/or prophylactic measures targeting the intercurrent IMV) on viral spread and persistence at herd level was also assessed. The aims of this study were therefore (1) to decipher HEV infection dynamics on farrow-to-finish pig farms; (2) to evidence control strategies that could be implemented on farrow-to-finish pig farms to reduce HEV spread and persistence in the pig production sector. The overall goal of this project was to support risk management decisions regarding HEV.

2. Material and methods

2.1. Population dynamics model

The population model represents the population dynamics on a typical farrow-to-finish pig farm managed according to a specific batch rearing system (BRS) (Cador et al., 2016). As such, three main hierarchical levels were considered: individual, population and facilities (Andraud et al., 2009b).

2.1.1. Individuals

Individuals are characterised by an identity number, their age, sex, physiological stage and their location on the farm (room and pen numbers). The individual physiological stage defines the subpopulation the animal belongs to: growing pigs or breeding sows. Additional state variables describe the sow's reproduction cycle: parity rank, time to next oestrus, time to next parturition, and time to next artificial insemination (AI).

2.1.2. Population

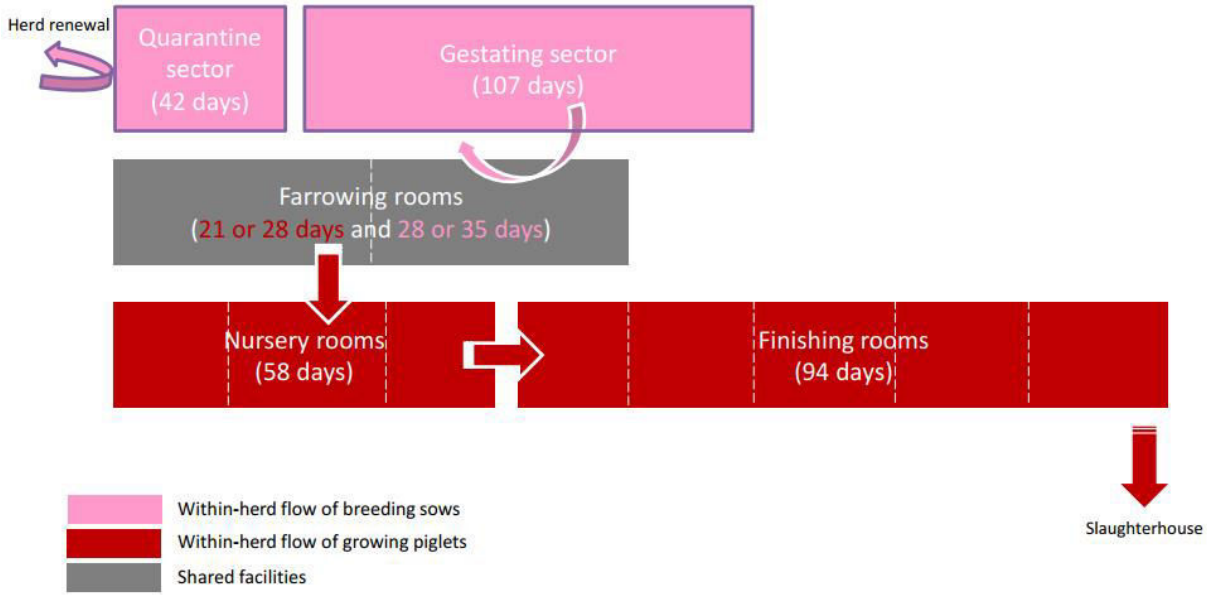
The farm is managed according to a BRS, meaning that the herd population is divided into batches. The reproductive cycle of sows in a given batch are synchronised so that all breeding events (i.e. AI, farrowing and weaning) occur at the same time. Consequently, a given batch of sows gives birth to piglets simultaneously, these contemporary piglets forming a group of growing pigs also constituting a batch.

2.1.3. Facilities

According to their physiological stage, animals evolve through five types of facilities: the quarantine, gestating and farrowing facilities for breeding sows; the farrowing, nursery (i.e. weaning) and finishing facilities for growing pigs (Figure 1). Farrowing, nursery and finishing facilities are divided into several rooms, managed in line with an all-in-all-out principle, i.e. all animals from the same batch leave the facility at the same time and immediately enter an empty room. Each batch is therefore managed independently, with limited relationships

through environmental components. The quarantine sector is composed of a single room used for replacement gilts to become used to the herd's microbiota. The two subpopulations (breeding sows and growing pigs) physically interact only in farrowing rooms.

Figure 1. Facilities modelled in the farrow-to-finish pig farm and duration of stay in each compartment. Adapted from Cador et al., 2016



2.1.4. Processes related to population dynamics

The parameters governing population dynamics are summarised in Table 1. More details on the population dynamics model are given in Supplementary File 1.

The breeding sow cycle: the sow's reproductive cycle lasts 145 days. Gilts are placed in the quarantine room for 42 days, whatever the BRS. After quarantine or weaning, both gilts and sows are moved to the gestation sector, where they are inseminated five days later. They remain in this sector until they reach 107 days of gestation. In the event of AI failure or abortion, the affected sows are transferred to the following batch.

Lactating stage: seven days before farrowing, sows enter the farrowing sector, where they give birth to a batch of piglets. Dams remain with their litter for three or four weeks until weaning, depending on the BRS. Cross-fostering practices are considered after colostrum

intake. At the end of the lactation period, sows are moved back to the service room to begin a new reproductive cycle, while piglets are moved to an empty nursery room.

The growing pig cycle: piglets stay in the nursery sector until 86 days of age, when they are moved to a finishing room. When they weigh over 115 kg or when they are older than 180 days of age, they are sent to the slaughterhouse.

All population events (death, litter size, culling and reproductive failures) are governed by probabilities related to the age of the animals or the time spent in each specific physiological state (Supplementary File 1). Only the movement between rooms and sectors is set deterministically with respect to the batch rearing system being considered (Table 1).

Table 1. Parameters governing the population dynamics model in 4-, 7- and 20-batch rearing systems.

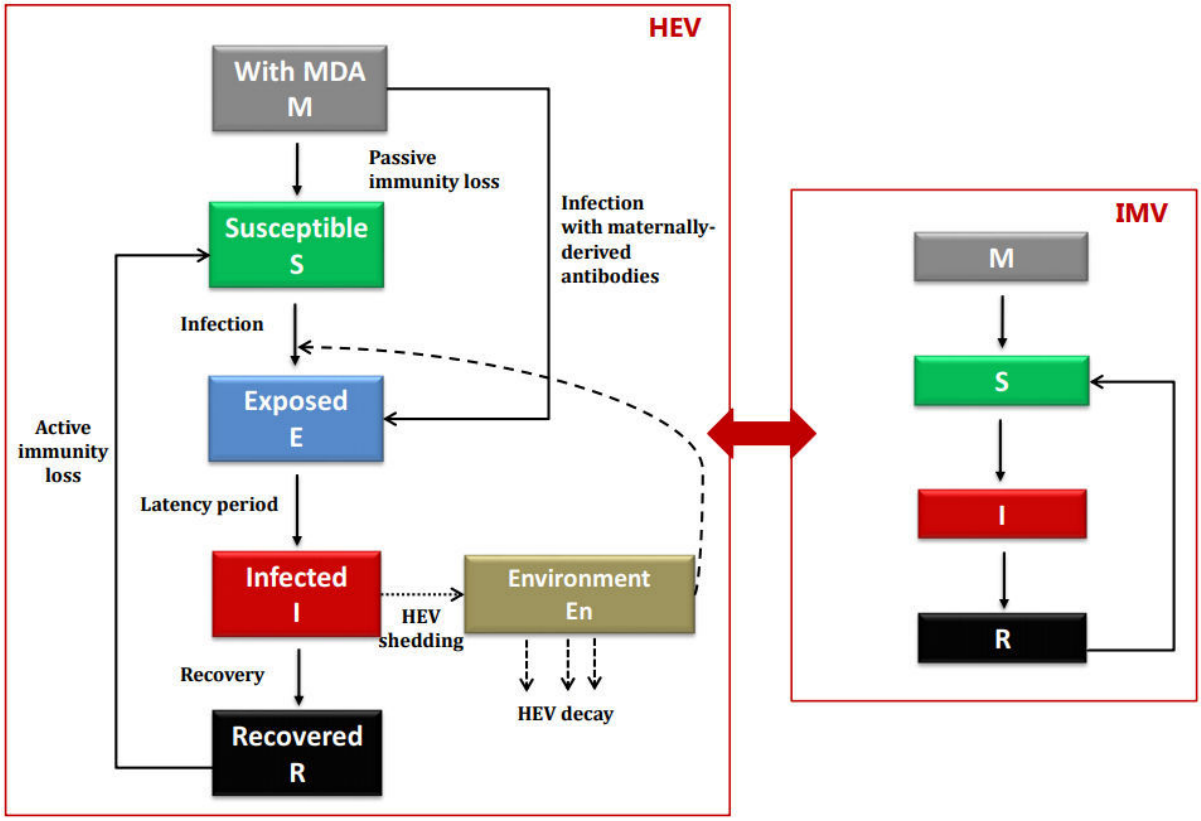
Parameter description (unit)	**Value / Distribution**		
Type of batch rearing system	**4 batches**	**7 batches**	**20 batches**
Duration of a sow's reproductive cycle (days)	135	142	135
- Days in the gestating sector	107		
- Days in the farrowing room	28	35	28
Days in the quarantine sector	42		
Duration of a growing pig's cycle (days)	180		
- Days in the farrowing room	21	28	21
- Days in the nursery room	58		
- Days in the finishing room	94		
Interval between two successive batches (days)	35	21	7
Probability of success for artificial insemination	0.95		
Average number of piglets per litter	N (13 ; 3.6), min=1, max=22		
Total number of sows	200	196	1000
Number of sows per batch	50	28	50
Average number of piglets per batch	650	364	650

2.2. Multi-pathogen epidemiological model

2.2.1. Epidemiological processes

The epidemiological model is a multi-pathogen model combining two epidemiological models representing the interacting dynamics of HEV and an IMV (Figure 2).

Figure 2. HEV and IMV infection states for breeding sows and growing pigs.



HEV model: both the environment and maternally-derived antibodies (MDAs) have been shown to influence HEV infection dynamics. Therefore, an MSEIR – Maternally Immune (M), Susceptible (S), Exposed (E), Infectious (I) and Recovered (R) – model was considered to describe HEV infection dynamics taking those factors into account. Basically, newborn piglets born to immune sows acquire anti-HEV MDAs by colostrum intake (health state M), providing partial and temporary protection from infection. HEV transmission occurs through the faecal-oral route, either by direct contact with an infectious pig or by ingestion of viable virus in the contaminated environment: the pen or its vicinity (Bouwknegt et al., 2008; Bouwknegt et al., 2011). Susceptible (S) or partially protected pigs (M) can be infected, entering the exposed (E) state. After the latency period, the infectious animal (I) sheds HEV in the environment, where the virus can continue to be viable, feeding the environmental viral pool. Thus, the overall virus load in a pen's environment corresponds to the accumulation of

viral particles shed by all infectious individuals, partially compensated by faeces removal through the slatted floor, the natural decay of the virus and the cleaning/disinfecting operations on empty pens which are carried out whenever the room is emptied (Andraud et al., 2013). Assuming a gamma distribution for antibody waning, recovered pigs (R) lose their immunity over time, and eventually revert to full susceptibility (S).

IMV model: to describe the spread of an IMV on a pig farm, a generic MSIRS model accounting for partial protection conferred by MDAs was developed. We assumed the IMV is transmitted by the oral-nasal route, either by direct contact between pen mates or through airborne transmission at room and sector levels.

Several transmission pathways have been considered for HEV and the IMV, given their different biological characteristics (see-below). Given its oro-faecal transmission route, within- and between-adjacent-pen transmission have been taken into account for HEV. For the IMV, both direct and airborne transmission routes have been considered, hence broader transmission possibilities have been included: within-pen, between-adjacent-pen, within-room and within-herd transmission routes.

Transitions between epidemiological statuses occur stochastically. At each time step and for each individual, Monte Carlo procedures are used to assess the occurrence of all stochastic events.

2.2.2. Forces of HEV infection and HEV transmission probability

Each day, the force of HEV infection is calculated taking into account two components (Supplementary File 2):

Within-pen force of infection: one HEV infectious animal can infect its pen mates by direct contact or indirectly through its contaminated faeces, accumulated in the environment:

$$\lambda_{\mathrm{p,r}}^{\mathrm{HEV,wp}}(t) = \frac{\beta_{HEV} \times I_{p,r}^{HEV}(t) + \beta_E^{wp} \times Q_{p,r} \times Q_{ing}}{N_{p,r}(t)}, \textbf{(1)}$$

where $N_{p,r}(t)$ and $I_{p,r}$ correspond to the total number of animals and the number of infected animals in pen p of room r at time t, respectively. β_{HEV} denotes the individual HEV transmission rate. The second term of the right-hand side corresponds to the environmental

contribution to the force of infection. β_E^{wp} is the HEV environmental transmission rate within a pen, corresponding to the average number of animals that can be infected by a single genome equivalent present in the pen environment, i.e. to the inverse of the average number of viral particles in the environment that is needed in the environment to infect one pig (Andraud et al., 2013; Salines et al., 2015). Q_{ing} is the quantity of faeces ingested by a pig per day (Bouwknegt et al., 2011).

$Q_{p,r}$ is the HEV quantity accumulated in pen p, calculated as follows:

$$Q_{p,r}(t) = Q_{p,r}(t-1) \times (1-\varepsilon_1)(1-\varepsilon_2) + \sum_{i=1}^{N_{p,r}(t)} \frac{w_{HEV}^i \times Q_{shed}^i}{\sum Q_{shed}^i}, \textbf{(2)}$$

where w_{HEV}^i is the quantity of HEV particles shed in the environment by an infectious pig per gram of faeces, following a symmetric bell shape function calibrated on experimental data (data not shown) (Andraud et al., 2013; Salines et al., 2015) depending on the number of days post-infection, and Q_{shed}^i is the quantity of faeces it sheds per day. $\varepsilon_1$and ε_2 are respectively the daily proportion of faeces passing through the slatted floor and the daily HEV mortality rate. A third decay rate, ε_3, corresponding to the proportion of faeces eliminated through cleaning operations, is sporadically applied when the room is emptied and the batch is transferred to the next sector.

Between-adjacent-pens force of infection: contaminated faeces shed by pigs in a given pen can be transferred to an adjacent pen and are therefore likely to infect a susceptible animal in that pen. Thus, the between-adjacent-pens force of infection of a pen p is equal to the sum of the weighted force of infection of its two neighbours.

$$\lambda_{p,r}^{HEV,bap} = Q_{ing} \times \beta_E^{bap} \times \left(\frac{Q_{p-1,r}+Q_{p+1,r}}{N_{p,r}}\right), \textbf{(3)}$$

where β_E^{bap} is the HEV indirect environmental transmission rate between pens (Andraud et al., 2013).

Transmission probability: the HEV transmission probability at time t in pen p of room r is thus equal to:

$$\pi_{p,r}^{HEV}(t) = 1 - \exp\left(-\left(\lambda_{\mathrm{p,r}}^{\mathrm{HEV,wp}}(t) \times \Delta t + \lambda_{\mathrm{p,r}}^{\mathrm{HEV,bap}}(t) \times \Delta t\right)\right), \textbf{(4)}$$

where Δt is the time step ($\Delta t = 1$).

2.2.3. Forces of IMV infection and IMV transmission probability

For the IMV, airborne transmission is assumed within and between all rooms, leading to four components for the force of IMV infection (Supplementary File 2):

Within-pen force of infection: the within-pen force of infection is:

$$\lambda_{\mathrm{p,r}}^{\mathrm{IMV,wp}}(t) = \beta_{IMV} \times \frac{I_{p,r}^{IMV}(t)}{N_{p,r}(t)}, \textbf{(5)}$$

where β_{IMV} is the individual IMV transmission rate and $I_{p,r}^{IMV}(t)$ is the number of IMV infected animals in pen p of room r.

Between-adjacent-pens force of infection: keeping the same notations, the between-adjacent-pens force of infection is the sum of the forces of infection of the two neighbouring pens weighted by a coefficient C_{IMV}^{bap}:

$$\lambda_{p,r}^{IMV,bap}(t) = \beta_{IMV} \times C_{IMV}^{bap}\left(\frac{I_{p-1,r}^{IMV}(t)}{N_{p-1,r}(t)} + \frac{I_{p+1,r}^{IMV}(t)}{N_{p+1,r}(t)}\right), \textbf{(6)}$$

Within-room force of infection: a within-room force of infection is also defined to account for airborne transmission at room level. It is assumed to be proportional to the within-room prevalence weighted by coefficient C_{IMV}^{wr} :

$$\lambda_{r}^{IMV,wr}(t) = \beta_{IMV} \times C_{IMV}^{wr}\left(\frac{I_{r}^{IMV}(t)}{N_{r}(t)}\right), \textbf{(7)}$$

where I_r^{IMV} is the number of infected animals in room r.

In farrowing rooms, a specific coefficient $C_{IMV}^{wr,fa} > C_{IMV}^{wr}$ is applied to take into account the numerous operations occurring in this sector (castration, piglet health care, etc.) with farmers entering pens and possibly transferring the virus from one pen to another through contaminated material, etc.

Between-rooms force of infection: based on the same assumptions, a between-rooms transmission possibility is represented to allow for potential viral transfer between the different farm sectors through air flow, material transportation, farmer movements, etc.:

$$\lambda^{IMV,br}(t) = \beta_{IMV} \times C_{IMV}^{br}\frac{I^{IMV}(t)}{N(t)}, \textbf{(8)}$$

where I^{IMV} is the total number infected animals on the farm and $C_{IMV}^{br} < C_{IMV}^{wr}$ is a between-rooms coefficient.

Transmission probability: the IMV transmission probability at time *t* is thus equal to:

$$\pi_{p,r}^{IMV}(t) = 1 - \exp\Big(-\big(\lambda_{\mathrm{p,r}}^{\mathrm{IMV,wp}}(t) \times \Delta t + \lambda_{\mathrm{p,r}}^{\mathrm{IMV,bap}}(t) \times \Delta t + \lambda_{\mathrm{r}}^{\mathrm{IMV,wr}}(t) \times \Delta t + \lambda^{\mathrm{IMV,br}}(t) \times \Delta t\big)\Big), \textbf{(9)}$$

with $\times\, \Delta t = 1$

2.2.4. Epidemiological parameters

The two epidemiological models run simultaneously in the population (Figure 2). The piglet's individual characteristics with respect to HEV dynamics vary depending on its state of health regarding the IMV (latency period, individual transmission rate, quantity of HEV shed).All the parameters involved in the infectious process are fully described in Table 2, along with their definition and the origin of input values. HEV parameters were derived from transmission experiments and other data in the literature. The values of the IMV model parameters were consensually chosen to represent the transmission of a typical airborne virus such as PRRSV or PCV2.

Table 2. Parameters governing the two models of viral infection dynamics.

HEV: hepatitis E virus, IMV: immunomodulating virus, ge: genome equivalent, MDAs: maternally-derived antibodies

Notation	Parameter description (unit)	Value / Distribution		Reference
Parameters of the HEV model				
		HEV-only	**HEV/IMV co-infected**	
D_{HEV}^{M}	Days of maternal immunity	Γ(7.9 ; 5.8)		Andraud et al. (2014)
p_{HEV}^{MDA}	Infection probability with MDAs	0.08		Andraud et al. (2014)
D_{HEV}^{E}	Latency (days)	Γ(5.2 ; 1.3)	Γ(25.7 ; 0.5)	Andraud et al. (2013) Salines et al. (2015)
β_{HEV}	Direct transmission rate (pigs/day)	0.15	0.69	
β_{E}^{wp}	Within-pen environmental transmission rate (g/ge/day)	6.10^{-6}		
β_{E}^{bap}	Between-adjacent-pens environmental transmission rate (g/ge/day)	7.10^{-8}		
D_{HEV}^{I}	Infectious period (days)	9.7	48.6	
w	Quantity of HEV particles shed in faeces depending on the post-infection time, weighted by maximum shed quantity Qmax (ge/g/day)	N (5 ; 1) Qmax = 10^6	N (25 ; 5) Qmax = 10^8	
Q_{shed}	Average amount of faeces shed by a pig	100 for piglets		Murai et al. (2018)

	(g/day)	1000 for finishing pigs 2000 for sows	
Q_{ing}	Average quantity of faeces ingested by a pig (g/day)	25	Bouwknegt et al. (2011)
ε_1	Faeces elimination rate through slatted floor (/day)	0.70	Best guess
ε_2	HEV decay rate in the environment (/day)	0.08	Johne et al. (2016)
ε_3	Faeces removal rate by cleaning	0.98	Best guess
D_{HEV}^{R}	Days of active immunity	Γ(6.3 ; 29.4)	Best guess
Parameters of the IMV model			
D_{IMV}^{M}	Days of maternal immunity	N (45 ; 8)	Consensual parameters representing the transmission of a typical airborne virus, such as PRRSV or PCV2 (Andraud et al., 2009a; Andraud et al., 2008; Rose et al., 2015)
p_{IMV}^{MDA}	Infection probability with MDAs	0.3	
β_{IMV}	Direct transmission rate (pigs/day)	0.13	
D_{IMV}^{R}	Days of active immunity (days)	Γ(6.3 ; 29.4)	
C_{IMV}^{bap}	Transmission coefficient between adjacent pens	0.1	
C_{IMV}^{wr}	Within-room transmission coefficient	0.05	
$C_{IMV}^{wr,fa}$	Within-room transmission coefficient in farrowing room	0.1	
C_{IMV}^{br}	Between-rooms transmission coefficient	0.01	

2.3. Initialisation and simulations

2.3.1. Stochasticity

The model has been developed in a C++ language (Visual Studio IDE). It is a discrete-time model and is implemented on a daily basis during which the individuals are subjected to two types of processes run sequentially. First, the demographic processes are considered with a biologically relevant and logical order: ageing and mortality for all individuals; reproduction processes for breeding animals along with birth of offspring, culling and replacement of sows. If time-relevant, batches are transferred into the sector and room corresponding to their physiological state, the individuals being distributed among the pens. The epidemiological process is then implemented both for the IMV and HEV.

At the beginning of a simulation, the herd is composed only of sows. The initial number of sows is equal to the number of batches multiplied by the number of pens in the farrowing room. Sows are 100 days old, of parity rank 0 and placed in the gestation room. The eleventh

year, when the herd is assumed to be demographically stable, a single IMV infectious gilt is introduced once in the quarantine sector to initiate the IMV infectious process. In the fifteenth year, a single HEV-exposed gilt is then introduced in the quarantine sector to initiate the HEV infectious process. We assume no subsequent introduction of IMV- or HEV-infected animals. The model is initialised in the same way for every simulation.

Two-hundred simulations were run for each tested scenario. Following visual inspection for model stability, this number of simulations was deemed sufficient to obtain stable outcomes in terms of means and variances (Supplementary File 3). The number of animals in each epidemiological state in every pen of every room was recorded daily. Furthermore, this individual-based model allowed the age at which each growing pig is infected to be recorded. Daily snapshots of the population were also recorded as model outputs to monitor the demographic process throughout the simulations.

2.4. Assessment of characteristics related to HEV on-farm spread and persistence and implementation of control strategies

2.4.1. Outcomes

Specific outcomes were selected to analyse on-farm spread and persistence of HEV and to assess the risk of its introduction into the food chain: *(i)* the age at HEV infection of growing pigs; *(ii)* the proportion of batches having HEV-infected animals at slaughter time (170-day-old pigs); *(iii)* the HEV prevalence in slaughter-aged growing pigs (170-day-old pigs); *(iv)* the probability of HEV on-farm persistence five years post-introduction.

2.4.2. Evaluation of different scenarios

The influence of several farm characteristics on these outcomes was evaluated (Table 3):

- The type of BRS (4, 7, or 20 batches, corresponding to 5, 3 and 1 week between-batch intervals respectively);
- The type of housing for gestating sows (large groups (i.e. collective pen), medium groups (i.e. one pen per batch), or small groups (i.e. six sows per pen));

- The farm's sanitary status regarding the IMV (IMV-free or IMV-infected).

The impact of several control measures was then assessed (Table 3). First, different farming practices were tested: *(i)* cross-fostering practices: high cross-fostering rate (i.e. higher than 15%), medium cross-fostering rate (i.e. less than 15%) or no cross-fostering; *(ii)* mingling practices at weaning: nursery pen size (small pens, i.e. less than 50 pigs per pen, or large pens, i.e. more than 50 pigs per pen) and type of mingling (by litter or randomly). An IMV control measure was also tested by vaccinating sows against IMVs at each reproductive cycle two years after the IMV was introduced (sows being thus transferred to status R as regards the IMV).

Table 3. Description of control scenarios tested in the HEV multi-pathogen model.

Scenario 1 can be considered as the reference scenario. Scenario 8 represents the "worst-case scenario" whereas scenario 11 represents the "best-case scenario".

	Type of housing for gestating sows	**Cross-fostering practices**			**Modalities for mingling at weaning**				**Control of the IMV**	
Scenario	Large groups	No	Medium rate (15 %)	High rate (> 15 %)	Small pens (< 50)	Large pens (> 50)	By litter	Randomly	No vaccination	Anti-IMV vaccination of sows
1	■		■		■		■		■	
2	■	■			■		■		■	
3	■			■	■		■		■	
4	■		■		■			■	■	
5	■		■			■	■		■	
6	■		■			■		■	■	
7	■		■		■		■			■
8	■			■		■	■		■	
9	■			■		■	■			■
10	■	■			■			■	■	
11	■	■			■			■		■

2.4.3. Statistical analyses

Cox-proportional hazard models were built to assess the influence of the different scenarios on age at HEV infection. The impact of the different explanatory variables on the proportion of batches having HEV-positive animals at slaughter time was assessed using a logistic

regression. A generalised estimating equation (GEE) logistic regression was used to evaluate the impact of the explanatory variables on HEV prevalence in slaughter-aged pigs, the simulation being included as a repeated statement to account for the non-independence of the proportions of positive pigs for the different batches in a given simulation. The impact of the different measures on HEV persistence probability was evaluated using non-parametric survival analyses (log rank test). These analyses were performed using R and SAS software (Ihaka and Gentleman, 1996; SAS, 2014).

The IMV's prevalence in growing pigs was also computed under the different scenarios, the descriptive results being included as supplementary material.

3. Results

Statistical analyses were performed to assess the relative impact of herd management and control measures on the dynamics of HEV infection. The results from univariate analyses are provided in Supplementary File 4 and in Figures 3 to 8.

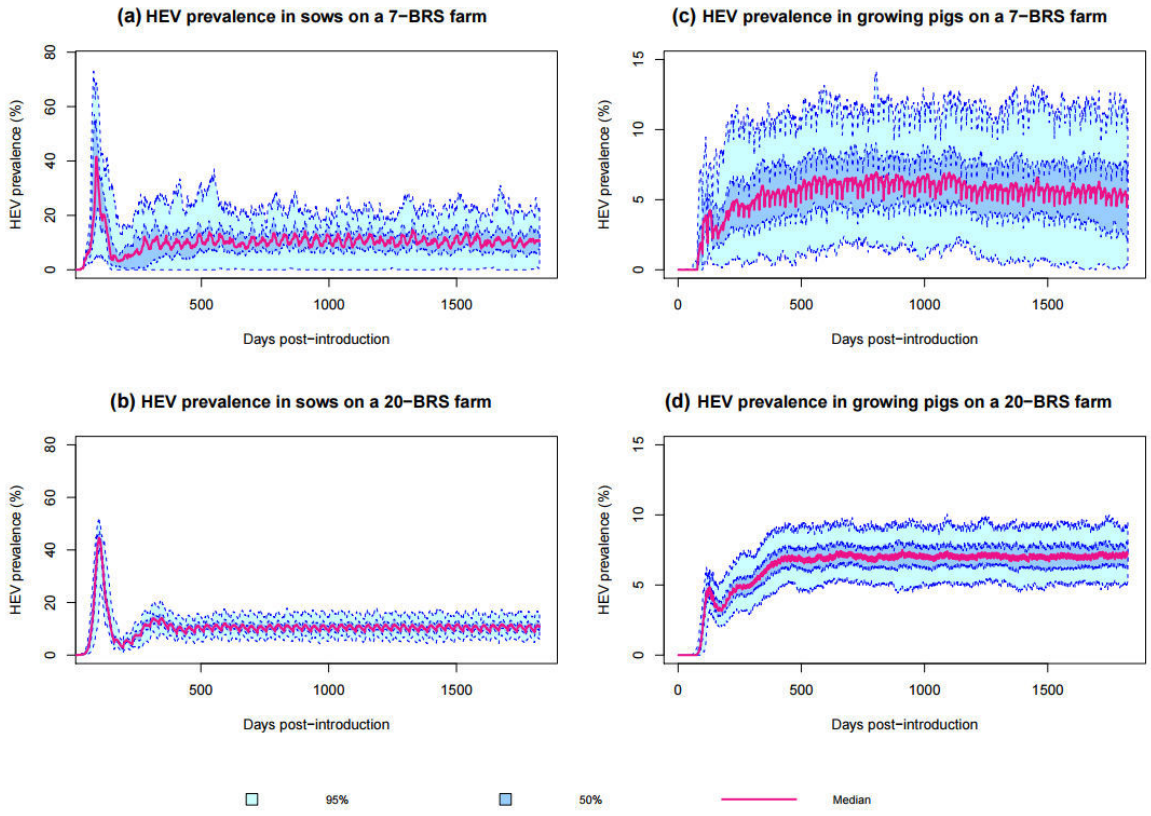
3.1. Description of simulations after HEV introduction on an IMV-positive farm (baseline scenario) and model validation

As shown in Supplementary File 5, the IMV spread enzootically both in the reproductive and growing pig herds, without fading out in any simulation.

After the introduction of an HEV-infected gilt in the quarantine sector, an epidemic peak was first observed in the breeding part of the herd due to massive infections of a large pool of naive animals (Figures 3a and 3b). Infected sows entering the farrowing sector then initiated the infectious process in growing pigs by infecting suckling piglets. The latter spread the infection in the nursery and finishing sectors. In this baseline scenario (scenario 1), pigs contracted HEV on average between 88 and 91 days of age, depending on the BRS. Without any subsequent HEV reintroduction, HEV persisted enzootically in most of the simulations up to five years post-introduction (between 60% and 100%, depending on the BRS, cf. infra), HEV extinction occurring first in the sow herd before fading out in the growing pigs (Supplementary File 6). The average HEV prevalence in slaughter-aged growing pigs ranged

between 2.8 and 4.6% on average, depending on the BRS. The average environmental viral load did not exceed 7 log genome equivalents per gram of faeces and ranged between 2 and 4 log (data not shown).

Figure 3. HEV prevalence in sows and growing pigs (median, 50% and 95%) on 7- and 20-batch rearing system farrow-to-finish pig farms if there is no fade-out (88 and 195 out of 200 simulations for sows on 7- and 20-BRS farms respectively, 119 and 195 out of 200 simulations for growing pigs on 7- and 20-BRS farms respectively).



The baseline scenario (scenario 1) shows that pigs become infected when they are 88 days old on average, which is consistent with the field study of Salines and colleagues who described a mean age at infection of 91 days (Salines et al., 2019b). Moreover, the simulations led to a mean prevalence of infectious pigs at slaughter age ranging between 2.8% and 4.6%, in line with a nationwide French study conducted by Rose et al. (2011) that reported 4% [2-6] of HEV-positive livers at the slaughterhouse. The HEV loads accumulated in the environment were consistent with viral loads found in the liquid manure of pig farms investigated in previous studies. For instance, Guillois et al. (2016) estimated the viral load in the liquid

manure of a chronically HEV-infected pig farm at between 3.10^4 and 5.10^6 copies of HEV RNA/g, depending on the type of room that was sampled.

3.2. Impact of farm characteristics on HEV infection dynamics

3.2.1. Batch rearing system

HEV prevalence appeared globally higher on 20-BRS farms than on 7-BRS ones throughout the simulation period, with lower variability (Figure 3). The HEV infection of growing pigs occurred significantly earlier on a 20-BRS farrow-to-finish pig farm (on average 84 days of age) than on 7-BRS farms (87 days; Supplementary File 4, Table a). The proportion of batches being HEV-positive at slaughter time was significantly associated with the BRS, reaching 80% [79-81] of batches for the most intensive system (20-BRS; Supplementary file 4, Table b). Although lower, the difference obtained between the 4- and 7-BRS was also found significant, with on average 56% [54-58] and 45% [44-46] of positive batches respectively (Supplementary file 4, Table b). Moreover, the HEV prevalence in slaughter-aged growing pigs was higher on a 20-BRS farm than on a 7-BRS farm (on average 4.5% [3.7-5.1] versus 3.3% [3.1-3.5], p-value < 0.01; Supplementary file 4, Table c, Figure 4b). Finally, a quasi-systematic persistence was observed up to five years post-introduction in herds managed according to the 20-BRS (Figure 4a). The behaviour was significantly different for the other two BRS farms, where the virus was found in only 55 and 60% of the herds for the 4- and 7-BRS farms respectively five years post-introduction (p-value < 0.01, Figure 4a). Since infection dynamics on 7- and 20-BRS farms were the most significantly different and 4- and 7-BRS farm patterns were highly similar, the following control measures were evaluated on 7- and 20-BRS farms only.

Figure 4. HEV persistence probability (a) and HEV prevalence in slaughter-aged growing pigs (b) on a farrow-to-finish pig farm depending on the type of batch rearing system (n = 200 simulations).

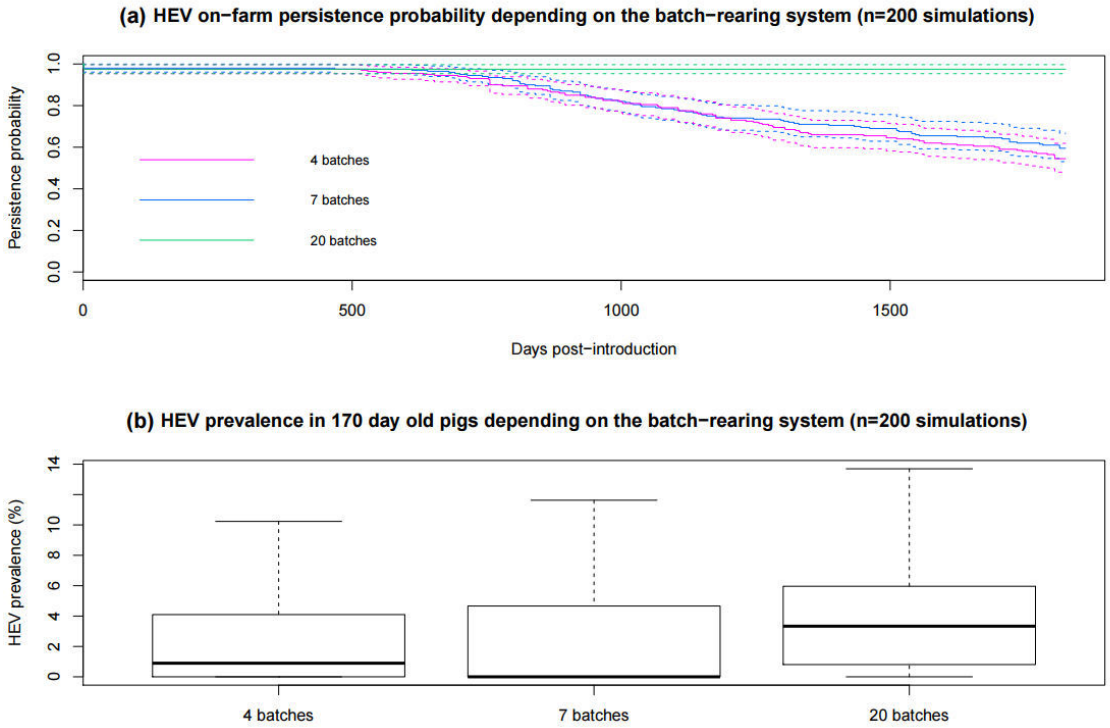


Figure 5. Proportion of batches having HEV-infected pigs at slaughter time on a 7- or 20-batch rearing system farrow-to-finish pig farm depending on farming practices and health management measures (n = 200 simulations).

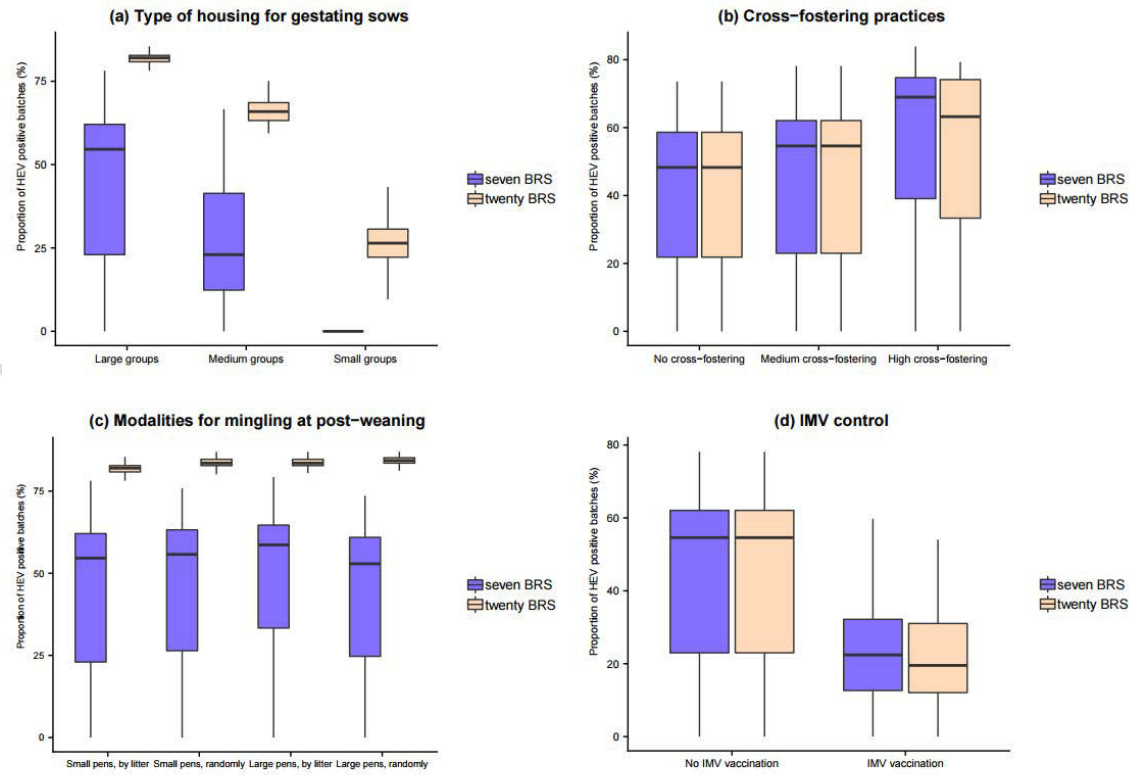


Figure 6. HEV prevalence in slaughter-aged growing pigs on a 7- or 20-batch rearing system farrow-to-finish pig farm depending on farming practices and health management measures (n = 200 simulations).

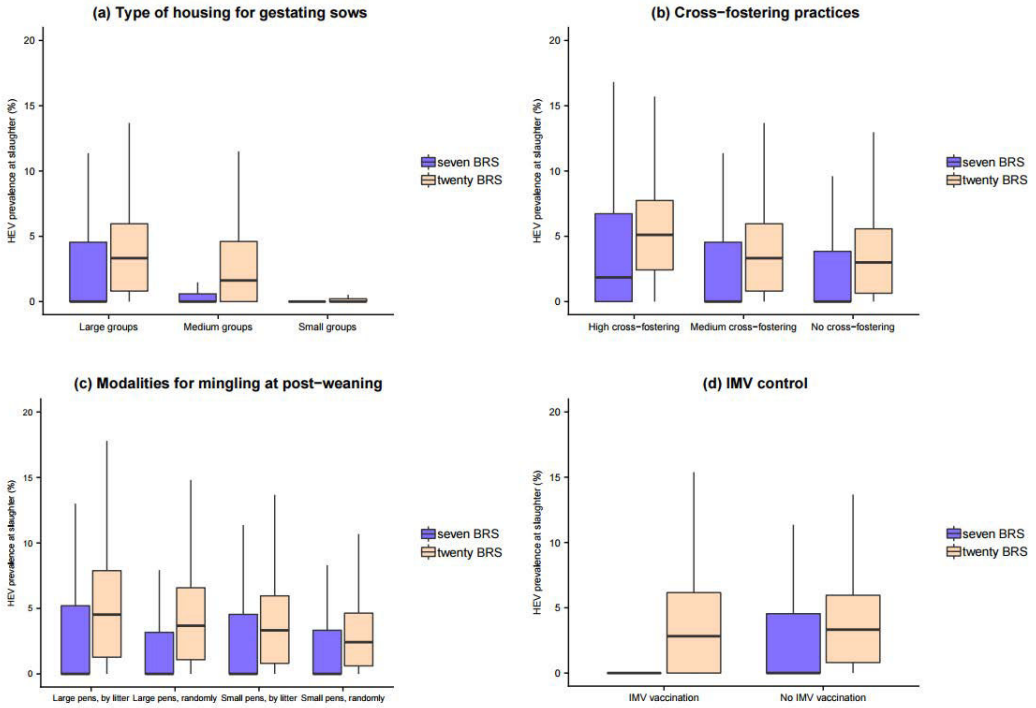


Figure 7. HEV persistence probability on a 7- (a) or 20- (b) batch rearing system farrow-to-finish pig farm depending on the type of housing for gestating sows (n = 200 simulations).

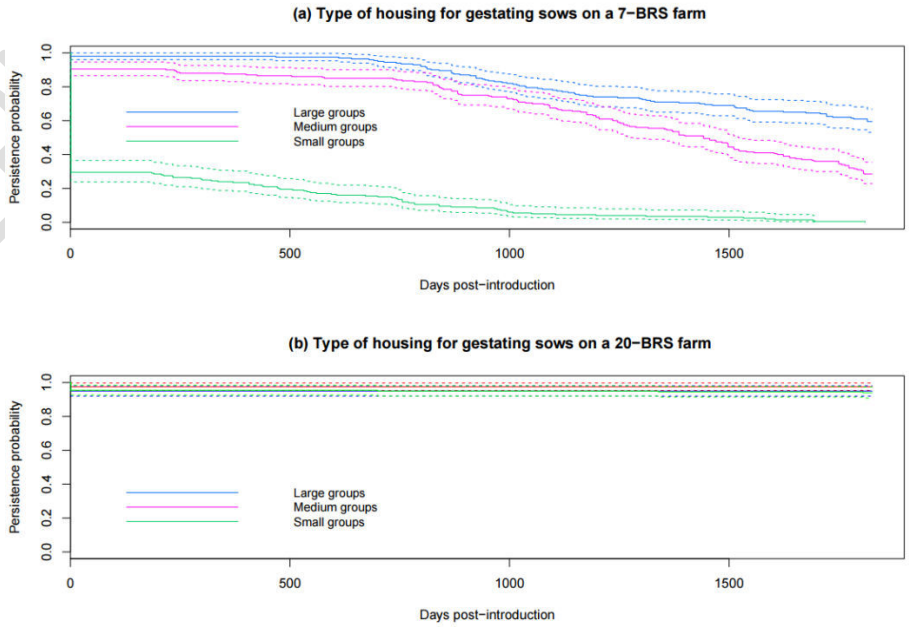
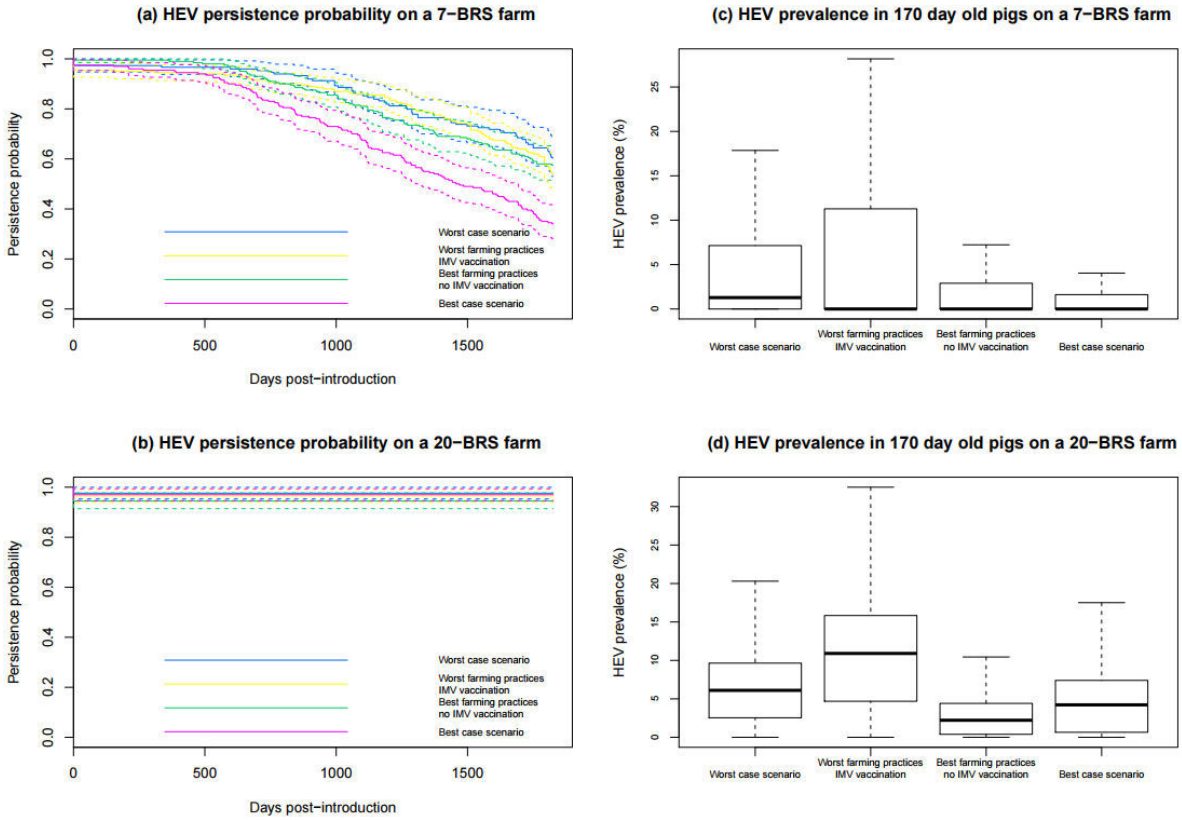


Figure 8. HEV persistence probability and prevalence in slaughter-aged pigs on 7- and 20-batch rearing system farms in combined HEV control scenarios (n = 200 simulations).



3.2.2. Type of housing for gestating sows

Both on a 7- and 20-BRS farm, when sows were housed in medium or small groups, pigs were infected later than when they were housed in large gestation pens (on average 90, 103 and 87 days respectively on a 7-BRS farm; and 87, 102 and 84 respectively on a 20-BRS farm) (Supplementary File 4, Table a). The proportion of batches with HEV-positive livers at slaughter time was significantly lower when sows were housed in medium or small groups rather than large groups, both on a 7- and a 20-BRS farm (Supplementary file 4, Table b, Figure 5a), dropping to 1% of batches when sows were managed in small groups on a 7-BRS farm. However, the results obtained for the 20-BRS farms were more contrasted, with up to 25% of batches found HEV-positive in the presence of small groups of sows. Moreover, sow housing management had a similar impact on HEV prevalence in growing pigs at slaughter, which was found to fall below 1% for both BRS farms when sows were kept in small pens

(0.1% [0.06-0.2] and 1% [0.9-1.1] for 7- and 20-BRS farms respectively; Supplementary file 4, Table c, Figure 6a). Moreover, the size of sow groups in the gestating stage was significantly associated with the persistence probability on 7-BRS farms (p-value < 0.01, Figure 7a). Indeed, disease extinction was systematically observed when sows were kept in small groups, and the probability of persistence dropped to 29% [23-35] when sows were housed in medium groups. Interestingly, these results were not transposable to 20-BRS farms, for which sow housing modalities did not have any significant impact on the probability of HEV persistence (p-value > 0.05, Figure 7b). As HEV did not persist at all on a 7-BRS farm with small gestation pens, the effectiveness of the following control measures was evaluated only on farms housing sows in large groups.

3.2.3. Farms' sanitary status

On a 7-BRS farm, pigs contracted HEV 40 days earlier on average when the herd was IMV-free compared to an IMV-infected farm leading to infections in the nursery stage (55 days of age), whereas the average age of infection in IMV-infected farms corresponded to the fattening stage (95 days of age; Supplementary file 4, Table a). The absence of IMV led to a decrease in positive batches (11% [10-12]) and positive pigs (0.2% [0.1-0.2]) at slaughter age (Tables 5 and 6). Furthermore, the persistence probability dropped to 0.34 [0.28-0.41] after five years post-introduction in an IMV-free herd (p-value < 0.01).

A more contrasted effect was observed on a 20-BRS IMV-free farm in which infections were slightly — but significantly — postponed (90 days of age) compared to the infection process in an IMV-infected farm (Supplementary file 4, Table a). The proportion of batches having HEV-infected animals at slaughter time was only decreased by 2.5% on average [1.9-3.1] (Supplementary file 4, Table b) and no significant impact of the farm's IMV status on HEV prevalence in growing pigs at slaughter age was observed on a 20-BRS farm (Supplementary file 4, Table c). HEV persistence was not affected by the farm's IMV status when managed according to the 20-BRS (p-value > 0.05).

3.3. Assessment of the effectiveness of control measures

3.3.1. Impact of farming practices

Cross-fostering practices: all outputs were found to be significantly influenced by cross-fostering practices (Tables 4, 5, 6). More precisely, the higher the cross-fostering rate, the sooner the infection was contracted in growing pigs. Intensive cross-fostering led to infections on average one week earlier than the two alternative strategies (on average 89 days of age; Supplementary file 4, Table a).On a 7-BRS farm, the proportion of HEV-positive batches at slaughter time was significantly lower when there was no adoption (41% [40-43.5]) compared to a medium cross-fostering rate, whereas high cross-fostering rate increased the probability of HEV-positive batches at slaughter (59% [56-59.5]; Supplementary file 4, Table b, Figure 5b). Similar results were obtained concerning HEV prevalence at slaughter age, with proportions varying with the level of cross-fostering from 2.6% to 3.9% on a 7-BRS farm and from 3.6 to 5% on a 20-BRS farm (Supplementary file 4, Table c, Figure 6b). On a 7-BRS farm, cross-fostering practices were associated with the HEV persistence probability (p-value < 0.01), with an average persistence probability equal to 0.55 [0.49-0.62] when no adoption was allowed, compared to 0.61 [0.67-0.80] in the event of a high cross-fostering rate (Supplementary File 7). Cross-fostering practices did not affect HEV persistence probability on a 20-BRS farm (p-value > 0.05, Supplementary File 7).

Modalities for mingling in the nursery: HEV infection occurred on average one week later when pigs were housed in large rather than small nursery pens (Supplementary file 4, Table a). Keeping piglets with their litter mates was also found to postpone average age at infection by 4 days. Infections occurred earlier when pigs were randomly mixed compared to by-litter mingling (on a 7-BRS farm: on average 82 versus 87 days in small pens, 87 versus 92 days in large pens; on a 20-BRS farm: 78 versus 84 days in small pens, 84 versus 90 days in large pens; Supplementary file 4, Table a). The proportion of positive batches at slaughter was increased by 5% when pigs were housed in large rather than small nursery pens, and increasing to up to 50% of batches. A random mixing of pigs was found to reduce the proportion of positive batches at slaughter when pigs were housed in large pens on a 7-BRS farm (44% [42.3-45.8]) while the opposite results were obtained in all other cases when random mixing was practised (Supplementary file 4, Table b, Figure 5c). The HEV prevalence in growing pigs at slaughter age was higher when pigs were housed in large weaning pens compared to small pens, rising from 3.2% [3.0-3.5] to 4.0% [3.4-4.7] on a 7-BRS farm (from 4.4% [4.3-4.6] to 4.9% [4.7-5.3] on a 20-BRS farm). Random mixing lowered this proportion compared to by-litter mingling, particularly on a 20-BRS farm with small pens in the weaning facilities (3.5% [3.3-3.7]) (Supplementary file 4, Table c, Figure

6c). Modalities for mingling in the nursery did not affect HEV persistence probability significantly either on a 7-BRS farm or on a 20-BRS farm (p-value > 0.05, Supplementary File 7).

3.3.2. Impact of IMV control through vaccination of sows

Anti-IMV sow vaccination decreased the IMV spread in growing pigs both on a 7- and a 20-BRS farm (data not shown).

Vaccinating sows against IMV postponed HEV infection in growing pigs by about one week, with an average age at infection of 93 days irrespective of the BRS (Supplementary File 4, Table a). The proportion of positive batches at slaughter was significantly reduced for both BRS farms, with a higher impact on 7-BRS farms where only 22% [21-24] of batches were found positive (Supplementary file 4, Table b, Figure 5d). This result was also reflected in HEV prevalence among growing pigs with 2% ([1.6-2.4]) of positive animals at slaughter age for the 7-BRS farm, whereas no significant impact was observed in a herd managed according to the 20-BRS (Supplementary file 4, Table c, Figure 6d). Five years after introduction, the probability of HEV persistence was also lower when sows were vaccinated against the IMV on 7-BRS farms only (0.34 [0.28-0.41] versus 0.60 [0.53-0.67], p-value < 0.01, Supplementary File 7).

3.3.3. Results from combined scenarios

Four scenarios, hereinafter denoted scenarios 13 to 16, and a combination of improving management practices and vaccination campaigns against the IMV, were considered. For statistical comparison, the worst scenario in terms of management practices (i.e. presenting high levels of mingling at all production stages; scenario 13) was taken as a reference. In this context, the vaccination of sows against the IMV without improving farming practices (scenario 14) led to later HEV infections in growing pigs, which occurred on average at 109 days of age versus 90 days on a 7-BRS farm (103 versus 85 days of age on a 20-BRS farm; Supplementary file 4, Table a). This strategy also led to a significant decrease in the proportion of positive batches at slaughter time; from 53.6% to 46.1% on 7-BRS farms (from 83.6 to 81.6% on 20-BRS farms). However, IMV vaccination of sows was related to an increased HEV prevalence in slaughter-aged growing pigs when farming practices were not improved. Indeed, a 2% increase in the proportion of positive pigs at slaughter age was

observed, reaching 7% [5.8-8.4] on 7-BRS farms. This tendency was even clearer on 20-BRS farms, reaching an average 12.2% [11.4-13.0] of slaughter-aged piglets (Tables 5 and 6, Figure 8d). Combining all the best farming practices, even without vaccinating sows against the IMV (scenario 15), led to an earlier age at HEV infection of growing pigs compared to the worst-case scenario (82 days on a 7-BRS farm; 78.2 days on a 20-BRS; Supplementary file 4, Table a). In this case, the proportion of HEV-positive batches at slaughter decreased both on 7- and 20-BRS farms (on average 43.5 [41.6-45.5] and 78.2% [77.2-79.2] respectively). HEV prevalence among slaughter-aged growing pigs also fell to 2.3% [1.8-2.8] on 7-BRS farms (3.3% [3.1-3.5] on 20-BRS farms; Tables 5 and 6, Figures 8c and 10d). In the best-case scenario (scenario 16), which combined best farming practices and IMV vaccination, growing pigs contracted HEV later than in the worst-case (reference) scenario (94.3 days of age on a 7-BRS farm, 87 days of age on a 20-BRS farm; Supplementary file 4, Table a). IMV vaccination did not impact the model outcomes at slaughter age, with a similar proportion of positive batches and positive animals as scenario 15, when the herd was managed according to the 7-BRS. In contrast, vaccination practised in a 20-BRS herd was found counter-effective when optimal farming management was implemented, with a higher proportion of positive pigs at slaughter age than with scenario 15 (5.4% [5.1; 5.7]; Tables 5 and 6, Figure 8d). On a 7-BRS farm, the HEV persistence probability was reduced in the best-case scenario compared to the worst-case one, dropping from 0.60 [0.53-0.69] to 0.34 [0.28-0.41] (p-value < 0.01). No significant impact of the combined scenarios on the HEV persistence probability was observed on a 20-BRS farm (p-value > 0.05, Figure 8b). In this 16th scenario, IMV prevalence in growing pigs was also much lower than for the worst-case scenario (Supplementary File 8).

4. Discussion

Although understanding HEV infection dynamics in pig populations is clearly pivotal to managing the risk of human exposure to the virus, there are still substantial knowledge gaps on HEV infection at pig farm level (Van der Poel et al., 2018). Mathematical models incorporating the epidemiological characteristics of pathogens appear to be relevant tools for an in-depth understanding of infection dynamics through the identification of influential factors. We therefore developed a model representing within-herd HEV infection dynamics. The model combines population dynamics at a farm level with the on-farm viral spread at an

individual level. Interactions are of primary importance regarding the spread of infectious diseases within a population. In the present case, individuals interact at different levels depending on the process considered. Indeed, the population is made up of two distinguishable sub-populations, sows and growing pigs, which physically interact only in the farrowing sector during lactation. However, even during this period, contacts are restricted to sows and their respective (possibly fostered) newborns. These interactions may allow not only the transfer of maternally-derived antibodies to piglets but also the transmission of infectious agents from sows to their litter. Batch rearing management systems generate batches of animals at specific locations in the herd depending on their physiological status. These groups are in turn distributed among several pens generating multiple sub-populations inside the rooms. Pen mates are in direct contact and share the same environment; neighbouring pens are also in close interaction either through airborne contact (for the IMV) or the environmental route (for HEV). An airborne transmission route was also considered for IMV at room and global herd levels, taking the relative prevalence of infectious individual as a proxy for viral load in the air. Finally, although the batches of animals are managed according to an all-in-all-out strategy, with cleaning and disinfection procedures, the animals may be exposed to any viral particles remaining in the environment when settled in a new room.

The specificity and originality of our model lies in the multi-pathogen modelling framework: the model integrates the epidemiological interactions between HEV and a generic immunomodulating pathogen on an individual scale. These interactions have been proven to dramatically affect HEV dynamics both under experimental and natural conditions (Salines et al., 2019a; Salines et al., 2015; Salines et al., 2019b). Factoring an environmental compartment into the HEV model design is also of particular importance, since the key role of viral environmental accumulation in HEV dynamics has already been demonstrated: indeed, despite frequent cleaning and disinfection procedures in pig herds, the accumulation of viral particles in the pigs' environment can explain HEV persistence on farms (Andraud et al., 2013). Most of the epidemiological parameter values were derived from published data when available. In particular, the model uses different parameters for HEV dynamics depending on the pig's status regarding an IMV; these parameters were obtained from several experimental trials. The IMV parameters were chosen to represent the typical behaviour of an airborne immunomodulating virus; they were not selected to specifically represent the dynamics of PRRSV and/or PCV2 but the chosen R0 was consistent with the ones reported for PRRSV and PCV2 in the literature (5.4 and 5.9, respectively) (Andraud et al., 2009a; Rose et al.,

692 2015). Following animals on an individual and daily basis grants a detailed and subtle
693 understanding of HEV dynamics, especially in the situation of individual co-infections.
694
695 Complementary outputs were selected to assess HEV on-farm spread and persistence both
696 comprehensively and as precisely as possible. Firstly, the age at HEV infection reflects the
697 speed of HEV transmission and the force of HEV infection on the herd. The proportion of
698 HEV-positive batches at slaughter time and HEV prevalence at slaughter age provide direct
699 information on the risk of HEV-positive livers entering the food chain, and are therefore a key
700 indicator of the risk of human exposure to the virus. These two outcomes are also particularly
701 relevant from a risk management point of view: for instance, they can be used to design liver
702 testing programmes at slaughterhouses with an appropriate sampling size both as regards the
703 number of batches and number of livers to be selected. Finally, HEV on-farm persistence
704 probability five years post-introduction expresses the ability of the virus to remain on the farm
705 and thus gives an indication of the risk for public health as well. It also reflects the probability
706 of the infection spreading from one farm to another: the longer the farm hosts the virus, the
707 more likely the virus can be transmitted to another farm. It should be noted that these
708 indicators should be interpreted all together. For instance, a late HEV infection could be
709 considered risky because pigs are more likely to be still hosting the virus at slaughter age, but
710 if it is combined with a more limited viral spread, the risk for public health would end up to
711 be lower. Moreover, the statistical significance highlighted by tests may sometimes be of
712 limited practical importance. Indeed, the outcomes of such models represent a tremendous
713 quantity of data which induces a very high statistical power. Therefore, the effect of the
714 sample size should be considered in order not to give too much importance to insignificant
715 (but statistically significant) results. For instance, even when it is statistically significant, a
716 difference of only a few days in the age at HEV infection may have a limited practical impact,
717 unlike differences in HEV prevalence at slaughter.
718
719 Comparison with field data has shown that all outcomes of the baseline scenario were
720 consistent with field data: age at HEV infection (88 versus 91 days of age), HEV prevalence
721 in slaughter-aged pigs (2.8-4.6% versus 2-6%), HEV persistence on farms (64% 5 years after
722 introduction versus 2 years in 80% of tested farms), HEV loads accumulated in the
723 environment. Indeed, the baseline scenario (scenario 1) shows that pigs become infected when
724 they are 88 days old on average, which is consistent with the field study of Salines and
725 colleagues who described a mean age at infection of 91 days (Salines et al., 2019b). The age

726 at infection is known to be strongly related to the basic reproduction number and the host
727 lifespan ($R_0 \approx \frac{L}{A}$) (Anderson and May, 1991). Owing to this relationship and the numerical
728 results obtained in our study (assuming an average lifespan of 180 days for growing pigs), the
729 basic reproduction number for hepatitis E would vary between 1.6 and 2.3. These values
730 appear relatively low in regard to the estimates of Bouwknegt et al. (2008) or Satou and
731 Nishiura (2007). However, in the context of batch rearing systems, the animals are housed in
732 relatively small groups with limited (but real) contact between groups. Based on these
733 considerations, the estimates provided here could be considered as resulting from several
734 locally clustered transmission processes, as was the case in Backer et al. (2012), who
735 estimated similar reproduction numbers from field data. Furthermore, the protection conferred
736 by maternally-derived antibodies was also considered in the model structure and may be
737 responsible for delaying the infectious process and consequently reducing the reproduction
738 ratio (estimated at population level). The simulations led to a mean prevalence of infectious
739 pigs at slaughter age ranging between 2.8% and 4.6%, in line with a nationwide French study
740 conducted by Rose et al. (2011) that reported 4% [2-6] of HEV-positive livers at the
741 slaughterhouse. It is also consistent with the meta-analysis conducted by Salines et al. (2017)
742 using 31 international studies, which resulted in a figure of 6.1% [1.2-15.4] of pigs being
743 infectious at slaughter age. In around 60% of simulations, our baseline scenario evidenced
744 that HEV could persist five years after HEV introduction without any subsequent viral
745 reintroduction. This is a conservative scenario, as HEV is likely to be reintroduced on farms,
746 especially through herd renewal practices. To the best of our knowledge, no study specifically
747 designed to assess HEV on-farm persistence duration is available in the published literature,
748 but a few cases of natural HEV fade-out have been reported on some farms (ANSES, personal
749 communication). Wang et al. (2019) also reported that an HEV strain can persist on a farm for
750 at least two years in four out of five cases. For all these reasons, one can reasonably consider
751 these results (baseline scenario) as trustful. The predictions of the other scenarios cannot be
752 validated since no field data have been published yet.
753
754 From our results, it appears that farms using a 20-BRS have a particularly high risk of HEV
755 spread and persistence. Indeed, all other things being equal, HEV prevalence at slaughter age
756 was on average 1.3 times higher and HEV persistence five years post-introduction was 1.6
757 times more likely on a 20-BRS farm than on a 7-BRS farm. The large population and short
758 between-batch intervals probably play a major role in the differences observed between the

two BRSs, viral spread being less easy to manage in a large population. Moreover, the higher environmental load linked to the greater number of infected pigs on the farm (data not shown) may also be responsible for a greater HEV on-farm spread. To our knowledge, no data is available yet on HEV dynamics depending on the type of BRS, but this same difference between BRSs has already been observed for other viral pig diseases, e.g. influenza viruses (Cador et al., 2016). The type of housing for gestating sows, another characteristic of farm structures, has been found to play a pivotal role in HEV infection dynamics: housing gestating sows in small groups drastically reduced HEV prevalence at slaughter age (dropping from 2.9 to 0.1%) and HEV on-farm persistence (dropping from 0.60 to 0.29), particularly on a 7-BRS farm. This may be related to limited viral spread in the reproductive herd linked to the fact that the simulated infection was introduced through a gilt, and to particularly marked segregation between sows, and consequently in the growing pig population. Thus, though pigs were on average infected later, the more confined viral spread eventually reduced the HEV risk for public health. The farm's status regarding the IMV was also shown to greatly influence HEV infection dynamics, especially on a 7-BRS farm, with HEV prevalence in slaughter-age pigs being 17 times lower on an IMV-free farm than on an IMV-positive one, and HEV persistence probability being divided by more than two. These outcomes confirm the major impact of IMV infection on HEV dynamics previously evidenced under experimental and natural conditions, thus the interest of implementing IMVs' eradication programmes on pig farms. Interestingly, pigs were found to contract HEV much earlier (HR = 1.70 [1.69-1.70]) when the herd was IMV-free, which was related to low HEV infection levels of sows in this context, leading to a limited number of passively immune piglets that could contract HEV at an early age. This result clearly shows the impact of the protection conferred by MDAs.

The model has also made it possible to evaluate the effectiveness of three farming practices on reducing the risk of HEV. Firstly, the model has revealed that a lower cross-fostering rate would decrease the risk of HEV spread and persistence. Indeed, HEV prevalence in slaughter-age growing pigs was 1.5 times lower when no cross-fostering was allowed, and HEV on-farm persistence was 1.1 times lower in this case also. This is consistent with the results of the field study conducted by Walachowski et al. (2014). Drastically reducing cross-fostering is likely to confine HEV spread to fewer litters, which limits the overall on-farm dissemination and persistence. Our results have also shown that HEV prevalence at slaughter age would be lower when weaning pen groups are smaller, which is also consistent with the study of

Walachowski et al. (2014). Surprisingly, mixing pigs randomly when moving them from the farrowing sector to small nursery rooms reduced HEV prevalence at slaughter age compared to by-litter mixing. On a 20-BRS farrow-to-finish pig farm, the impact of these farming practices on HEV prevalence at slaughter age was lower than on a 7-BRS, and there was no impact at all on HEV on-farm persistence probability. Again, the large population and short between-batch intervals probably make virus control particularly difficult on this kind of farm. From a health management point of view, a key finding of this study is that implementing anti-IMV vaccination of sows at each reproduction cycle would positively affect HEV infection dynamics — if farming practices are satisfactory — with HEV prevalence at slaughter being 1.7 times lower and HEV persistence 1.8 times less frequent on a 7-BRS farm on which sows are IMV-vaccinated (assuming 100% efficacy of the IMV vaccine represented in the model). Health management measures for IMVs on pig farms may therefore be a potential lever with which to mitigate the HEV risk indirectly, at least on 7-BRS farms. This would be a valuable strategy for controlling both HEV, which is a public health issue, and immunomodulating pathogens that can lead to serious animal health disorders and economic losses for farmers. Besides, while no HEV vaccine is available for pigs, there are vaccines against some immunomodulating pathogens such as PRRSV and PCV2. However, the vaccine's efficacy in controlling the IMV needs to be considered. For instance, PRRSV vaccines are all modified live vaccines, and the interactions between HEV and the PRRSV strains used in vaccines are difficult to predict. Further studies, e.g. experimental co-infection of pigs with HEV and PRRSV vaccine strains, would help shed light on this issue.

Combining all the effective farming practices appeared helpful in reducing HEV risk, especially on a 7-BRS farm. The effect was even higher when adding sow vaccination against the IMV on a 7-BRS farm. These synergetic measures had both direct and indirect impacts as they affected HEV infection dynamics as well as the IMV prevalence level — when sows are vaccinated — and thus HEV indirectly. However, in the event of unsatisfactory husbandry practices, IMV vaccination even had an adverse effect by increasing the risk of HEV entering the food chain. One hypothesis for this would be that vaccinating sows against IMV leads to a later IMV infection of pigs, once they have lost their maternal immunity; in that case, and in combination with bad farming practices, HEV/IMV co-infections occur less frequently but later, which increases the risk of still having HEV-infected pigs at slaughter time. The priority should therefore be given to the improvement of farming practices and, if health measures are

827 planned to be implemented, they should be considered in synergy with good farming
828 practices.
829
830
831 ## 5. Conclusion
832
833 In conclusion, our model revealed difficulties in containing HEV spread once the virus was
834 introduced on a 20-BRS farm, with a low fade-out probability. On a 7-BRS farm, housing
835 gestating sows in smaller groups and controlling intercurrent pathogens could be major levers
836 with which to mitigate the risk of HEV for public health. These results bring to light the
837 relevance of using indirect ways to control HEV and of considering animal and public health
838 in an integrated manner. In the case of more intensive BRSs such as 20-BRS farms, for which
839 few control measures have shown their efficacy in the present study, other control strategies
840 could be evaluated in the future using this model. These could include stricter biosecurity
841 practices (e.g. increasing the efficacy of cleaning and disinfection operations), different herd
842 renewal modalities, a lower mingling rate in the finishing sector and comprehensive
843 eradication plans for intercurrent pathogens. HEV infection dynamics on farms using other
844 BRSs could also be explored. Having more field data (e.g. data on the duration of the active
845 immunity, the possible HEV re-infection of recovered animals) would also be valuable for a
846 more accurate validation of the model. From a more operational perspective, it would be
847 worthwhile to test all these control measures on the field as well by carrying out an
848 intervention study on pig farms. The first step to carry out this kind of study would be to
849 select relevant farms (i.e. having risky farm practices and/or bad health situation, and where
850 HEV circulated) and where farmers would be voluntary to adopt other farming practices.
851 Interventions that could be studied would include cross-fostering reduction, decrease in the
852 size of nursery pens and PRRSV and/or PCV2 eradication programme, depending on the
853 health status of the farm. Further investigations should also focus on studying HEV spread
854 and persistence all along the pig production chain, from farms to slaughterhouses and
855 processed products. Fostering research efforts in this way would lead to a better
856 understanding of HEV risk at each step of the food chain. Taken together, modelling and field
857 data would make it possible to design a comprehensive HEV control plan and support public
858 health policies on this issue.
859

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MS and MA developed the mathematical model and drafted the manuscript. NR coordinated the study. All the authors participated in data analysis and interpretation, and revised the manuscript. All the authors read and approved the final manuscript.

Supplementary Files

Supplementary file 1. Further details on the population dynamics model.

Mortality: the probability p_m that an animal dies depends on its age. The daily mortality rate m_r is equiprobable in the time interval Δt and follows the equation:

$$m_r = 1 - \exp(\frac{\log(1 - p_m)}{\Delta t})$$

When entering a new room, pigs are stressed and the probability they die a few days after the change is higher. Mortality probabilities and associated age limits are presented in Table 3a.

Abortion: the probability p_a that a sow has aborted in a time interval Δt depends on the number of days before farrowing. The daily abortion rate a_r follows the equation:

$$a_r = 1 - \exp(\frac{\log(1 - p_a)}{\Delta t})$$

Abortion probabilities associated to the number of days before farrowing are presented in Table 3b.

Culling: if the sow is satisfying one of the following conditions, it may be culled:

- Parity rank: if its parity rank is higher than 7, the sow is culled.
- Litter size: if the sow has just left farrowing room and its litter size is less than 8, it has a 0.50 probability to be culled.
- Failed AI: if there has been one failed AI since the last time the sow farrowed, the culling probability is 0.50. If the second AI fails too, the sow is culled.
- Abortion: if the sow has aborted twice, it is culled. If it has aborted once and the following AI has also failed, the probability it is culled is 0.70. If it has aborted once and the two following AIs have also failed, it is culled.
- Specific parameters for gilts: if the gilt is aged between 260 and 290 days, the culling probability is 0.50. If it is older than 290 days, it is culled.

Supplementary table 1. Parameters used to calculate daily mortality and abortion rates in the population dynamics model

Supplementary table 1a. Mortality probabilities associated with age limits

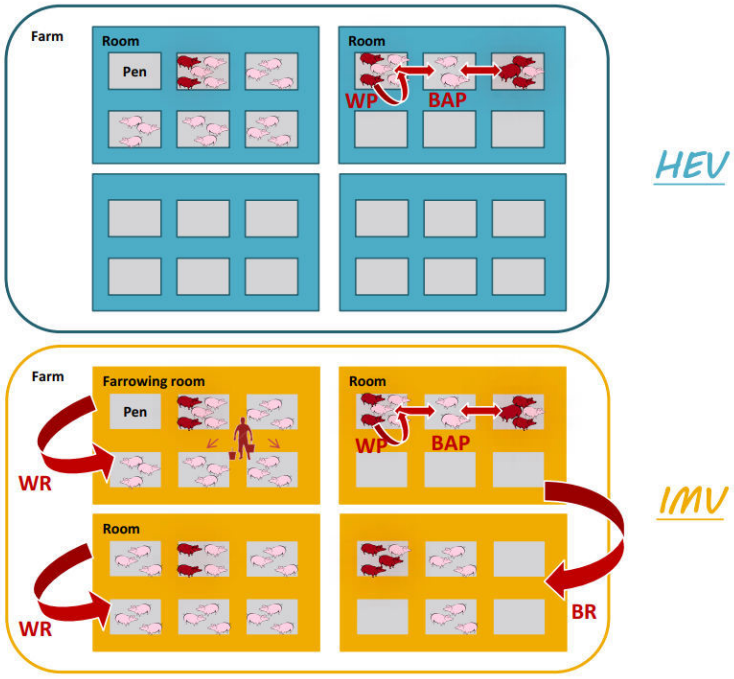
Age limit (days)	**Associated mortality probability (p_m)**
3	0.088
Age at weaning	0.052

Age at weaning +2	0.006
Age at the end of post-weaning	0.0023
Age at the end of post-weaning + 5	0.0025
180	0.04
200	0.02
355	0.01
700	0.02
1,400	0.02
2,000	0.02

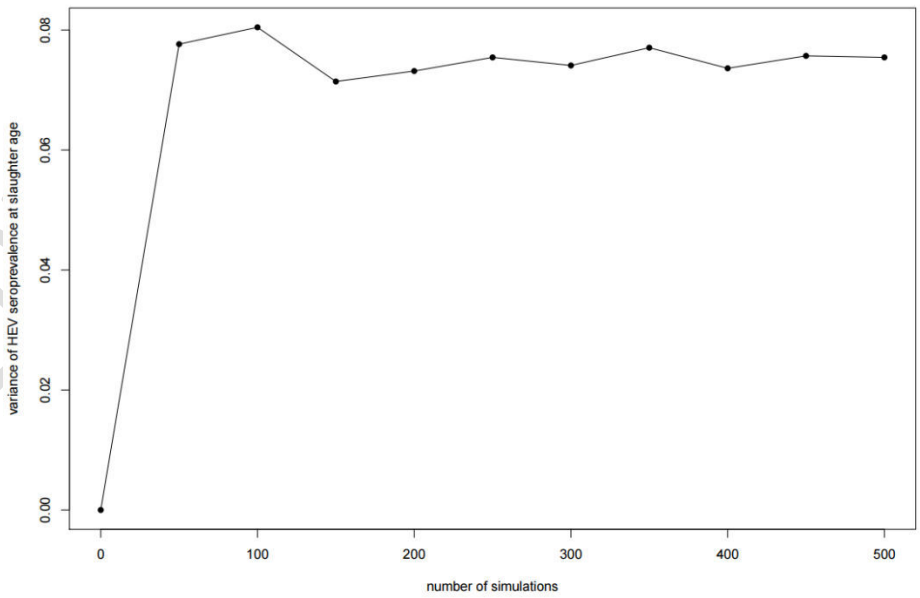
Supplementary table 1b. Abortion probabilities associated with the number of days before farrowing

Number of days before farrowing	**Associated abortion probability (p_a)**
11	0
55	0.005
94	0.01
113	0.03
115	0

Supplementary file 2. HEV and IMV transmission routes and associated forces of infection. WP: within-pen; BAP: between-adjacent-pens; WR: within-room; BR: between-rooms



Supplementary file 3. Variance of HEV seroprevalence at slaughter age depending on the number of simulations.



Supplementary file 4. Relative impact of herd management and control measures on the dynamics of HEV infection (results from univariate analyses)

Table a. Influence of the farm's structure, farming and health practices on the age at which growing pigs contract HEV

Survival analysis of the age at which growing pigs contract HEV using Cox proportional hazard models. Scenarios are detailed in Table 3.

Scenario	Variable	Modality	Age at which growing pigs contract HEV			
			Hazard Ratio [95% CI]	p-value		
1	Type of batch rearing system	7 batches	-			
2		4 batches	0.97 [0.96-0.97]		p < 0.01	
3		20 batches	1.03 [1.03-1.03]		p < 0.01	
			7-batch rearing system		20-batch rearing system	
			Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
1	Type of housing for gestating sows	Large groups	-		-	
4		Medium groups	0.93 [0.92-0.93]	p < 0.01	0.94 [0.93-0.94]	p < 0.01
5		Small groups	0.77 [0.76-0.78]	p < 0.01	0.75 [0.75-0.75]	p < 0.01
1	IMV status	IMV-positive	-		-	
6		IMV-free	1.70 [1.69-1.70]	p < 0.01	0.99 [0.99-0.99]	p < 0.01
1	Cross-fostering practices	Medium rate	-		-	
7		No adoption	0.98 [0.98-0.98]	p < 0.01	0.99 [0.99-0.99]	p < 0.01
8		High rate	1.09 [1.09-1.10]	p < 0.01	1.14 [1.14-1.15]	p < 0.01
1	Modalities for mingling at weaning	Small pens, by litter	-		-	
9		Small pens, randomly	1.20 [1.20-1.20]	p < 0.01	1.26 [1.26-1.26]	p < 0.01
10		Large pens, by litter	0.93 [0.92-0.93]	p < 0.01	0.90 [0.90-0.90]	p < 0.01
11		Large pens, randomly	1.06 [1.06-1.06]	p < 0.01	1.08 [1.08-1.08]	p < 0.01
1	Control of the IMV by vaccinating sows	No	-		-	
12		Yes	0.86 [0.86-0.87]	p < 0.01	0.83 [0.83-0.83]	p < 0.01
13	Worst-case scenario		-		-	
14	Worst farming practices, IMV vaccination		0.73 [0.72-0.73]	p < 0.01	0.70 [0.70-0.70]	p < 0.01
15	Best farming practices, no IMV vaccination		1.26 [1.25-1.26]	p < 0.01	1.22 [1.22-1.22]	p < 0.01
16	Best-case scenario		0.94 [0.93-0.94]	p < 0.01	0.96 [0.96-0.96]	p < 0.01

Table b. Influence of the farm's structure, farming and health practices on the proportion of batches having HEV-infected animals at slaughter time

Logistic regression was used to evaluate the impact of explanatory variables on the proportion of batches having HEV-positive animals at slaughter time.

Scenario	Variable	Modality	Proportion of batches having HEV-infected animals at slaughter time			
			Odds Ratio [95% CI]	p-value		
1	Type of batch rearing system	7 batches	-	p < 0.01		
2		4 batches	1.54 [1.47-1.62]	p < 0.01		
3		20 batches	4.79 [4.62-4.97]	p < 0.01		
			7-batch rearing system		20-batch rearing system	
			Odds Ratio [95% CI]	p-value	Odds Ratio [95% CI]	p-value
1	Type of housing for gestating sows	Large groups	-	p < 0.01	-	p < 0.01
4		Medium groups	0.43 [0.41-0.45]	p < 0.01	0.43 [0.42-0.44]	p < 0.01
5		Small groups	0.020 [0.018-0.022]	p < 0.01	0.086 [0.083-0.088]	p < 0.01
1	IMV status	IMV- positive	-		-	
6		IMV-free	0.15 [0.14-0.15]	p < 0.01	0.86 [0.84-0.89]	p < 0.01
1	Cross-fostering practices	Medium rate	-	p < 0.01	-	p < 0.01
7		No adoption	0.86 [0.83-0.90]	p < 0.01	0.97 [0.94-1.01]	p > 0.05
8		High rate	1.66 [1.59-1.74]	p < 0.01	1.49 [1.40-1.58]	p < 0.01
1	Modalities for mingling after weaning	Small pens, by litter	-	p < 0.01	-	p < 0.01
9		Small pens, randomly	1.06 [1.01-1.10]	p < 0.05	1.04 [1.01-1.07]	p < 0.01
10		Large pens, by litter	1.23 [1.18-1.28]	p < 0.01	1.07 [1.04-1.10]	p < 0.01
11		Large pens, randomly	0.95 [0.91-0.99]	p < 0.05	1.13 [1.09-1.16]	p < 0.01
1	Control of the IMV by vaccinating sows	No	-		-	
12		Yes	0.36 [0.34-0.37]	p < 0.01	0.54 [0.52-0.56]	p < 0.01
13	Worst-case scenario		-	p < 0.01	-	p < 0.01
14	Worst farming practices, IMV vaccination		0.74 [0.71-0.77]	p < 0.01	0.87 [0.84-0.90]	p < 0.01
15	Best farming practices, no IMV vaccination		0.67 [0.64-0.70]	p < 0.01	0.70 [0.68-0.73]	p < 0.01
16	Best-case scenario		0.34 [0.32-0.35]	p < 0.01	0.68 [0.66-0.70]	p < 0.01

928 **Table c. Influence of the farm's structure, farming and health practices on HEV prevalence in growing pigs at slaughter time**

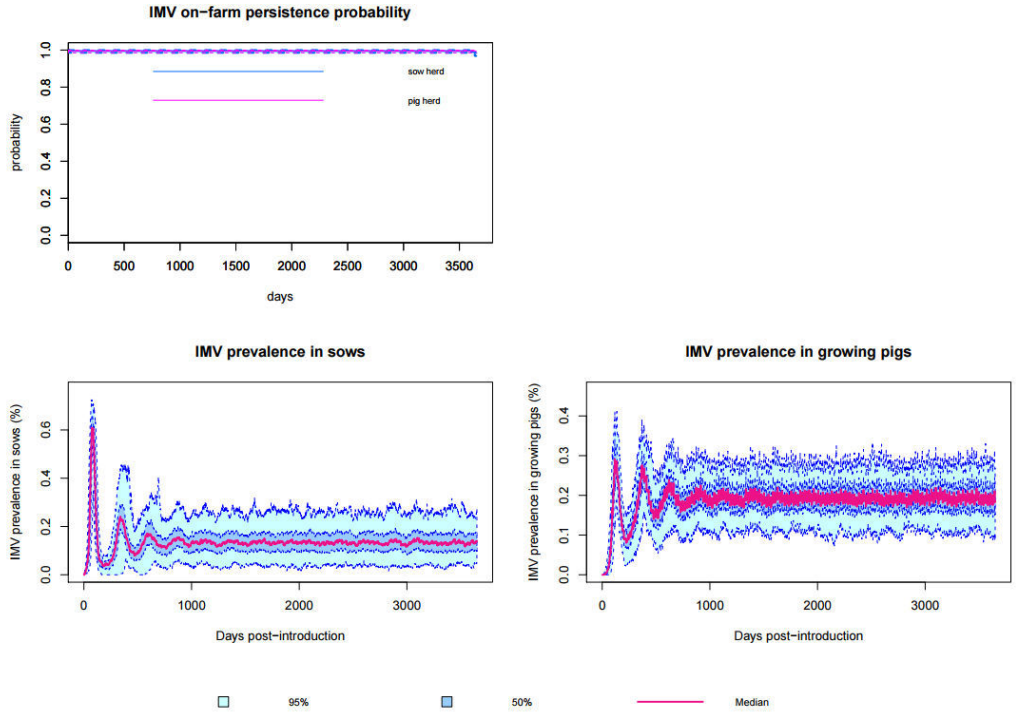
929 Generalised estimating equation (GEE) logistic regression was used to evaluate the impact of explanatory variables on HEV prevalence in
930 slaughter-age pigs.

931

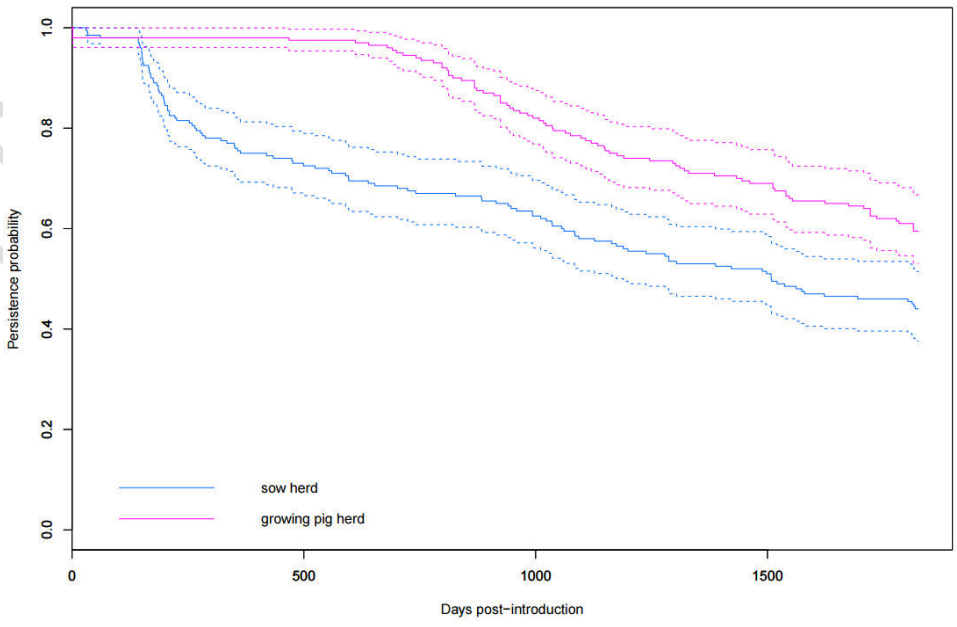
Scenario	Variable	Modality	HEV prevalence in slaughter-aged growing pigs			
			Odds Ratio [95% CI]		p-value	
1	Type of batch rearing system	7 batches	-		p < 0.01	
2		4 batches	0.84 [0.75-0.93]		p < 0.01	
3		20 batches	1.37 [1.27-1.49]		p < 0.01	
			7-batch rearing system		20-batch rearing system	
			Odds Ratio [95% CI]	p-value	Odds Ratio [95% CI]	p-value
1	Type of housing for gestating sows	Large groups	-	p < 0.01	-	p < 0.01
4		Medium groups	0.61 [0.53-0.69]	p < 0.01	0.71 [0.68-0.74]	p < 0.01
5		Small groups	0.033 [0.021-0.051]	p < 0.01	0.22 [0.21-0.24]	p < 0.01
1	IMV status	IMV- positive	-		-	
6		IMV-free	0.057 [0.051-0.063]	p < 0.01	0.97 [0.93-1.02]	p > 0.05
1	Cross-fostering practices	Medium rate	-	p < 0.01	-	p < 0.01
7		No adoption	0.91 [0.82-1.01]	p > 0.05	0.93 [0.90-0.96]	p < 0.01
8		High rate	1.45 [1.31-1.60]	p < 0.01	1.40 [1.35-1.46]	p < 0.01
1	Modalities for mingling after weaning	Small pens, by litter	-	p < 0.01	-	p < 0.01
9		Small pens, randomly	0.78 [0.71-0.86]	p < 0.01	0.78 [0.75-0.81]	p < 0.01
10		Large pens, by litter	1.23 [1.11-1.36]	p < 0.01	1.36 [1.31-1.41]	p < 0.01
11		Large pens, randomly	0.84 [0.73-0.96]	p < 0.01	1.23 [1.09-1.17]	p < 0.01
1	Control of the IMV by vaccinating sows	No	-		-	
12		Yes	0.60 [0.53-0.67]	p < 0.01	0.98 [0.92-1.04]	p > 0.05
13	Worst-case scenario		-	p < 0.01	-	p < 0.01
14	Worst farming practices, IMV vaccination		1.42 [1.26-1.59]	p < 0.01	1.73 [1.65-1.81]	p < 0.01
15	Best farming practices, no IMV vaccination		0.44 [0.39-0.50]	p < 0.01	0.42 [0.41-0.44]	p < 0.01
16	Best-case scenario		0.45 [0.39-0.51]	p < 0.01	0.71 [0.69-0.74]	p < 0.01

932

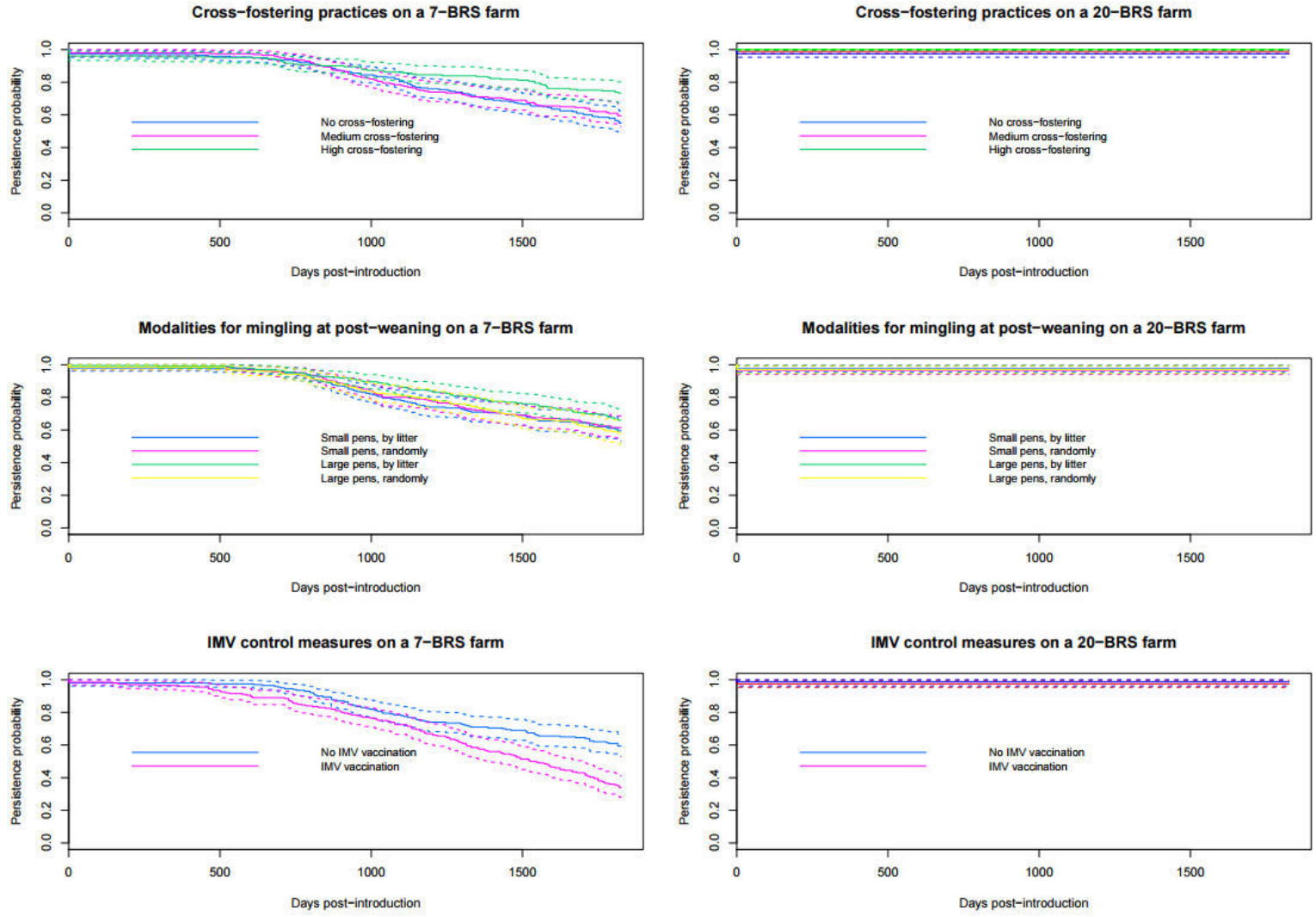
Supplementary file 5. IMV persistence and prevalence in sows and growing pigs (median, 50%, 95%) on a 7-batch rearing system farrow-to-finish pig farm.



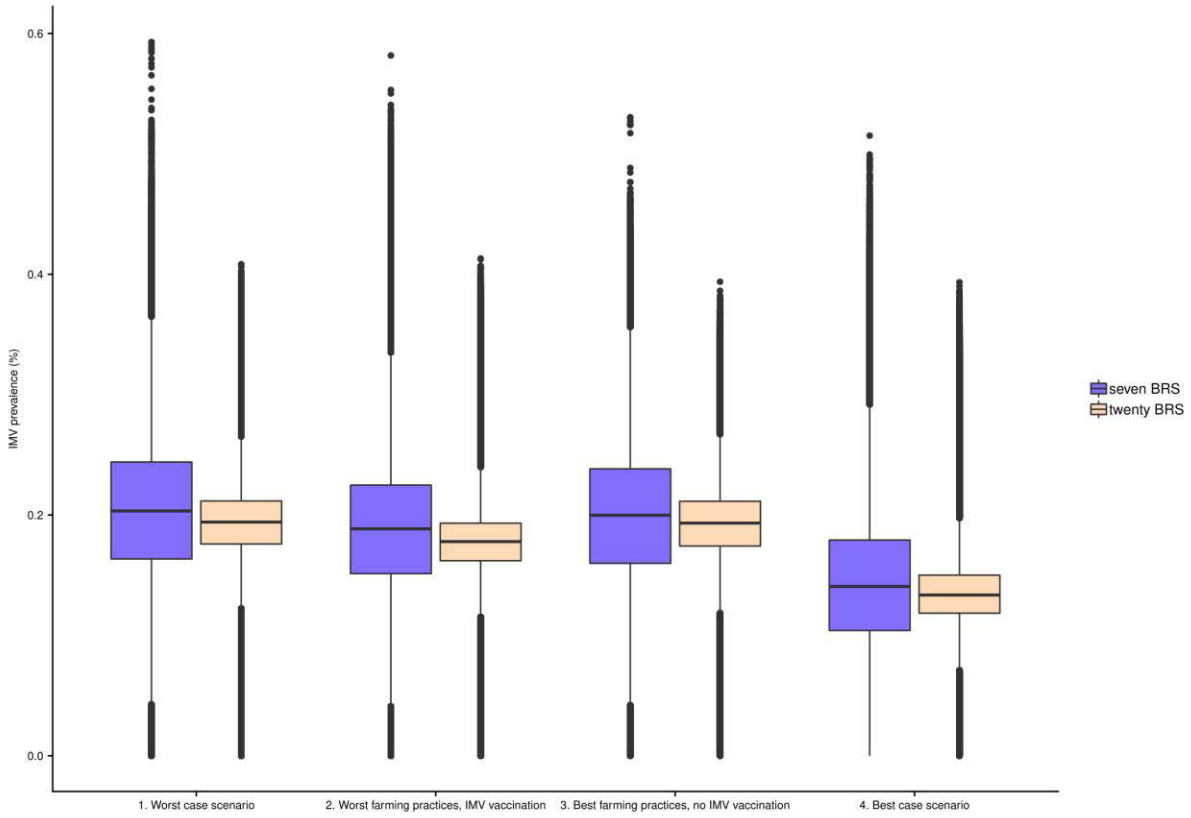
Supplementary file 6. HEV on-farm persistence five years post-introduction in the sow herd and growing pigs, on a 7-batch rearing system farrow-to-finish pig farm (n = 200 simulations).



Supplementary file 7. HEV persistence probability on a 7- or 20-batch rearing system farrow-to-finish pig farm depending on farming practices and health management measures (n = 200 simulations).



Supplementary file 8. Immunomodulating virus (IMV) prevalence in growing pigs on a 7- or 20-batch rearing system farrow-to-finish pig farm in combined HEV control scenarios (n = 200 simulations).



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Ce qu'il faut retenir

A partir d'une approche innovante de modélisation multi-pathogènes, le modèle développé a apporté de nouveaux éléments dans la compréhension de la dynamique de l'infection par le HEV dans un élevage de porcs naisseur-engraisseur. Il a permis de mettre en évidence l'influence majeure de la structure de l'élevage (type de conduite en bandes, système de logement des truies gestantes) ainsi que de certaines pratiques d'élevage (modalités d'adoption, taille des cases en post-sevrage, modalités de mélange au sevrage) et sanitaires (vaccination des truies contre les pathogènes intercurrents). En particulier, ce dernier point souligne la pertinence d'utiliser des moyens indirects pour cibler le HEV et de considérer la santé animale et la santé publique de manière intégrée.

Ce travail contribue à une meilleure connaissance des facteurs expliquant la propagation et la persistance du HEV au sein d'un élevage de porcs. Il apparaît également nécessaire de comprendre les voies de diffusion préférentielle du HEV entre les élevages et ainsi la persistance du virus dans la filière de production porcine. Pour ce faire, une approche de modélisation multi-échelles a été développée dans la suite du projet de recherche, tenant compte des échanges de porcs entre élevages pour la construction d'un modèle inter-troupeaux de la dynamique du HEV.

Take home message

Based on an innovative multi-pathogen modelling approach, the model we have developed has given insights for the understanding of HEV infection dynamics on a farrow-to-finish pig farm. It made it possible to evidence the major role of the farm's structure (type of batch management system, type of housing facilities for gestating sows) as well as of some farming practices (cross-fostering practices, size of the nursery pens, modalities for mingling weaned piglets) and health control measures (sow vaccination against immunomodulating pathogens). In particular, the latter point underlines the relevance of using indirect ways to target HEV and of considering animal and public health in an integrated manner.

This work contributes to a better understanding of the factors explaining HEV spread and persistence on a pig farm. It also appears necessary to understand the preferential distribution pathways of HEV between farms and thus the persistence of the virus in the pig production chain. To do this, a multi-scale modelling approach has been developed in the next steps of the research project. It integrates between-farm pig trade to build a between-herd model of HEV dynamics.