Analyse de la propagation et de la persistance du virus de l’hépatite E dans la filière de production porcine

PARTIE 3.1. Les mouvements de porcs comme point d'intérêt pour l'étude du risque lié au virus de l'hépatite E dans la filière de production porcine

I. Etude des caractéristiques du réseau des mouvements de porcs en France

Avant d'initier la construction d'un modèle inter-troupeaux représentant la diffusion du HEV entre les élevages de porcs par l'intermédiaire des échanges d'animaux, il est apparu opportun de commencer par une **analyse descriptive du réseau des mouvements de porcs en France**. Ainsi, à partir des échanges de porcs enregistrés dans la base de données BDporc sur la période 2012-2014, **deux types de réseaux** ont été construits **selon les caractéristiques épidémiologiques du pathogène considéré** : le premier réseau est adapté aux pathogènes transmis uniquement par l'introduction d'animaux infectés dans un élevage (*Animal Introduction Model* - AIM) ; l'autre réseau correspond à des pathogènes transmis également par voie indirecte lors du passage des camions dans les élevages sans déchargement d'animaux (*Transit Model* - TM). Ces deux réseaux ont été étudiés par des méthodes de *Social Network Analysis* (statistiques descriptives, recherche de composants connectés et de communautés, analyse temporelle).

Ce travail a été publié dans le journal *PLoS One* (Salines *et al.*, 2017b). Pour faciliter la compréhension de cet article, un tableau définissant et illustrant les principaux indicateurs utilisés pour l'analyse du réseau est présenté en Annexe 6.

Publication 7

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RESEARCH ARTICLE

Pig movements in France: Designing network models fitting the transmission route of pathogens

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Abstract

Pathogen spread between farms results from interaction between the epidemiological characteristics of infectious agents, such as transmission route, and the contact structure between holdings. The objective of our study was to design network models of pig movements matching with epidemiological features of pathogens. Our first model represents the transmission of infectious diseases between farms only through the introduction of animals to holdings (Animal Introduction Model AIM), whereas the second one also accounts for pathogen spread through intermediate transit of trucks through farms even without any animal unloading (i.e. indirect transmission–Transit Model TM). To take the pyramidal organisation of pig production into consideration, these networks were studied at three different scales: the whole network and two subnetworks containing only breeding or production farms. The two models were applied to pig movement data recorded in France from June 2012 to December 2014. For each type of model, we calculated network descriptive statistics, looked for weakly/strongly connected components (WCCs/SCCs) and communities, and analysed temporal patterns. Whatever the model, the network exhibited scale-free and small-world topologies. Differences in centrality values between the two models showed that nucleus, multiplication and post-weaning farms played a key role in the spread of diseases transmitted exclusively by the introduction of infected animals, whereas farrowing and farrow-to-finish herds appeared more vulnerable to the introduction of infectious diseases through indirect contacts. The second network was less fragmented than the first one, a giant SCC being detected. The topology of network communities also varied with modelling assumptions: in the first approach, a huge geographically dispersed community was found, whereas the second model highlighted several small geographically clustered communities. These results underline the relevance of developing network models corresponding to pathogen features (e.g. their transmission route), and the need to target specific types of holdings/areas for surveillance depending on the epidemiological context.

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1. Introduction

Swine infectious diseases have economic consequences for the pig industry and can affect public health. They can be transmitted from farm to farm through animal trade, either because of the introduction of infected animals, or only because of transit movements of contaminated trucks acting as mechanical vectors [1]. Disease spread is closely linked to the movement network topology [1, 2]; gaining insights into spatial and contact patterns of pig trade could therefore be a major lever to control the spread of swine infectious diseases. To do so, animal movement data are increasingly modelled into networks and studied using social network analysis (SNA) methods [2–22]. Animal trade networks are composed of nodes, which are either farms or slaughterhouses, markets, trade operators, etc., and of links, which are shipments of animals between these units. These networks are directed: animal movements along the network links are considered directed paths for the spread of a disease from one farm to another. Cattle, sheep, pig and poultry markets have already been modelled in several countries [2, 4–22], using either movements reported by farmers through questionnaires, or movements systematically recorded in a harmonised database. Unlike cattle movements, a special feature of swine trade data is that pig movements are reported at a batch scale, without the possibility of tracking animals individually. Moreover, the pig production sector is organised in a pyramidal way, with movements going from the nucleus and multiplying farms at the top, to the production farms at the bottom (from farrowers to finishers). This particular structure affects the network topology and has to be accounted for [6]. Pig movements can exhibit intricate patterns, for instance when trucks collect pigs at several farms before unloading all of them at a single site (e.g. a slaughterhouse). To our knowledge, most of swine trade networks published in the literature have simplified these complex trajectories going through several farms by representing only direct operations from the loading locations to the unloading sites [2, 7–10, 19, 23]. By doing so, intermediate transit movements of trucks in farms without any animal unloading have been neglected. Yet these movements can contribute to the spread of diseases for which indirect transmission through mechanical vectors occurs (e.g. African Swine Fever—ASF, Porcine Epidemic Diarrhoea—PED, Foot and Mouth Disease–FMD, Porcine Reproductive and Respiratory Syndrome Virus—PRRSV) [24–26]. To fit as closely as possible with the pathogens' epidemiological features, network models should take their various transmission routes into account. To explore the role of trucks in indirect disease spread, some research teams developed two-mode networks with trucks or rounds being considered as a second class of nodes in addition to holdings [6, 21]. This method makes it possible to obtain relevant data regarding the functioning of rounds, such as the number of rounds concerning a given farm, or the number of holdings connected in a round. However, two-mode networks are not easy to analyse: centrality measures cannot all be computed, contact chains are not calculated, and communities and connected components are usually not looked for [6, 21]. Two-mode networks are thus often altered in a one-mode network to be more deeply analysed [6].

The objective of our study was therefore to design two one-mode network models matching with the transmission route of pathogens, and to analyse empirical data of French pig trade. We focused our model analysis on the different levels of the pyramidal structure inherent to the pig production system.

2. Materials and methods

2.1. Data

2.1.1. Database description. Since 2010, pig movements in France have been recorded and stored in the National Swine Identification Database (BDporc). This database is managed by swine industry professionals and is recognised by the French Ministry for Agriculture. For the present study, we analysed the data from June 2012 to December 2014. Two levels of information were gathered in the dataset: the characteristics of swine production units and the details of the animal movements between the different production sites. The main features of all swine holdings in mainland France are included in the database: identification number, type of holding (farm, slaughterhouse, rendering company, market, assembly centre, trading company), type of farming activity (boar station *BS*, nucleus *SEL*, multiplication *MU*, farrowing *FA*, farrowing-to-finishing *FF*, finishing *FI*, farrowing-post-weaning *FPW*, post-weaning *PW*, post-weaning-finishing *PWF*, small producers *SP*), type of production (free-range or not), and location (post code and GPS coordinates). Movements of pigs were reported at a batch level: groups of animals were sent off the production sites (loadings, further denoted L) and dispatched to either alternative production units or slaughterhouses (unloadings, further denoted U). A single truck could load and unload animals at several production sites: one round corresponds to a series of movements of a truck, from the first loading operation to the last unloading event making the truck empty. Each loading and unloading operation was individually reported for each round with several pieces of information: the farm and the round IDs, the chronological sequence of the operations during the round, the batch size and the animal category (breeding animals, piglets, and growing pigs).

2.1.2 Data cleaning and pre-processing. Data included both movements occurring within France and movements from/to foreign countries. However, imports and exports of animals were recorded at the country level, with a lower data resolution than movements occurring within France. Therefore, movements from/to foreign countries were considered separately to have a global overview of international trade movements, when a thorough analysis of within-France data was performed.

A series of cleaning processes were performed on the dataset, discarding records for which the principal pieces of information were unavailable (e.g. round or herd identification numbers, animal category). Farms were categorised into 11 groups according to their major activity; markets, assembly centres and trading companies were gathered into the single "trade operators" category. Direct movements to slaughterhouses and rendering plants were excluded from the analysis as they do not play a major role in pathogen spread. When these movements were part of longer rounds collecting pigs from several herds before going to the slaughterhouse/rendering plant, only the last movement (from the last farm to the slaughterhouse) was excluded. Considering the absence of any seasonality in pig trade shown in previous studies [2, 7, 23, 27, 28], movement data were aggregated on a six-month basis.

2.2. Model design

One-mode directed networks were built: holdings were considered as nodes, movements between two nodes were considered as links. All movements between two given holdings during the time period were aggregated into a single link. We designed two types of network to model a round (Fig 1A) in two different ways depending on the route of transmission of the considered pathogen. *(i)* In the first network model, called hereafter the Animal Introduction Model (AIM) (Fig 1B), links between holdings represented movements of animals being unloaded at farms. In-between movements forming a round were replaced by direct movements between holdings, i.e. intermediate transit movements of a truck through a farm without unloading any animal were excluded. All sites corresponding to unloading operations were assumed to be linked to all prior loading sites of the same round. For example, assuming successive loadings at sites L1 and L2 followed by an unloading operation at site U4, then holding U4 was linked to L1 and L2. This model is relevant for pathogens that spread between

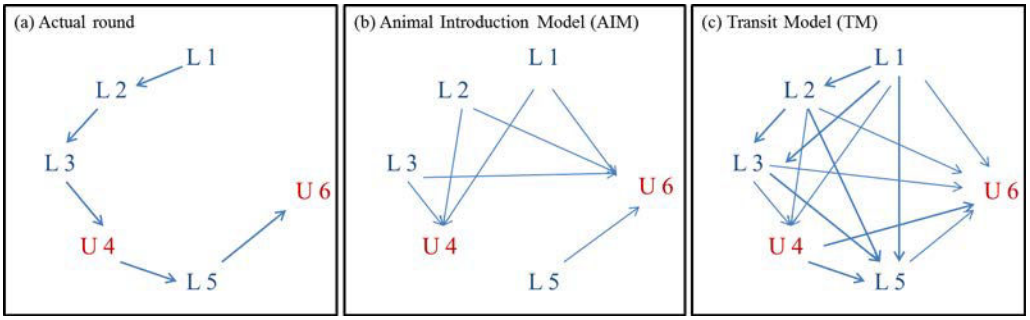

Fig 1. Types of network models built to represent pig movements. Nodes L and U correspond to holdings where loading and unloading operations occurred, respectively. The number corresponds to the chronology of animal collection by a truck in one round. Fig 1.a describes the actual round of a given truck, whereas Fig 1.b and Fig 1.c describes how the links between holdings were modelled, depending on the transmission route of the pathogen considered. In the Animal Introduction Model—AIM (Fig 1.b), movements forming a round were replaced with direct movements between holdings, i.e. intermediate transit movements of a truck through a farm without unloading any animal were neglected. This network accounts for the transmission of a disease only through the introduction of animals into farms. In the Transit Model—TM (Fig 1.c), each holding was assumed to be linked to every other upstream and downstream farm in a given round through incoming and outgoing links, respectively. This type of network can be used to explore the spread of a pathogen both through the introduction of animals to farms and through the indirect route.

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holdings only through the introduction of animals to farms (i.e. diseases that spread via physical contact and for which the indirect transmission route is negligible). *(ii)* In the second network model, further denoted Transit Model (TM) (Fig 1C.), links between holdings represented both movements of animals and truck transit through a farm without any animal unloading. In a given round, each holding was therefore linked to all upstream and downstream farms (incoming and outgoing links, respectively). In other words, each round was modelled as a full graph. This model could be used for pathogens that spread not only because of the introduction of animals to farms but also through the transit of trucks through farms even without any animal introduction (i.e. diseases for which indirect transmission occurs, with trucks acting as mechanical vectors).

2.3. Network analysis

Considering the pyramidal structure of the pig production sector, all analyses presented below were performed at three different scales: the whole network, the breeding farm subnetwork (boar stations, nucleus/multiplication farms) and the production farm subnetwork. Network analysis was performed on within-France movements only.

2.3.1. Network descriptive indicators. Several descriptive statistics of the network characteristics were calculated for each network model and for each semester to analyse changes in network properties over the study period. The first semester was running from January 1st to June 30th, the second one from July 1st to December 31st. The classical metrics that were computed were: the *size* (number of active nodes and links), the *average degree* (mean of the total number of ingoing and outgoing links for each node), the *average path length* (the average number of links along the shortest paths–or geodesics–between all pairs of nodes), the *diameter* (the longest geodesic), and the *density* (ratio of the number of links and the number of possible links for active nodes). We also calculated the *clustering coefficient* (proportion of neighbours of a node that are linked to each other), the *Jaccard similarity coefficient* (the JSC of two nodes being the number of common neighbours divided by the number of neighbours of each of the two nodes considered), the *assortativity degree* (Pearson correlation coefficient between the degrees of linked nodes), and the *reciprocity ratio* (proportion of mutual connections, in a directed graph). The distributions of the four main centrality measurements were computed for each holding type: *degree*, *in-degree* (number of different holdings from which a holding receives animals), *out-degree* (number of links going from a node), *closeness* (number of steps required to access every other node from a given node) and *betweenness* centralities (number of geodesics going through a node). For each network model, a power-law distribution defined as $p(x) \sim x^{\alpha}$ was fitted to the observed degree distribution. We used a maximum-likelihood estimator to estimate scaling parameter (α) and the Kolmogorov–Smirnov (KS) goodness-of-fit statistic to test power law fit of the data as described by Clauset et al. [29].

2.3.2. Detection of connected components and communities. **Connected components.** *Weakly connected components* (WCCs) are sections of the network where every holding can be reached from every other holding whatever the link direction. Based on this definition, no connection exists between two WCCs and they can be considered as independent subnetworks. *Strongly connected components* (SCCs) are subgraphs in which every node can be reached from every other node via one or several directed paths. The number of WCCs and SCCs and the size of the largest WCCs and SCCs were determined with the two network models AIM and TM, and for the whole population as well as separately for the breeding farm and production farm subpopulations.

Communities. Detection of *network communities*, defined as subsets of nodes in which there are significantly more links than expected by chance, i.e. groups of highly connected farms, was performed using the Infomap algorithm [30]. Briefly, the hierarchical map equation measures the per-step average code length necessary to describe a random walker's movement on a network, given a hierarchical network partition, and looks for the community structure that minimises the expected description length of the random walker trajectory. In the core algorithm, each node is first assigned to its own module. Then, in random sequential order, each node is moved to the neighbouring module that results in the largest decrease of the map equation. When adding movements does not result in a decrease of the map equation, the node stays in its original module. This procedure is repeated, each time in a new random sequential order, until no move generates a decrease of the map equation. The network is then rebuilt, with the modules of the last level forming the nodes at this level, and, exactly as at the previous level, the nodes are joined into modules. This hierarchical rebuilding of the network is repeated until the map equation cannot be reduced further. The Infomap algorithm is the only one that can be applied on directed networks and it is considered to have the best performance [31]. We ran the algorithm with 1,000 trials, on the two network models AIM and TM. Like for the connected component detection, we looked for communities in the whole graph and in the two subgraphs (breeding/production farms). We also calculated the percentages of links connecting two different communities (i.e. bridges, or crossing links).

2.3.3. Temporal network analysis. **Link and node preservation.** We counted the number of nodes remaining active from one semester to another, as well as the number of links being preserved from one semester to another.

Node loyalty. In order to explore the nodes' tendency to re-establish connections with the same herds or to change trade partners over time, the *node loyalty* was computed for each kind of model. The loyalty measures the fraction of preserved links of a node for a pair of two consecutive network configurations in time, the time window in our case being a semester. It involves values between 0 and 1, a loyalty value of zero indicating that all connections were different between the two time windows, a loyalty of one indicating that exactly the same set of links was preserved. We computed the loyalty on the incoming contacts of nodes, thus quantifying the tendency of a farmer to purchase animals from the same sellers.

Outgoing and ingoing contact chains. The *outgoing and ingoing contact chains* (OCC and ICC, respectively) were computed for each type of holding over a one-month period. These measures capture the sequence of contacts through direct and indirect movements, taking into account the order in which movements happen during a fixed time-period. The OCC is the number of nodes in contact with a certain node, the root, through movements of animals leaving the root. In other words, the *set of influence* of the root corresponds to the set of nodes that can be reached from the root through time-respecting paths within the observation window. Similar to the OCC, the ICC is the number of nodes in contact with the root holding through movements reaching the root. The *source set* of the root is defined as the set of nodes that can reach the root through time-respecting paths within the observation window. These two measures reflect the potential epidemic size of a disease in the network [32].

Network analyses were performed using the Igraph package in R software [33].

3. Results

3.1. Swine trade description

3.1.1. Within-France movements. A total of 21,446 sites were recorded in the BDporc database, among them 97.9% were farms, 1.5% slaughterhouses and rendering plants, and 0.6% trade operators (Table 1). The number of farms decreased by 2.9% between June 2012 and December 2014.

The database contained 2,382,510 movement records, from which 9% were discarded after the cleaning process (16, 44, and 40% due to missing or incomplete round, foreign movements or missing herd identification numbers, and animal mortality or missing animal category, respectively). A total of 838,777 rounds occurred between June 2012 and December 2014. They were composed of several loading and unloading operations: rounds between farms implied on average 2.5 holdings (range: 2–32), whereas rounds going to slaughterhouses were on average composed of a single movement. The leading destination of movements was slaughterhouses/rendering plants (75.2% of unloading operations), followed by farms (22.8%) and trade operators (2.0%). Growing pigs were the main animal category involved in movements (67% of unloaded animals), followed by piglets (31%) and breeding pigs (2%). The average number of animals transported in a given round varied with the destination site: in the second half of 2014, a round going to farms transported on average 188 animals, whereas those going to slaughterhouses and trade operators transported on average 84 and 25 pigs, respectively. The number of animals transported in a single round increased by 4%, 1.6% and 24.8% over the study period for rounds going to farms, slaughterhouses and trade operators, respectively. The number of rounds decreased by 4% over the same period, leading to an overall decrease of 0.6% in the total number of unloaded animals. The decline in exchanges mainly affected breeding pigs and trade operators. These data are detailed in S1 Table.

The distribution of distances travelled by pigs in a round varied with the animal category. Excluding movements to slaughterhouses, rendering plants and trade operators from distance calculations, breeding pigs travelled on average 270 km (median: 200, range: 0–1,000), whereas growing pigs travelled on average 74 km (median: 42, range: 0–999).

3.1.2. Movements from/to foreign countries. A total of 12,065 rounds came from or went abroad over the study period, corresponding to 1.4% of the total number of rounds recorded in the whole database. Animals sent abroad were mostly growing pigs (59.4% of animals unloaded abroad), culled sows and boars (28.7%) and breeding pigs (9.6%). Outgoing shipments mainly went to Belgium and Germany (48.6% and 32.1%, respectively—mainly pigs and culled sows/boars to slaughterhouse), Italy (7.0%—mainly pigs to slaughterhouses) and Spain (7.2%—mainly pigs to slaughterhouses and breeding pigs). Animals imported from abroad were growing pigs, piglets and breeding pigs (43.6%, 38.0% and 18.1%, respectively). Incoming shipments came primarily from Spain (47.3%—mainly pigs to slaughterhouses),

Table 1. Number and proportion of sites categorised according to their major activity.

	Abbreviation	Type	Number	Percentage
Breeding farms	BS	Boar Station	73	0.35
	SEL	Nucleus	117	0.56
	MU	Multiplier	343	1.63
Production farms	PW	Post-weaning	162	0.77
	PWF	Post-weaning—Finishing	2,273	10.83
	FA	Farrowing	465	2.21
	FF	Farrowing-to-Finishing	5,064	24.12
	FPW	Farrowing—Post-weaning	288	1.37
	FI	Finishing	4,414	21.02
	SP*	Small Production	7,457	35.51
	WB	Wild-boar	342	1.63
Total no. of farms			**20,998**	**100**
	TR	Trade operators	117	
	SR	Slaughterhouses / Rendering plants	331	

As expected given the pyramidal structure inherent to the pig production system, PWF, FF, FPW, FI and SP are the most represented farm types in France.
* Small Production farms were defined as farms rearing fewer than 80 animals.

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Belgium (33.3%—mainly piglets) and Denmark (11.5%—mainly breeding pigs). Shipments to and from non-EU countries represented only 0.5% and 0.4% of foreign movements, respectively.

3.2. Network description

3.2.1. Network mapping. The density of active holdings and movements varied with regions, e.g. the network in north-western France was much denser than in south-eastern France (Fig 2.1). Breeding farms were mostly located in the upper left diagonal part (Fig 2.2). The network appeared denser using the TM than the AIM. Node degree was higher in the TM approach than in the AIM, especially for farrowing and farrow-to-finish farms, and particularly in the centre of France (Fig 2.3.B). Network maps were similar over the five semesters (data not shown).

3.2.2. Network descriptive indicators. **Whole network.** Network descriptive statistics are summarised in Table 2.

In the second half of 2014 for example, the network contained 11,013 and 13,784 active holdings when using the AIM and the TM, respectively. The number of links per semester was around six times higher in the TM than in the AIM (132,677 and 21,691 links, respectively). Regarding link multiplicity, 51% of links between two holdings happened only once per semester in the AIM versus 68% in the TM. A holding exchanged animals on average with four different farms in the AIM, while a holding was in contact with 19 other farms on average in the TM (average degree). Fig 3 shows the degree distributions of holdings on a log–log scale for the AIM and the TM. Whatever the model, the distribution appeared similar in the five semesters (data not shown) and showed power-law-like behaviour (power-law exponent *alpha* values being equal to 2.78 and 5.82 with p-values of the KS test being 0.29 and 0.78 for the AIM and the TM, respectively), suggesting a scale-free structure of the network.

Distance indicators varied with the model used: a given pair of connected nodes was separated by approximately two animal movements in the AIM versus six movements in the TM (average path length). The average path length was shorter in the AIM and similar in the TM

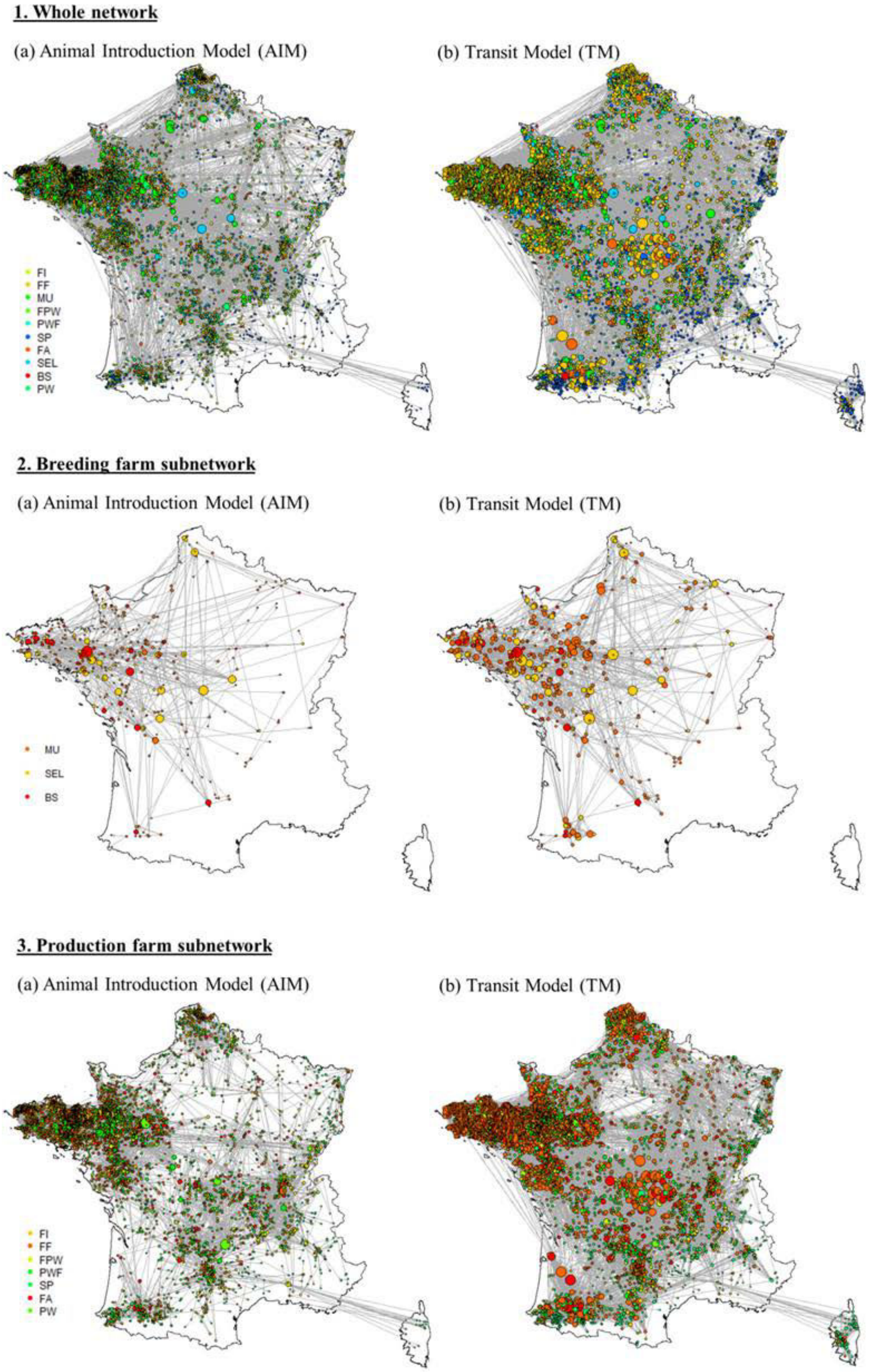

Fig 2. Mapping of the pig movement network in France (second half of 2014) applying the two different models (Animal Introduction Model [AIM] and Transit Model [TM]) to the whole network, the breeding farm subnetwork and the production farm subnetwork. The points are active holdings only (i.e. farms having had at least one movement over the semester). Their size is proportional to their degree. Direct

movements to slaughterhouses are excluded. BS: boar station, SEL: nucleus, MU: multiplication, FA: farrowing, FF: farrowing-to-finishing, FI: finishing, FPW: farrowing-post-weaning, PW: post-weaning, PWF: post-weaning-finishing, SP: small producers.

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to in a random graph of the same size. The diameter also increased from 10 links in the AIM to 20 links in the TM. The network modelled with the TM was four times denser than the AIM one. The clustering coefficients of the network were low, but ten times higher in the TM than in the AIM, suggesting that nodes tended to gather when considering the TM. Moreover, the clustering coefficient was higher in the AIM and the TM than in a random graph of the same size. Whatever the model, the Jaccard similarity coefficient was equal to zero for almost all pairs of nodes, showing the dissimilarity of nodes. The assortativity of the AIM network was negative (i.e. the network was disassortative). On the contrary, the assortativity degree of the TM network was positive, indicating that nodes were more often linked to nodes with similar degrees. Whatever the model, the reciprocity ratio was low, reflecting that links were rarely bidirectional. All these indicators were globally stable over time, at a semester scale.

Specificities of breeding/production farms. The modelling approach was found to affect more the indicators of the production farm subnetwork than the ones of the breeding farm subnetwork (Table 2). For example, comparing the TM and AIM approaches, the number of links in the production farm subnetwork was increased by a factor of eight, while it was only three-times higher in the breeding farm subnetwork. Centrality values within farm type were highly heterogeneous (Fig 4): for example, degree centrality ranged from 1 to 121 (median: 17) for multiplication farms in the AIM. For the two types of models, there were significant differences in the centrality values (degree, closeness and betweenness) between types of pig farms (Kruskal-Wallis test: p-value < 0.0001). In the AIM, nucleus, multiplication and post-weaning farms had higher values for degree and betweenness centrality, whereas farrowing and farrow-to-finish herds presented higher values for in-degree centrality in the TM (Fig 4).

3.2.3 Detection of connected components and communities.

Connected components. In both models, few weakly connected components (WCCs) were detected, the largest one gathering around 90% of holdings (Table 3). In the whole network, the number of WCCs increased by four times between the AIM and the TM, whereas it decreased by a factor of 1.5 in the breeding farm subnetwork, and increased by a factor of 14 in the production farm subnetwork. In the AIM, a high number of strongly connected components (SCCs) was found, the largest one containing less than 1% of farms. On the contrary, the TM network was less fragmented, with a lower number of SCCs and the detection of a giant SCC (GSCC) containing more than 70% of pig herds. The TM production farm network was more cohesive than the TM breeding farm one. Removing all farrow-to-finish herds from the production farm network led to a decrease in the size of the GSCC from 70% to 30% of the nodes contained in the GSCC. All connected components were globally stable over time, at a semester scale.

Communities. The topology of network communities varied with the modelling assumptions. In the AIM approach, a huge geographically dispersed community was found in the whole network, whereas the TM highlighted several small geographically clustered communities (Fig 5).

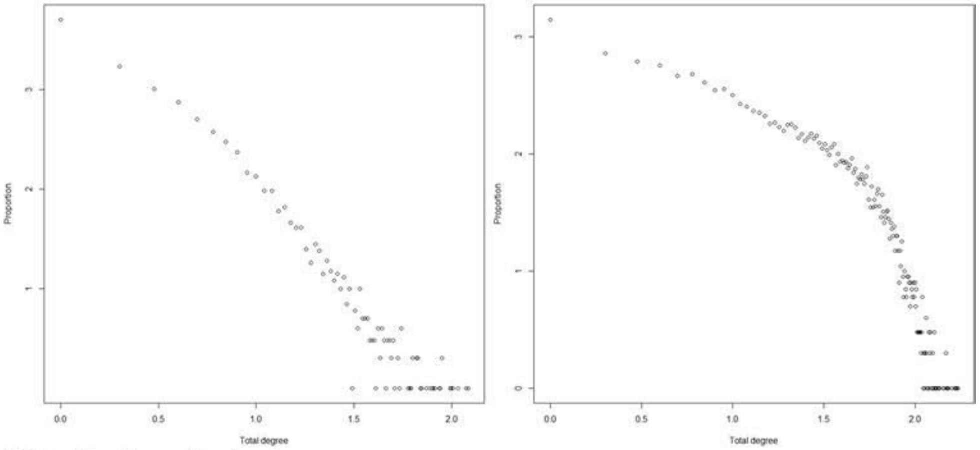
In the breeding farm subnetwork, a similar number of communities was detected using the two different models, but breeding pig communities were geographically more dispersed and contained approximately four times more holdings in the AIM than in the TM (Table 4). In the production farm subnetwork, more communities were detected in the AIM than in the TM, and they gathered twice more farms. Communities were found to be permeable, since at

Table 2. Descriptive indicators of the pig movement network in France (2012–2014) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]) and for three different considered populations (whole network, breeding farm subnetwork, production farm subnetwork).

Whole network																				
Semester	**No. of active nodes**		**No. of links**		**Average degree**		**Average path length**		**Diameter**		**Density ($x10^{-4}$)**		**Clustering coefficient**		**% of pairs of nodes with Jaccard similarity coefficient = 0**		**Assortativity degree**		**Reciprocity ratio**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	11,558	14,166	23,477	137,348	4.06	19.39	2.55	5.78	10	20	1.76	6.84	0.015	0.27	99.59	98.11	-0.079	0.19	0.0045	0.090
2013–1	11,419	14,161	22,969	134,901	4.02	19.05	2.28	5.78	10	20	1.76	6.73	0.015	0.26	99.60	98.12	-0.097	0.17	0.0050	0.090
2013–2	11,223	13,817	22,367	136,235	3.99	19.72	2.36	5.75	11	18	1.77	7.14	0.015	0.27	99.59	98.05	-0.11	0.18	0.0051	0.097
2014–1	11,013	13,784	21,691	132,677	3.94	19.25	2.46	5.88	9	20	1.79	6.98	0.014	0.27	99.60	98.07	-0.085	0.18	0.0061	0.093
2014–2	10,872	13,360	20,842	129,155	3.83	19.33	2.22	5.82	11	21	1.76	7.24	0.013	0.27	99.63	98.00	-0.11	0.20	0.0055	0.094
Breeding farm subnetwork																				
Semester	**No. of active nodes**		**No. of links**		**Average degree**		**Average path length**		**Diameter**		**Density**		**Clustering coefficient**		**% of pairs of nodes with Jaccard similarity coefficient = 0**		**Assortativity degree**		**Reciprocity ratio**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	404	453	703	1,826	3.48	8.06	1.78	6.16	5	20	4.31	8.92	0.035	0.30	94.97	89.64	-0.040	0.15	0.010	0.13
2013–1	396	446	716	1,879	3.62	8.43	1.71	5.92	4	16	4.58	9.47	0.035	0.30	94.12	88.67	-0.038	0.15	0.0042	0.12
2013–2	395	452	648	1,796	3.28	7.95	1.73	7.18	4	21	4.16	8.81	0.031	0.33	95.33	90.86	-0.029	0.18	0.014	0.13
2014–1	401	454	654	1,806	3.26	7.96	1.78	7.56	5	23	4.08	8.78	0.029	0.32	95.25	90.61	-0.047	0.09	0.011	0.13
2014–2	392	445	616	1,753	3.14	7.88	1.73	6.99	5	22	4.02	8.87	0.034	0.35	95.52	90.70	-0.039	0.17	0.0065	0.12
Production farm subnetwork																				
Semester	**No. of active nodes**		**No. of links**		**Average degree**		**Average path length**		**Diameter**		**Density**		**Clustering coefficient**		**% of pairs of nodes with Jaccard similarity coefficient = 0**		**Assortativity degree**		**Reciprocity ratio**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	9,730	12,653	14,243	119,657	2.93	18.91	2.01	6.21	8	23	1.50	7.47	0.019	0.28	99.82	98.18	-0.058	0.27	0.0068	0.10
2013–1	9,561	12,559	13,742	116,842	2.87	18.61	1.64	6.20	7	21	1.50	7.41	0.021	0.27	99.83	98.19	-0.056	0.26	0.0078	0.10
2013–2	9,340	12,193	13,538	118,333	2.90	19.41	1.64	6.09	7	20	1.55	7.96	0.020	0.28	99.83	98.08	-0.017	0.26	0.0074	0.11
2014–1	9,130	12,053	12,895	115,194	2.82	19.11	1.60	6.27	7	22	1.55	7.93	0.017	0.28	99.83	98.06	-0.00074	0.26	0.0089	0.10
2014–2	8,955	11,820	12,675	111,939	2.83	18.94	1.64	6.22	10	21	1.58	8.01	0.016	0.28	99.82	98.01	-0.019	0.28	0.0083	0.10

https://doi.org/10.1371/journal.pone.0185858.t002

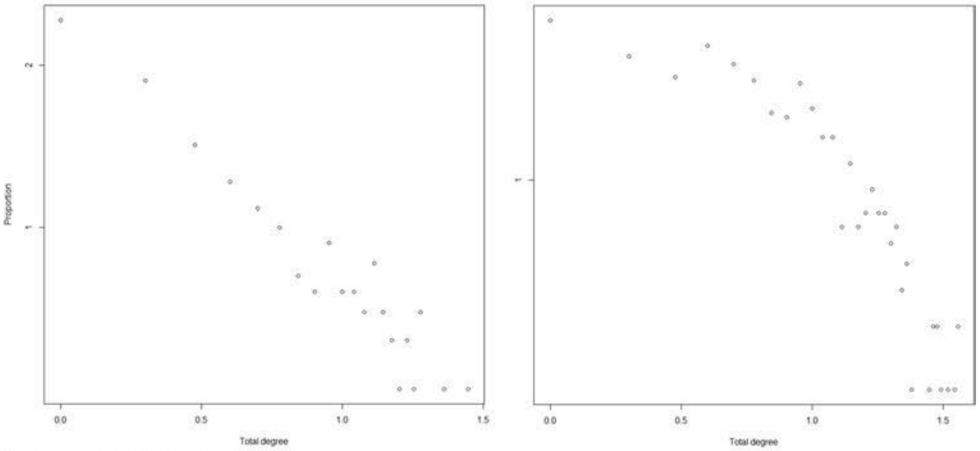
1. Whole network



(a) Animal Introduction Model (AIM)

(b) Transit Model (TM)

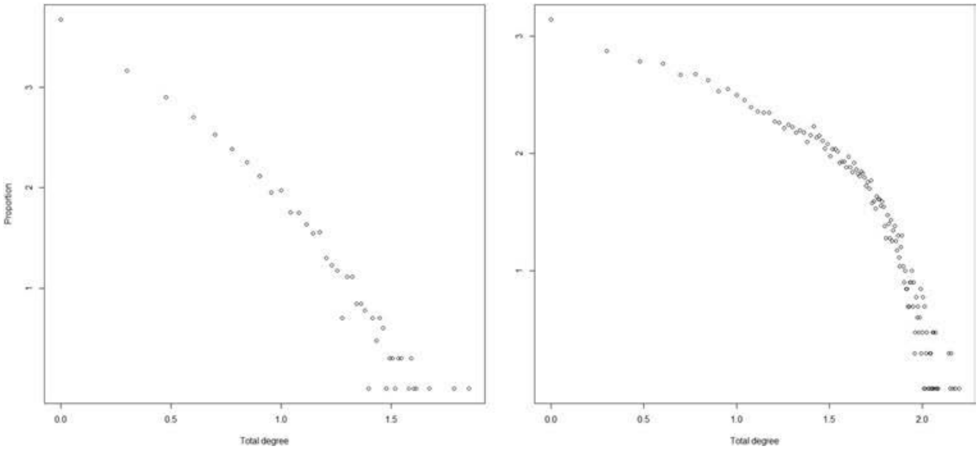
2. Breeding farm subnetwork



(a) Animal Introduction Model (AIM)

(b) Transit Model (TM)

3. Production farm subnetwork



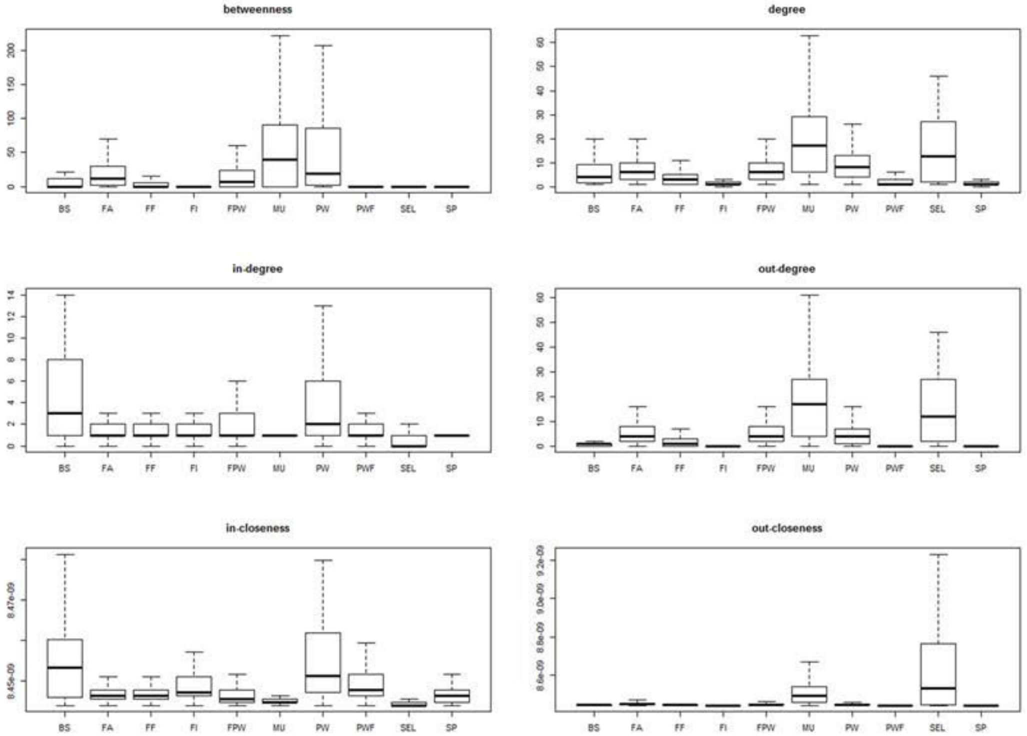
(a) Animal Introduction Model (AIM)

(b) Transit Model (TM)

Fig 3. Distribution of pig farm degrees (log scale) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]) and in three different considered populations (whole network, breeding farm subnetwork, production farm subnetwork) (second half of 2014).

https://doi.org/10.1371/journal.pone.0185858.g003

(a) Animal Introduction Model (AIM)



(b) Transit Model (TM)

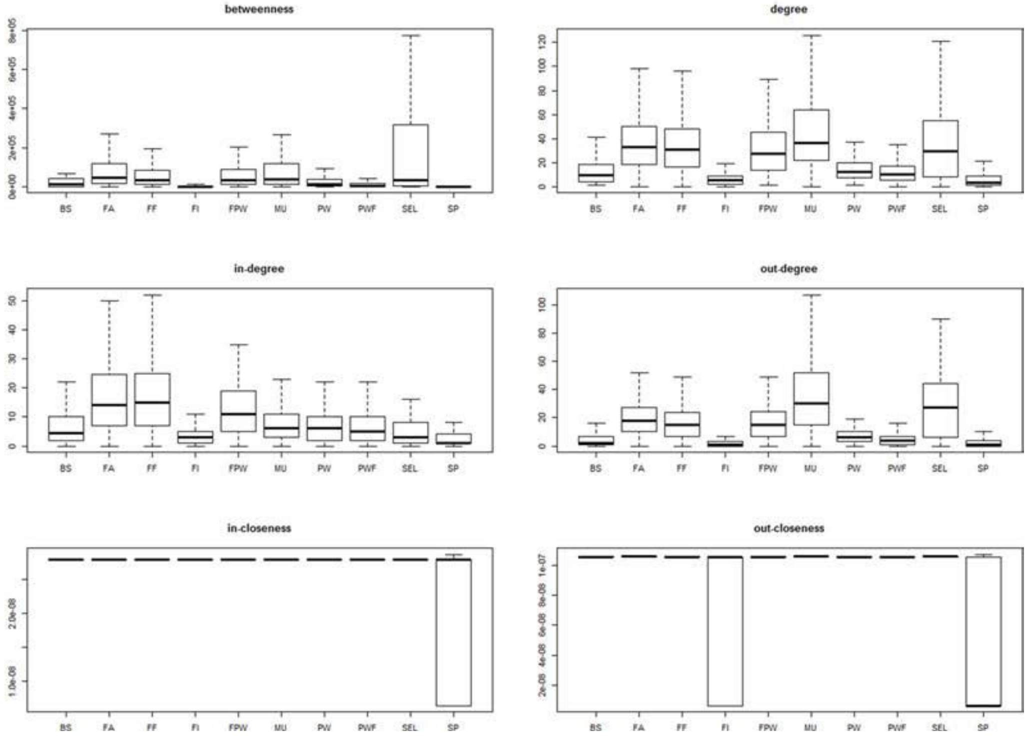


Fig 4. Distribution of degree, betweenness and closeness centralities of pig holdings in France according to different farm categories (second half of 2014) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]). BS: boar station, SEL: nucleus, MU: multiplication, FA: farrowing, FF: farrowing-to-finishing, FI: finishing, FPW: farrowing-post-weaning, PW: post-weaning, PWF: post-weaning-finishing, SP: small producers.

https://doi.org/10.1371/journal.pone.0185858.g004

Table 3. Connected components in the pig movement network in France (2012–2014) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]) and in three different considered populations (whole network, breeding farm subnetwork, production farm subnetwork).

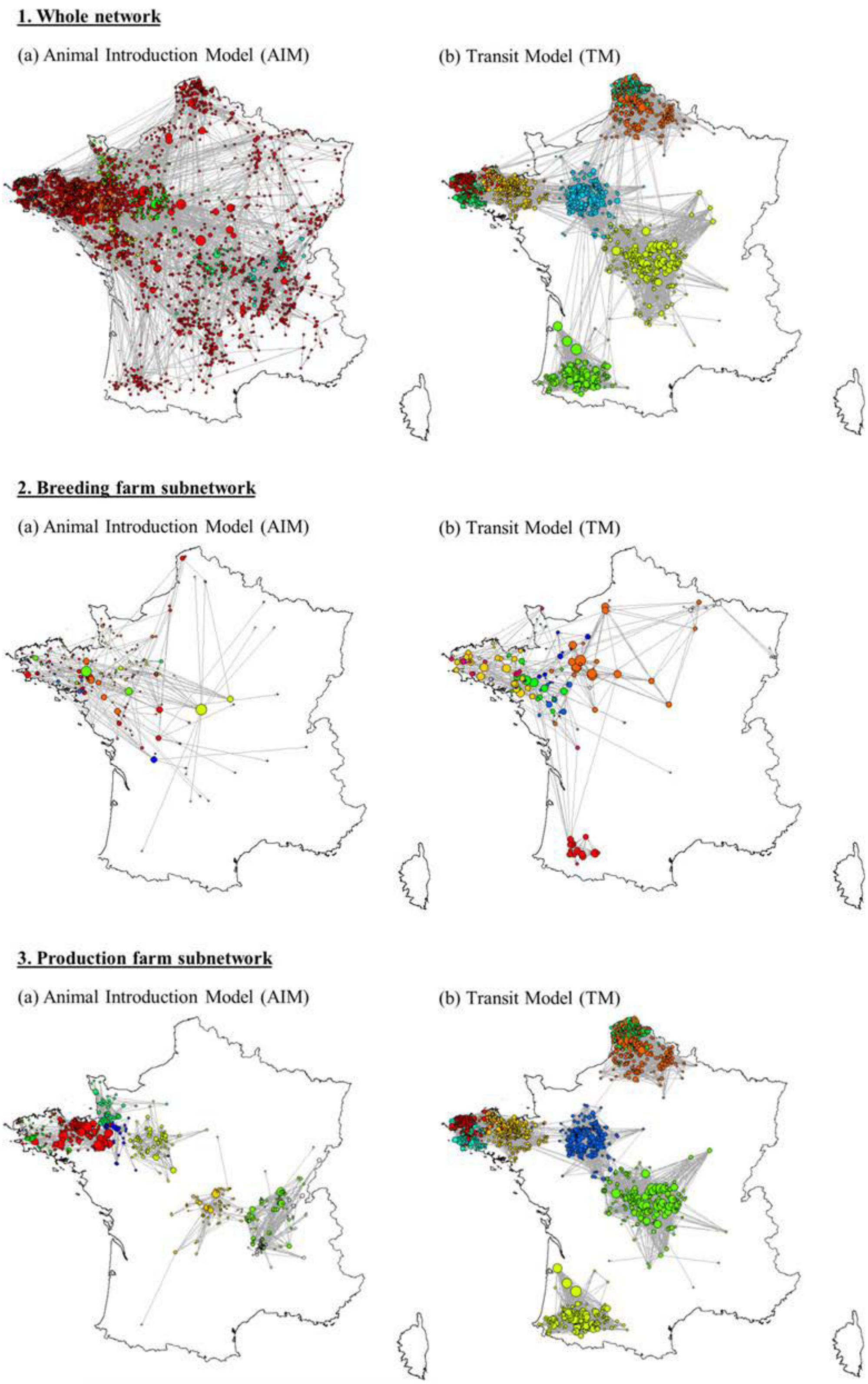
Whole network								
Semester	Weakly connected components (WCCs)				Strongly connected components (SCCs)			
	No. of WCCs		Size of largest WCC (% of active nodes)		No. of SCCs		Size of largest SCC (% of active nodes)	
	AIM	TM	AIM	TM	AIM	TM	AIM	TM
2012–2	226	995	10,885 (94.2%)	13,063 (92.2%)	11,436	4,006	18 (0.2%)	10,075 (71.1%)
2013–1	227	1,091	10,703 (93.7%)	12,970 (91.6%)	11,290	4,087	19 (0.2%)	9,954 (70.3%)
2013–2	211	1,113	10,510 (93.7%)	12,629 (91.4%)	11,089	3,990	24 (0.2%)	9,700 (70.2%)
2014–1	232	1,207	10,261 (93.2%)	12,511 (90.8%)	10,871	4,092	17 (0.2%)	9,542 (69.2%)
2014–2	220	1,045	10,156 (93.4%)	12,182 (91.2%)	10,746	3,851	22 (0.2%)	9,381 (70.2%)
Breeding farm subnetwork								
Semester	**Weakly connected components (WCCs)**				**Strongly connected components (SCCs)**			
	No. of WCCs		**Size of largest WCC (% of active nodes)**		**No. of SCCs**		**Size of largest SCC (% of active nodes)**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	9	6	387 (95.8%)	439 (96.9%)	396	170	3 (0.7%)	254 (56.1%)
2013–1	7	3	382 (96.5%)	441 (98.9%)	393	197	2 (0.5%)	223 (50.0%)
2013–2	14	5	360 (91.14%)	444 (98.2%)	385	174	6 (1.5%)	255 (56.4%)
2014–1	12	5	375 (93.5%)	445 (98.0%)	394	174	3 (0.7%)	242 (53.3%)
2014–2	20	6	321 (81.9%)	435 (97.8%)	388	216	2 (0.5%)	178 (40.0%)
Production farm subnetwork								
Semester	**Weakly connected components (WCCs)**				**Strongly connected components (SCCs)**			
	No. of WCCs		**Size of largest WCC (% of active nodes)**		**No. of SCCs**		**Size of largest SCC (% of active nodes)**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	810	59	7,222 (74.2%)	12,450 (98.4%)	9,623	3,086	18 (0.2%)	9,475 (74.9%)
2013–1	817	65	6,888 (72.0%)	12,385 (98.6%)	9,443	3,040	19 (0.2%)	9,398 (74.8%)
2013–2	844	60	6,546 (70.1%)	12,046 (98.8%)	9,224	2,930	24 (0.3%)	9,130 (74.9%)
2014–1	861	61	6,199 (67.9%)	11,912 (98.8%)	9,008	2,902	17 (0.2%)	9,001 (74.7%)
2014–2	839	80	6,120 (68.3%)	11,593 (98.1%)	8,838	2,869	22 (0.2%)	8,826 (74.7%)

https://doi.org/10.1371/journal.pone.0185858.t003

least 25% of links connected two communities (Table 4). Communities were also found to be stable over the five semesters (maps not shown).

3.2.4. Temporal network analysis. **Link and node preservation.** More than 98% and 77% of nodes remained active during two consecutive semesters in the AIM and in the TM, respectively. Most holdings that were not active from one semester to another were small producers. Only 51% and 36% of links were preserved from one semester to another in the AIM and in the TM, respectively.

Node loyalty. The distribution of loyalty values computed in the AIM showed two peaks in 0 and 1, whereas the TM loyalty distribution was skewed to the right (Fig 6). In both cases, the distributions reflected a diverse range of patterns between establishing new connections versus repeating existing ones. The distributions of loyalty values did not exhibit variation moving along consecutive time windows (data not shown). The 0 and 1 loyalty values corresponded to low degree nodes for which few loyalty values are available, given the loyalty definition. Node degree and node loyalty were found to be correlated in both network models (Pearson correlation coefficient p-value < 0.001).



1. Whole network

(a) Animal Introduction Model (AIM)

(b) Transit Model (TM)

2. Breeding farm subnetwork

(a) Animal Introduction Model (AIM)

(b) Transit Model (TM)

3. Production farm subnetwork

(a) Animal Introduction Model (AIM)

(b) Transit Model (TM)

Fig 5. Mapping of the eight largest communities in the pig movement network in France (second half of 2014) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]) and in three different considered populations (whole network, breeding farm subnetwork, production farm subnetwork).

https://doi.org/10.1371/journal.pone.0185858.g005

Table 4. Communities in the pig movement network in France (2012–2014) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]) and in three different concerned populations (whole network, breeding farm subnetwork, production farm subnetwork).

Whole network						
Semester	**No. of communities**		**Size of largest community (% of active nodes)**		**No. of crossing links (% of total no. of links)**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	1,673	1,816	3,079 (26.6%)	417 (2.9%)	9,541 (40.6%)	47,143 (34.3%)
2013–1	1,653	1,937	3,283 (28.8%)	384 (2.7%)	9,249 (40.3%)	45,980 (34.1%)
2013–2	1,573	1,957	3,344 (29.8%)	393 (2.8%)	8,758 (39.2%)	45,241 (33.2%)
2014–1	1,553	2,073	3,326 (30.2%)	363 (2.6%)	8,511 (39.2%)	43,628 (32.9%)
2014–2	1,523	1,874	3,338 (30.7%)	351 (2.6%)	8,013 (38.4%)	43,289 (33.5%)
Breeding farm subnetwork						
Semester	**No. of communities**		**Size of largest community (% of active nodes)**		**No. of crossing links (% of total no. of links)**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	73	70	81 (20.0%)	21 (4.6%)	303 (43.1%)	857 (46.9%)
2013–1	60	72	162 (40.9%)	32 (7.2%)	311 (43.4%)	831 (44.2%)
2013–2	66	71	152 (38.5%)	37 (8.2%)	236 (36.4%)	682 (38.0%)
2014–1	66	71	174 (43.4%)	21 (4.6%)	239 (36.5%)	739 (40.9%)
2014–2	75	66	66 (16.8%)	31 (7.0%)	254 (41.2%)	645 (36.8%)
Production farm subnetwork						
Semester	**No. of communities**		**Size of largest community (% of active nodes)**		**No. of crossing links (% of total no. of links)**	
	AIM	**TM**	**AIM**	**TM**	**AIM**	**TM**
2012–2	1,802	825	123 (1.3%)	407 (3.2%)	3,999 (28.1%)	38,452 (32.1%)
2013–1	1,787	863	178 (1.9%)	388 (3.1%)	3,655 (26.6%)	37,007 (31.7%)
2013–2	1,705	848	175 (1.9%)	337 (2.8%)	3,420 (25.3%)	37,181 (31.4%)
2014–1	1,684	872	136 (1.5%)	351 (2.9%)	3,335 (25.9%)	35,625 (30.9%)
2014–2	1,653	874	181 (2.0%)	335 (2.8%)	3,217 (25.4%)	34,996 (31.3%)

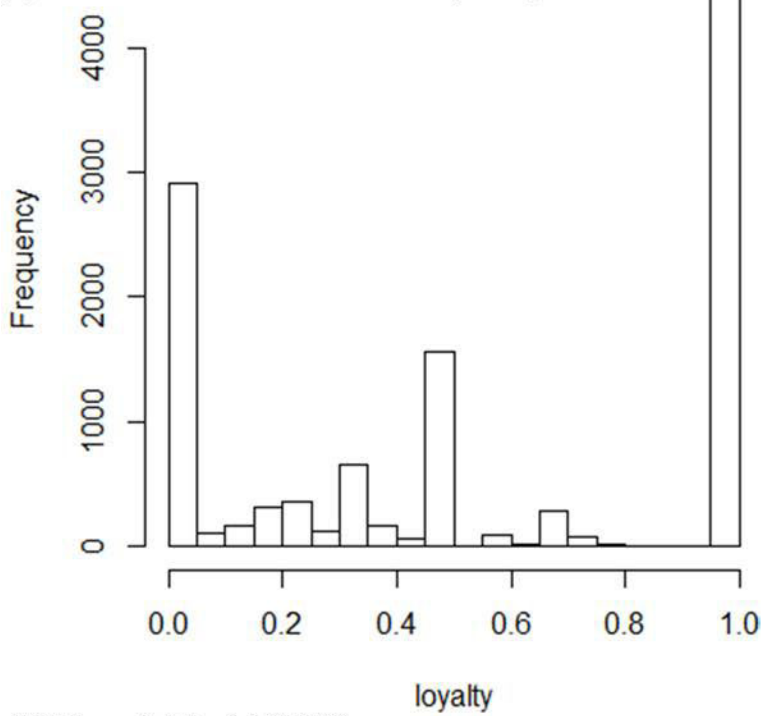
https://doi.org/10.1371/journal.pone.0185858.t004

Ingoing and outgoing contact chains. Ingoing and outgoing contact chains computed over a one-month period exhibited different distributions depending on the network model and the farm type (Fig 7). The TM contact chain figures were much higher than the AIM ones. In the AIM and in the TM, nucleus and multiplication farms showed a larger OCC than other farm types. In the TM, the ICC was found to be higher for production farms than for the other holding types. The contact chain distributions computed over one-month periods were stable over time (data not shown).

4. Discussion

Exploring the topology of animal movements provides insights into disease epidemiology and gives the opportunity to implement targeted surveillance strategies and control measures. The primary interest of our study lies in building pig movement network models adapted to the epidemiological features of pathogens, in particular to their transmission route. To our knowledge, most studies in the literature only took into account direct movements of animal introduction or built two-mode networks that cannot be explored as deeply as one-mode ones [2, 6, 8, 9, 21, 27]. Only a few studies mentioned the role of trucks, material, visitors or staff as potential indirect vectors, or explored the issue of shared trucks [19, 21]. Truck transit movements may nevertheless play a central role in the transmission of highly contagious diseases such as

(a) Animal Introduction Model (AIM)



(b) Transit Model (TM)

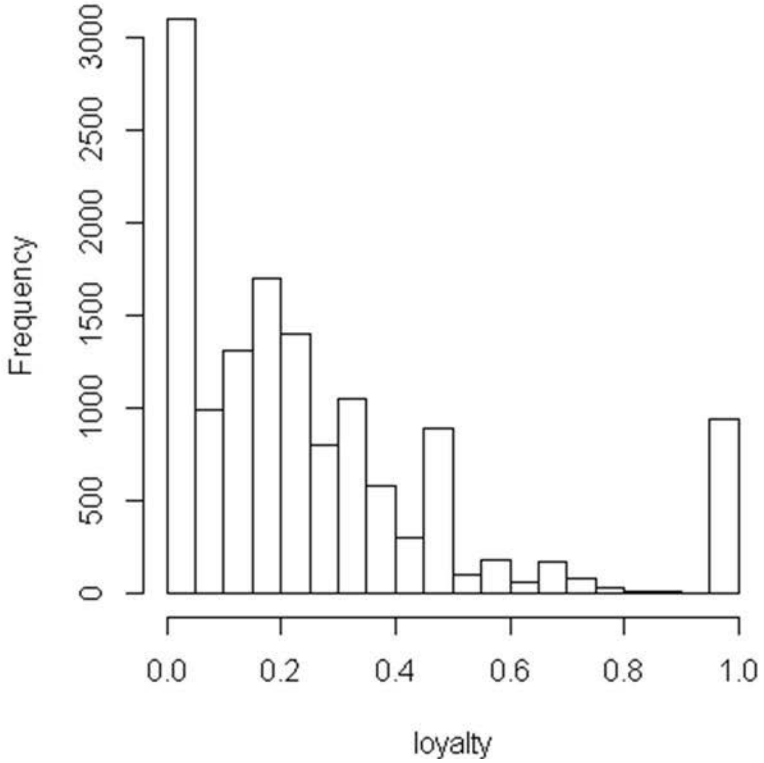
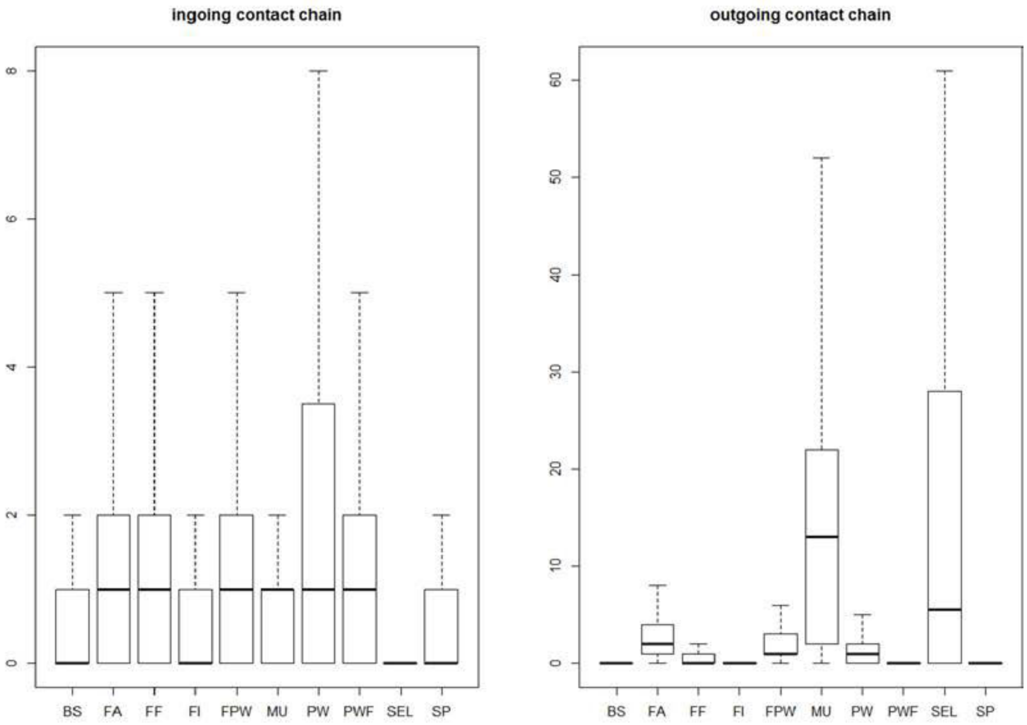


Fig 6. Node loyalty distributions in the pig movement network in France (second half of 2012 / first half of 2013) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]).

https://doi.org/10.1371/journal.pone.0185858.g006

(a) Animal Introduction Model (AIM)



(b) Transit Model (TM)

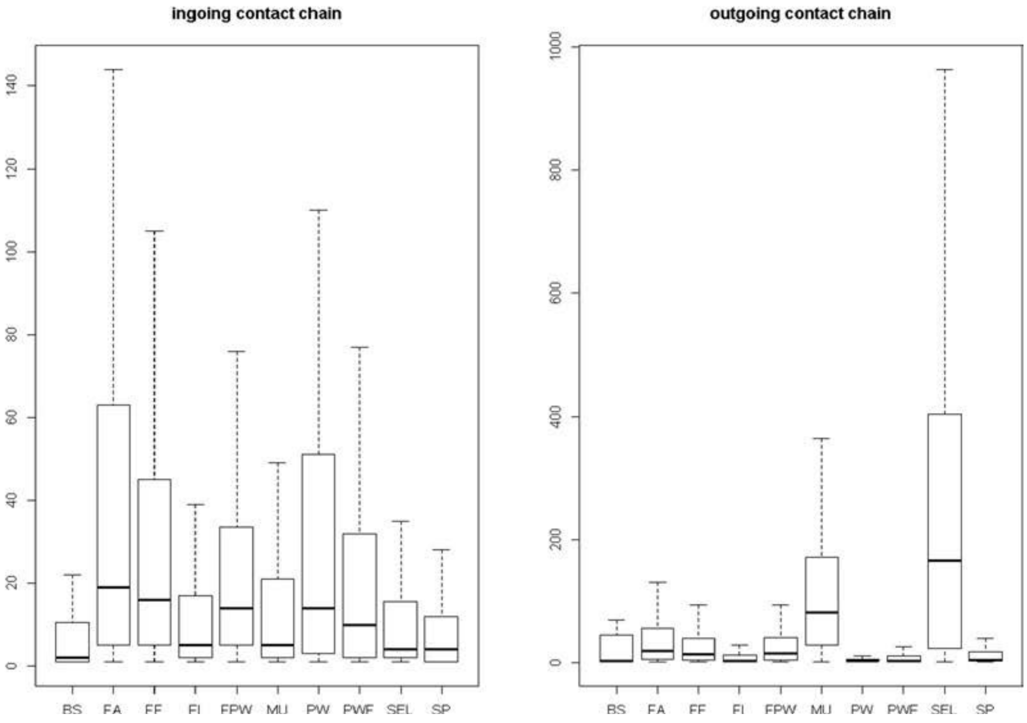


Fig 7. Distribution of ingoing and outgoing contact chains of pig holdings in France according to different farm categories (1 to 31 December 2014) using the two different network models (Animal Introduction Model [AIM] and Transit Model [TM]). BS: boar station, SEL: nucleus, MU: multiplication, FA: farrowing, FF: farrowing-to-finishing, FI: finishing, FPW: farrowing-post-weaning, PW: post-weaning, PWF: post-weaning-finishing, SP: small producers.

https://doi.org/10.1371/journal.pone.0185858.g007

ASF, PED, and FMD. The pig production sector is organised in a pyramidal way: at the top, nucleus farms provide purebred sows and boars to multiplication farms, which produce crossbred pigs and gilts to supply production farms, producing pigs for slaughter. Assuming that this specific structure leads to a particular topology of the movement network, we performed a multi-scale analysis suiting the pyramidal organisation: we analysed both the whole network and two subnetworks containing (1) only the breeding farms (nucleus, multipliers, and boar stations); and (2) only the production farms (from farrowers to finishers). Our network analysis did not account for movements to slaughterhouses, as they are considered as an epidemiological dead-end. Because several studies have proven that trade in the pig production sector does not show any seasonal pattern in France [2, 7, 23, 27, 28], we analysed the network at a semester scale. This temporal scale was considered appropriate to reflect the global trade behaviour of farms while making it possible to observe evolutions over the study period. Our two models were applied to all movement data recorded in France from June 2012 to December 2014 in the National Swine Identification Database (BDporc). The information provided by this database is managed by swine industry professionals, is recognised by the French Ministry for Agriculture, and can therefore be considered trustworthy. Moreover, a thorough cleaning stage was carried out to manage incorrect or incomplete data. This kind of electronic data is also more accurate than movements reported in questionnaires [34]. An even more accurate alternative would be to use GPS (Global Positioning System) to geographically locate trucks and precisely track their movements, but this would require the approval of transportation operators to share this kind of data, as well as advanced analytical methods to manage such data. In contrast with other studies that were limited to a single region or a sample of voluntary farms or to a short period of time [6, 9, 21], we used recent data from the whole country and covering a long period of time. Finally, the quality of data–in terms of accuracy, reliability, and comprehensiveness–guarantees the robustness of our results.

The analysis of movements over the study period showed a decline in the number of rounds, while the number of animals moved per round increased, leading to an overall slight decrease in animal trade movements, which was also reported in other European studies [8]. This is consistent with the intensification of the pig production industry (that is to say a decrease in the number of pig farms balanced by an increase in the number of animals reared), resulting in the observation of fewer movements involving larger pig batches. The level of round complexity was highly heterogeneous, the average number of holdings implied in a round being 2.5 but reaching 32. This is consistent with the distance travelled by pigs in a round (excluding foreign movements), ranging from 0 to 1,000 km. The distances reported in our study are longer than in other European countries such as Belgium or England/Wales [8, 19], in accordance with the results of the comparative study conducted by Relun et al. [23]. The longest and most complex rounds implied culled boar/sows and breeding pigs. They were mainly located in central and south-western France where the production is less intensive and rounds are thus composed of several movements of small batches. Movements from/to foreign countries represent a small fraction of the pig trade in France and are linked to specific markets, but they are nevertheless important to take into consideration in order to prevent the introduction of a disease that is absent from France (e.g. FMD, ASF, PED).

Whatever the modelling approach, network structure properties exhibited overall stability over the study period: *(i)* at a semester scale, active nodes globally remained the same from one semester to another, except for small production farms; *(ii)* network metrics were similar from one semester to another; and *(iii)* connected components and communities were also stable over the study period. This stability of the pig production network has already been described in several papers [8, 23, 27] and enables us to generalise the findings of our study to the current swine trade network. However, loyalty distributions showed relative volatility of farms' trade partners, indicating that future links may be difficult to predict. The same trend has already been described in a cattle movement network [35].

Our two network models exhibited two classical patterns of connectivity described in other studies [2, 6, 8, 9, 21, 23, 28], known as *(i)* small-world, and *(ii)* scale-free topologies. *(i)* Whatever the model, our networks had higher clustering coefficients and shorter or similar average path length than random graphs of the same size (corresponding to a small-world topology) [36, 37]. This means that most nodes are not directly connected to each other but can be reached through a small number of connections. This allows diseases to spread quickly within clusters but also to reach other clusters in the network by crossing a few links. This topology facilitates persistent infection in the pig population but the size of an epidemic in a small-world network tends to be smaller when compared to a random network. *(ii)* The holdings' degree in both networks showed power-law-like behaviour (heavy tailed distribution), meaning that many of the nodes had few connections while a few nodes had many connections (corresponding to a scale-free structure) [38]. This indicates the presence of highly connected nodes, i.e. of hubs, that are of central importance with regard to disease spread (also called super-spreaders). Epidemics can therefore spread faster in scale-free networks than in random ones. Scale-free networks can withstand random attacks but are highly vulnerable to targeted attacks towards the hubs [11, 39, 40].

Size, degree and distance metrics (average path length, diameter, density) observed in the AIM are consistent with the literature data, especially for the pig movement networks in France [23, 41]. As expected, given the model assumptions, these values increased when switching from the AIM to the TM. The differential modelling approach affected more production farms than breeding farms, suggesting that production farms may play a key role in the spread of indirectly transmitted diseases. The assortativity degree of the AIM was negative, in accordance with the results of previous studies [6, 7, 10]. However, the TM network was found to be assortative. According to [42], disassortative networks are particularly sensitive to the removal of high-degree farms since they are dispersed over the whole network. Thus, fewer holdings have to be removed to destroy the largest component compared to a network with positive assortativity degree. Like in Thakur et al. [21], the reciprocity ratio was very low, reflecting the pyramidal structure of the pig production sector with unidirectional links going from the top breeding farms to the bottom production farms. Similarly, the Jaccard similarity coefficient was zero for almost all pairs of nodes, showing that movements occurred mainly between different farm types.

Centrality values within a farm type were highly heterogeneous (except for closeness centrality, see below). In the AIM network, the high out-degree distributions observed for breeding farms compared with production farms is in accordance with previously published papers [6, 10, 21] and with the pyramidal structure of pig production. It shows their potential key role in disease spread to the whole network in case of introduction of the disease to this kind of farm. Their high betweenness score also proves that disease surveillance should be primarily directed towards these units. Indeed, holdings with a high betweenness centrality could build so-called bridges between different network components. Removing these specific holdings would fragment the network. In the TM network, farrow and farrow-to-finish farms exhibited high in-degree distribution, whereas post-weaners had the highest in-degree values in the AIM. This results in a similar total degree for farrow, farrow-to-finish, nucleus and multiplication farms in the TM. This could be explained by the fact that farrow and farrow-to-finish farms were part of more complex rounds involving more truck transit movements. It shows that farrow and farrow-to-finish farms are more vulnerable to the introduction of diseases for which indirect transmission can occur, and that surveillance measures specific to these diseases should target these farm categories. In the AIM, post-weaning and post-weaning—finishing farms exhibited the highest median ingoing closeness, which is consistent with the literature [10]. A high value for ingoing closeness centrality implies that the trade partners of a specific holding can reach the node in only a few movements. In the AIM, nucleus and multiplication farms had the highest median outgoing closeness [10]. High outgoing closeness means that a seller reaches its client in only a few steps. Thus, holdings with high outgoing closeness centrality can spread a pathogen in the production network faster. The distributions of the ingoing and outgoing closeness centralities were not highly informative in the TM because their range was too small. As explained in [43], the small range of closeness values implies that slight changes in the network structure greatly affect the ranking of farms according to the closeness centrality. Being used as additional information to the more powerful centrality parameters (see above) [10], closeness centrality is therefore not considered as the most appropriate measure for the detection of central holdings in a trade network, especially in terms of animal disease control and risk-based surveillance.

In both models, few WCCs were observed, the largest one containing around 90% of farms. This is consistent with the literature [6, 21, 27]. Like in previously published papers [6, 28], the AIM exhibited a high number of small SCCs, the largest one containing only 1% of farms. On the contrary, the TM network was less fragmented, with a low number of SCCs and the presence of a giant SCC joining 70% of farms. This is consistent with the clustering coefficient being ten times higher in the TM than in the AIM, reflecting a gathering trend. The GSCC disappeared when removing farrow and farrow-to-finish farms, showing their central role in TM network cohesion.

Community structures in networks are densely connected subgroups of nodes. Identification of communities in a trade network shows which holdings are preferentially linked. We looked for communities in both models of the swine trade network thanks to the Infomap algorithm. To our knowledge, this method has never been used in previous papers studying animal movements, although it is the only one applicable to directed networks and considered one of the best in terms of performance [30, 31]. The topology of the detected communities varied with the modelling approach: in the AIM, we detected one huge geographically dispersed community, while the TM exhibited several small geographically clustered communities. The topology of communities detected in the AIM is rather consistent with the literature, reporting communities forming spatial clusters and tending to cover quite large areas [6, 8, 23]. When considering the two subnetworks, the AIM breeding farm subnetwork presented larger communities than the TM one, whereas the AIM production farm subnetwork contained smaller communities than the TM one. Although these communities are permeable and crossing links can act as potential bridges for disease spread from one community to another, community borders could be used to define geographical compartments. Compartmentalisation can be an effective strategy for controlling disease epidemics while minimising disruption to trade business [8, 23]. Stopping disease spread within a community would reduce the probability of pathogen transfer to a connected community. Our results show that geographical compartmentalisation would be easier to limit the introduction of a disease transmitted through the indirect route than for a disease transmitted through animal introduction.

Timely movement tracking is of major interest to understand the origin of the pathogen introduction and the potential spread through downstream contacts. This is the reason why ingoing and outgoing contact chains were computed. The choice of a one-month duration period reflects the time needed to detect the occurrence of a disease and has been discussed in several papers [21, 27]. As expected, the ICC and OCC values were much higher in the TM than in the AIM, showing that the potential epidemic size would be larger for an indirectly transmitted disease than for a directly transmitted pathogen. Moreover, the AIM OCC was higher for breeding farms than for production ones, in line with their key role in the spread of a directly transmitted disease. In the TM, the ICC was higher for production farms, showing their vulnerability to indirectly transmitted disease. These results are in accordance with the other centrality measures (see above) and, for the AIM, with previously published papers [21, 27].

5. Conclusion

The primary interest of our study lies in developing, analysing and comparing two one-mode pig trade network models matching the transmission route of pathogens. From a modelling point of view, our data could be used to parametrise other models, such as exponential random graph models (ERGMs) aiming at explaining network structure [23, 44]. Our network models could also be coupled with epidemiological models of pathogen transmission within herds, this combination resulting in a between-herd epidemiological model. This kind of model would be particularly useful to understand or to assess the persistence and/or spread of a disease in a production sector. From a more operational perspective, our network models have produced useful outputs that can help to design risk-based disease surveillance and control programmes adapted to disease characteristics. They bring to light the relevance of accounting for transit movements to understand the indirect transmission of diseases. Depending on the epidemiological context, the potential epidemic size and the pathogen spread pattern would differ, as do the type of farming units that have to be targeted and the scale at which control measures should be implemented.

Author contributions

MS performed network analysis and drafted the manuscript. MA cleaned the database, designed the network models and supervised network analysis. NR initiated and coordinated the project. All co-authors revised the manuscript and approved the final submitted version.

Supporting information

S1 Table. Pig movements within France from June 2012 to December 2014 at a semester scale.
(DOCX)

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II. Combiner l’analyse de réseau et des données épidémiologiques pour définir des pistes de surveillance basée sur le risque

La structure particulière du réseau des mouvements de porcs analysé dans la publication ci-dessus montre la capacité des échanges de porcs à permettre la diffusion des pathogènes sur le territoire français. C’est dans ce contexte qu’une **méthode quantitative combinant analyse de réseau et données épidémiologiques** a été développée. Cette approche a permis de quantifier le rôle des mouvements d’animaux sur le risque lié au HEV à deux échelles : tout d’abord en mesurant l’**impact des mouvements d’animaux sur la prévalence du HEV dans les élevages**, puis en évaluant le **risque pour les départements français d’être exposés au HEV du fait de mouvements en provenance de départements infectés**. Outre les informations qu’elle apporte sur le risque HEV lié aux mouvements d’animaux, cette méthode a comme avantage d’être générique et ainsi **transposable à tout autre pathogène d’intérêt** pour la filière de production porcine.

Ce travail a donné lieu à une publication dans le journal *Preventive Veterinary Medicine* (Salines *et al.*, 2018a) ainsi qu’à un article associé à une communication orale aux *Journées Recherche Porcine* (Annexe 7) (Salines *et al.*, 2018b).

Publication 8

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Combining network analysis with epidemiological data to inform risk-based surveillance: Application to hepatitis E virus (HEV) in pigs

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ABSTRACT

Animal movements between farms are a major route of pathogen spread in the pig production sector. This study aimed to pair network analysis and epidemiological data in order to evaluate the impact of animal movements on pathogen prevalence in farms and assess the risk of local areas being exposed to diseases due to incoming movements. Our methodology was applied to hepatitis E virus (HEV), an emerging foodborne zoonotic agent of concern that is highly prevalent in pig farms. Firstly, the pig movement network in France (data recorded in 2013) and the results of a nation-wide seroprevalence study (data collected in 178 farms in 2009) were modelled and analysed. The link between network centrality measures of farms and HEV seroprevalence levels was explored using a generalised linear model. The in-degree and ingoing closeness of farms were found to be statistically associated with high HEV within-farm seroprevalence ($p < 0.05$). Secondly, the risk of a French *département* (i.e. French local administrative areas) being exposed to HEV was calculated by combining the distribution of farm-level HEV prevalence in source *départements* with the number of movements coming from those same *départements*. By doing so, the risk of exposure for *départements* was mapped, highlighting differences between geographical patterns of HEV prevalence and the risk of exposure to HEV. These results suggest that not only highly prevalent areas but also those having at-risk movements from infected areas should be monitored. Pathogen management and surveillance options in the pig production sector should therefore take animal movements into consideration, paving the way for the development of targeted and risk-based disease surveillance strategies.

1. Introduction

Developing risk-based surveillance programmes for animal diseases is essential to support both strategic and operational decision-making in the field of animal and veterinary public health (Reist et al., 2012). Indeed, mobilising resources towards targeted high-risk populations improves the sensitivity and cost-effectiveness of surveillance systems (Stärk et al., 2006). The sub-populations to be targeted are usually chosen based on epidemiological studies assessing the probability of occurrence of the hazard in the sub-population (e.g. farms with specific risk factors) and/or the consequences of the disease potentially being introduced in this sub-population (e.g. economic effects, spread to other herds or countries) (Stärk et al., 2006). However, most current pathogen surveillance programmes do not quantitatively include the risk related to animal movements, even though these are a major transmission route between farms. The exposure of farms or areas to pathogens is therefore closely related to the movement network's features. As such, animal movement data have been increasingly studied using social network analysis (SNA) methods, with farms being considered as nodes, and animal movements between farms as links (Wasserman and Faust, 1994; Bigras-Poulin et al., 2006; Bigras-Poulin et al., 2007; Martínez-López et al., 2009; Natale et al., 2009; Ribbens et al., 2009; Nöremark et al., 2011; Lindstrom et al., 2012; Rautureau et al., 2012; Buttner et al., 2013; Dorjee et al., 2013; Guinat et al., 2016; Thakur et al., 2016). Although in most studies network analyses have been motivated by the consequences of animal trade on the epidemiology of animal diseases (Keeling, 2005; Lloyd-Smith et al., 2005; Bigras-Poulin et al., 2007; Martínez-López et al., 2009; Rautureau et al., 2012; Buttner et al., 2013), the specific role of animal shipments in pathogen transmission and/or exposure has only scarcely been documented and rarely quantified, especially in the swine sector (Ortiz-Pelaez et al., 2006; Green et al., 2008; Martin et al., 2011; Porphyre et al., 2011; Frössling et al., 2012; Nicolas et al., 2013; Beaunee et al., 2015; Lee et al., 2017; Salines et al., 2017b; Sintayehu et al., 2017). Analysing contact patterns related to pig trade could provide new insight into infection dynamics, pathogen spread and risk factors, helping to design risk-based

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surveillance programmes.

Hepatitis E is an emerging foodborne zoonosis of concern for which pigs have been recognised as a major reservoir in industrialised countries (Dalton et al., 2008; Pavio et al., 2010; Adlhoch et al., 2016; EFSA et al., 2017). Indeed, several human hepatitis E cases have been related to the consumption of raw or undercooked products containing pig liver (Colson et al., 2010; Moal et al., 2012; Motte et al., 2012). HEV is highly prevalent in pig farms and is likely to spread between farms through the introduction of infected pigs, especially due to the pyramidal structure of the pig production sector (Salines et al., 2017a). To date, no continuing HEV surveillance programmes have ever been implemented in industrialised countries (Salines et al., 2017a).

The aim of our study was therefore to combine network analysis with disease epidemiology and propose methods to quantify the epidemiological role of animal movements on two different scales: firstly by measuring the impact of animal movements on pathogen prevalence at the farm level; and secondly by assessing the risk of French *départements*[1] being exposed to diseases due to incoming movements from infected areas. Our methodology was applied to hepatitis E virus (HEV) in the pig production sector.

2. Materials and methods

2.1. Data

2.1.1. Movement data

2.1.1.1. Pig movement database. As described by Salines et al. (2017b), pig movement data were obtained from the National Swine Identification Database (BDporc), managed by swine industry professionals and recognised by the French Ministry for Agriculture. All pig movements between farms and to slaughterhouses, rendering plants and trade operators are systematically recorded in this database. Movements of pigs are reported at the batch level: groups of animals are sent off production sites (loadings, further denoted L) and dispatched either to other production units or to slaughterhouses (unloadings, further denoted U). A single truck can load and unload animals at several production sites: one round corresponds to a series of movements by a truck, from the first loading operation to the last unloading event leaving the truck empty.

2.1.1.2. Design of the movement network (Fig. 1). Movement data recorded from January to December 2013 were modelled into a one-mode directed network aggregated on a one-year basis: holdings were considered as nodes, and movements between two nodes were considered as directed links. All movements between two given holdings during the time period were aggregated into a single link. In-between movements forming a round were replaced with direct movements between holdings, meaning that intermediate transit movements by a truck through a farm without any animal unloading were excluded. All sites corresponding to unloading operations were assumed to be linked to all prior loading sites for the same round. For example, assuming successive loadings at sites L1 and L2 followed by an unloading operation at site U1, then holding U1 was linked to L1 and L2.

2.2. Prevalence data

As described by Rose et al. (2011), a nation-wide study was undertaken in 2009 to collect representative HEV prevalence data accounting for the production level diversity throughout the country. In short, previous data had indicated a farm-level prevalence close to 70% (Rose et al., 2010); the number of herds required to estimate 70% with 10% relative precision and 95% confidence, was 165. This number was increased to 186 to anticipate uncontrolled events. The herds to be sampled were determined by random selection of a list of slaughter dates and times from a database table. The observed minimum within-herd prevalence in this same preliminary study was close to 10% (Rose et al., 2010) and this value was retained as the minimum within-herd target prevalence to be detected. Given the sensitivity and specificity of the commercial serological tests (Rose et al., 2010), this led to sampling of 30 pigs in batches with less than 50 pigs, 40 pigs in batches of 50–100 pigs and 50 pigs in batches with more than 100 pigs. Finally, 6565 sera and 3715 livers were randomly sampled from 186 pig farms located in 49 different French *départements*, corresponding to between 26 and 42 individual serum samples per farm and between 16 and 20 liver samples per farm collected at the slaughterhouse. Serum samples were tested with the anti-HEV total immunoglobulin for human diagnosis, EIAgen HEV Ab Kit® by Adaltis (Ingen, France) adapted to pig serum.

2.3. Statistical analyses

2.3.1. Farm centrality indicators and within-farm HEV seroprevalence

2.3.1.1. Farm centrality indicators. Only 178 farms out of the 186 sampled in the prevalence study were recorded in the movement database. Using the pig movement network, several centrality measures were calculated for each of the 178 farms: the *in-degree*, i.e. the number of different holdings from which a holding receives animals; the *out-degree*, i.e. the number of different holdings to which a holding sends animals; the *ingoing and outgoing closeness*, which focus on how close a farm is to all the others in the network through incoming or outgoing links; the *betweenness*, i.e. the number of geodesics going through a node; the average monthly *ingoing contact chain* (ICC), i.e. the number of holdings in contact with a given holding (called the root) through time-respecting paths reaching the root within a month; the average monthly *outgoing contact chain* (OCC), i.e. the number of holdings in contact with a root through time-respecting movements of animals leaving the root within a month; and the *node loyalty*, measuring the fraction of preserved links of a node for a pair of two consecutive network configurations over time, with the time window in our case being a half-year. All continuous variables were categorised according to the form of their distribution, with categories containing at least 10% of the sample size.

2.3.1.2. Within-farm HEV seroprevalence. The HEV seroprevalence of each of the 178 farms was defined as the number of HEV-seropositive pigs in relation to the total number of pigs sampled in the farm. The individual sensitivity and specificity of the test (Rose et al., 2010) were used to correct the apparent seroprevalence estimates (Rogan and Gladen, 1978).

2.3.1.3. Statistical model. A univariable analysis was conducted to assess the statistical link between each explanatory variable (i.e. the farms' centrality metrics) and the outcome (i.e. the unbiased within-farm HEV seroprevalence). To do so, a generalised estimating equation (GEE) logistic regression was performed using Proc GENMOD in SAS 9.4. with the "farm" effect being included as a repeated statement (SAS, 2014). Factors associated with the outcome ($p < 0.20$) were then subjected to bivariable analysis. The objective was to identify strong correlations between each explanatory variable to prevent multicollinearity. If variables did not show strong collinearity ($p > 0.05$), they were included in a multivariable model. We also investigated the role of farm type as a potential confounding factor, by testing the link between farm type and the explanatory variables and the outcome with chi-squared tests and logistic regression, respectively.

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[1] In France, départements are local administrative areas corresponding to NUTS level 3 (Nomenclature of Territorial Units for Statistics).

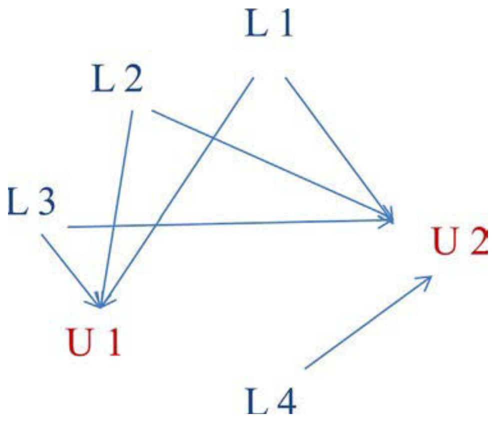

Fig. 1. Design of the network model representing pig movements in France in 2013. Nodes L and U correspond to holdings where loading and unloading operations occurred, respectively. The number corresponds to the chronology of animal collection by a truck in one round. Movements forming a round were replaced with direct movements between holdings, meaning that intermediate transit movements by a truck through a farm without unloading any animals were excluded.

2.4. Indicator of risk of exposure to HEV of French départements

2.4.1. Pig movements at département level

For each *département*, the number of pig shipments coming from each of the other *départements* in 2013 was calculated.

2.4.1.1. Departmental farm-level HEV seroprevalence (Fig. 2). HEV prevalence was defined at the *département* level as the number of farms having at least one HEV-seropositive pig out of the total number of farms sampled in the *département*. The standard deviation for farm-level HEV prevalence was calculated thanks to an exact binomial test and weighted with a correction factor reflecting the sampling rate (i.e. the proportion of sampled farms among the total number of farms in the *département*). For each of the 49 *départements* where data were available, uncertainty regarding the farm-level HEV prevalence estimate was represented by a beta distribution using the estimate and the confidence interval to define the parameters of the distribution ().

2.4.1.2. Estimation of the risk of exposure at departmental level. An indicator of the risk of a *département* being exposed to HEV was computed as follows: first, for each *département*, an HEV farm-level prevalence value was randomly sampled from the beta distribution; the corresponding number of HEV-positive farms in the *département* was then derived from this selected prevalence value and the individual status of the herds was randomly assigned. Source herds were then randomly selected according to the actual number of movements leaving the source *département*, leading to a number of infected outgoing movements. Lastly, the indicator of the risk of a *département* being exposed to HEV was calculated as the number of positive movements it had received from source *départements* divided by its total number of external incoming movements. To stabilise the outputs of the procedure, the whole calculation was repeated 10,000 times, resulting in a risk distribution of HEV exposure for each *département*. The exposure risk model was implemented in R (Ihaka, 1996).

3. Results

3.1. Farm centrality indicators and within-farm HEV seroprevalence

The farms' mean in- and out-degrees were 2.46 (range: 0–22) and 5.14 (range: 0–134), respectively. Mean ingoing and outgoing closeness were $2.17.10^{-9}$ and $2.18.10^{-9}$, respectively, with little variability. Mean betweenness was 27.06 (range: 0–1439). Mean monthly ingoing and outgoing contact chains were 0.98 (range: 0–5) and 1.15 (range: 0–29), respectively. Mean node loyalty was 0.65 (range: 0–1). In the 178 studied farms, HEV unbiased seroprevalence ranged from 0% to 100% HEV-seropositive pigs (mean: 29%, median: 17%).

The univariable analysis showed that two of the eight analysed centrality indicators were statistically associated with the outcome (Table 1): high in-degree and ingoing closeness for farms were significantly and positively associated with high within-farm HEV seroprevalence. Since in-degree and ingoing closeness were correlated (chi-squared test, $p < 0.01$), they were not included in a multivariable model. Farm type was associated with all explanatory variables ($p < 0.05$) but not with within-farm HEV seroprevalence ($p > 0.1$).

3.2. Indicator of risk ***of exposure to HEV of French départements***

3.2.1. Departmental farm-level HEV prevalence and related uncertainty

Departmental farm-level HEV prevalence distributions were plotted

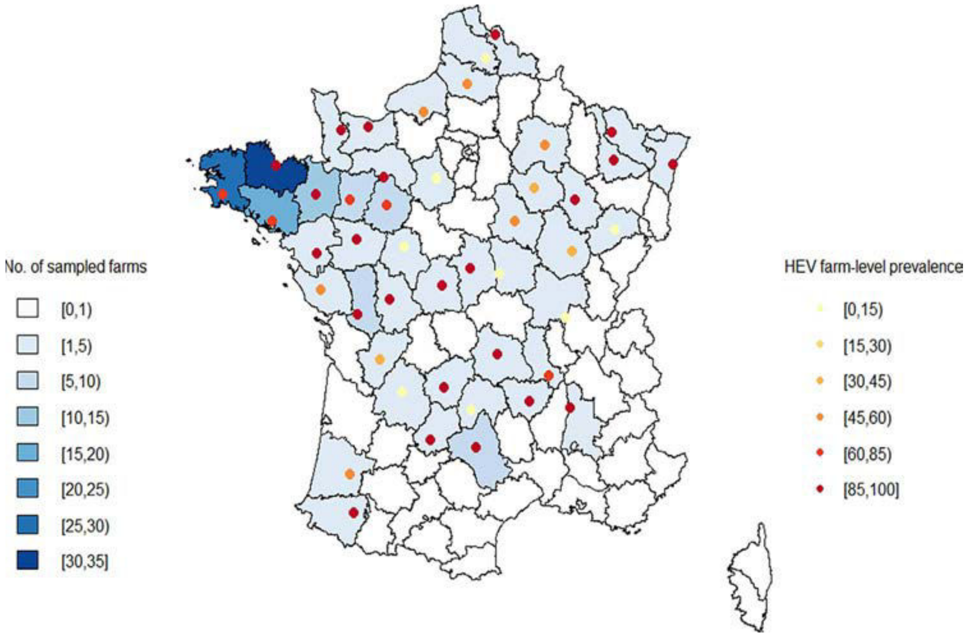

Fig. 2. Number of farms sampled per *département* in the 2009 nation-wide HEV survey and observed farm-level HEV prevalence by *département*. Farm-level HEV prevalence was defined as the number of farms having at least one HEV-seropositive pig among the total number of tested farms in the *département*.

Table 1
Statistical relationships between farms' network centrality indicators and within-farm HEV seroprevalence.

Centrality measures Category	Definition	Estimate	Standard Error	Odds Ratio [95% Confidence Interval]	p-value
In-degree	Number of different holdings from which a holding receives animals				
≤4		–	–	–	–
> 4		0.57	0.31	1.78 [0.97–3.26]	0.06*
Out-degree	Number of different holdings to which a holding sends animals				
≤1		–	–	–	–
> 1		0.21	0.25	1.23 [0.76–1.99]	0.4
Ingoing closeness	Focuses on how close a farm is to all the others in the network through incoming links				
≤ $2.176.10^{-9}$		–	–	–	–
> $2.176.10^{-9}$		0.65	0.29	1.91 [1.08–3.38]	0.02*
Outgoing closeness	Focuses on how close a farm is to all the others in the network through outgoing links				
≤$2.175.10^{-9}$		–	–	–	–
> $2.175.10^{-9}$		0.038	0.35	1.04 [0.52–2.06]	0.9
Betweenness	Number of geodesics (shortest paths) going through a vertex				
=0		–	–	–	–
> 0		−0.0009	0.001	0.999 [0.997–1.001]	0.4
Average monthly ingoing contact chain	Number of holdings in contact with a given holding (called the root) through time-respecting paths reaching the root within a month				
≤1		–	–	–	–
> 1		0.14	0.25	1.15 [0.71–1.87]	0.6
Average monthly outgoing contact chain	Number of holdings in contact with a root through time-respecting movements of animals leaving the root within a month				
=0		–	–	–	–
> 0		−0.028	0.24	0.97 [0.61–1.56]	0.9
Node loyalty	Fraction of preserved links of a node for a pair of two consecutive network configurations over time, with the time window in our case being a half-year				
≤ 0.65		–	–	–	–
> 0.65		−0.26	0.26	0.77 [0.46–1.30]	0.3

Summary statistics as obtained thanks to a generalised estimating equation (GEE) univariable logistic regression with the "farm" effect being included as a repeated statement. *statistically significant effect.

(see examples in Supplementary File 1, figure a). Due to the varying number of sampled farms depending on the *département* (Fig. 2), quite a few *départements* exhibited large farm-level prevalence distributions (e.g. *département* A in Supplementary File 1, Fig. a).

3.2.2. Estimated risk indicator of HEV exposure of *départements* through pig movements

Distributions of the risk indicator of French *départements* being exposed to HEV were plotted (see examples in Supplementary File 1, Fig. b). The median risk of exposure for each *département* was mapped (Fig. 3). Geographical patterns of HEV prevalence and HEV exposure risk showed major differences (Figs. 2 and Fig. 3).

4. Discussion

Understanding the features of movement networks is crucial to analyse infection dynamics, pathogen occurrence and risk factors and to support risk-based surveillance strategies.

Although network studies have often been motivated by the outcome of animal movements on pathogen epidemiology (Keeling, 2005; Rautureau et al., 2012; Buttner et al., 2015; Thakur et al., 2015), the specific role of animal shipments in pathogen transmission and/or exposure has rarely been quantified, especially in the swine sector. The primary advantage of our study lies in combining epidemiology and network analysis to quantify both the impact of animal movements on pathogen prevalence within farms and the risk of areas being exposed to diseases due to between-area movements. HEV was chosen as a pathogen for implementation. Indeed, pig movements are likely to play a pivotal role in HEV epidemiology (Salines et al., 2017a), although they have only scarcely been explored to date (Nantel-Fortier et al., 2016). We assessed the role of pig shipments in relation to within-farm HEV seroprevalence level and to the risk of exposure of French *départements* to HEV.

Pig movement data originated from the French National Swine Identification Database (BDporc), in which all pig shipments are systematically recorded. The information provided by this database is recognised by the French Ministry for Agriculture and can therefore be considered trustworthy. Moreover, a thorough cleaning stage was carried out to manage incorrect or incomplete data. The quality of data in terms of accuracy, reliability, and comprehensiveness guaranteed the robustness of our results (Salines et al., 2017b). The random selection process for tested farms and for individual pigs tested from each farm (Rose et al., 2011) ensured reliable estimates for the seroprevalence values used in our study. Moreover, the within-farm apparent seroprevalence estimates were corrected for serological test characteristics, providing true seroprevalence estimates. Eight production sites surveyed in 2009 ceased activity before 2013, limiting movement data availability to only 178 out of the 186 farms. This is consistent with the observed overall decrease in the number of pig farms in France (Salines et al., 2017b). On the *département* scale, the model involving the random sampling of farm-level HEV prevalence from beta distributions − with a weighted confidence interval − made it possible to take into account the low precision of some prevalence figures in quite a few *départements* where a low number of farms had been sampled. Temporal variability of both pig movements and HEV seroprevalence was a limitation of our study. Indeed, one should note that movement and

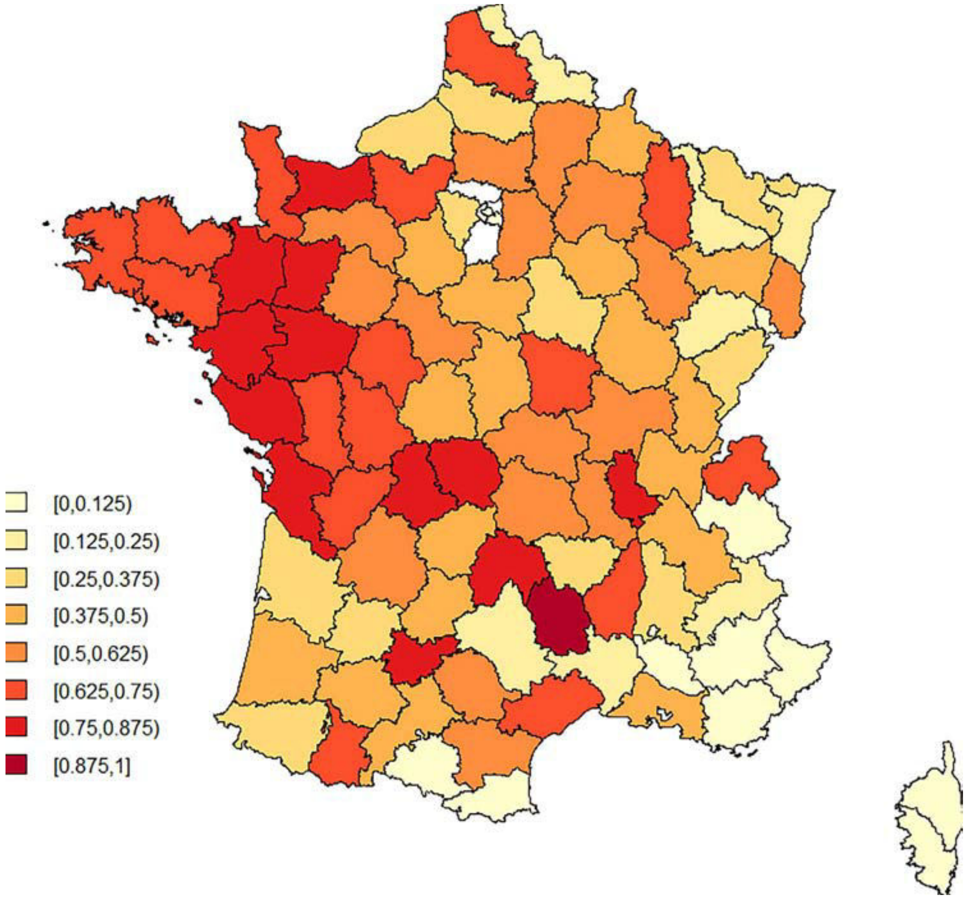

Fig. 3. Median risk of French *départements* being exposed to HEV through external incoming pig movements (10,000 simulations). An indicator of the risk of a French *département* being exposed to HEV was calculated as the number of infected movements it had received from source *départements* divided by its total number of external incoming movements.

prevalence data were not simultaneously collected. However, the French pig movement network has been found to be stable over time (Salines et al., 2017b), so we can assume that combining the 2009 prevalence data with the 2013 pig movement data is still consistent. Moreover, 70% of the 178 farms included in our study showed a loyalty equal to 1 (i.e. they exchanged animals with the same suppliers/buyers over the year), reflecting the stability of their movements. Regarding HEV prevalence, our data were dated (2009) and HEV prevalence is likely to vary over time. However, a more recent study also conducted in France reported similar prevalence figures (59% seroprevalence in Feurer et al. (2017) vs 65% in Rose et al. (2011)). Aggregating movement data on a yearly basis also appeared to be relevant due to the absence of seasonality in the French pig network (Relun et al., 2016; Salines et al., 2017b) and provided indicators representing the overall activity of farms over a year. A possible improvement to the network model may involve weighting links depending on the number of animals exchanged.

In the recent literature, several farm connectivity indicators were identified as risk factors for disease occurrence and spread (Martin et al., 2011; Frössling et al., 2012; Lee et al., 2017; Sintayehu et al., 2017). Our study found that the farms' in-degree was positively associated with high within-farm HEV seroprevalence. This is consistent with several studies conducted in livestock production sectors showing that farms having a high in-degree were more likely to be infected with a pathogen (Martin et al., 2011; Frössling et al., 2012; Lee et al., 2017; Sintayehu et al., 2017). Since repeated animal shipments to a farm from the same supplier were aggregated into a single link, the association between HEV seroprevalence and in-degree not only indicates that the HEV seroprevalence of farms increases with the number of incoming shipments, but it also proves that buying animals from several suppliers is linked to higher HEV seroprevalence. Our results also showed that the greater the ingoing closeness of a pig farm, the higher its HEV seroprevalence. A high value for the ingoing closeness centrality of a given farm indicates that the farm can be reached by its trade partners in only a few movements. Farm centrality in the network therefore appears to be a factor in vulnerability to HEV. This is consistent with the findings of previously published papers (Lee et al., 2017; Sintayehu et al., 2017). As Lee et al. (2017) demonstrated for PRRSV, we found that the odds of having higher within-herd HEV seroprevalence was increased more by ingoing closeness than by in-degree, meaning that the level of connectivity with all other holdings in the network is a better predictor of HEV infection than the number of directly connected farms. Unlike for other pathogens (Lee et al., 2017), no significant association was found between HEV within-farm seroprevalence and outdegree or outgoing closeness. The absence of an effect for these centrality indices was expected since HEV is mainly transmitted by infected pigs introduced into a naïve population. Introduction into a farm due to the sole transit of a possibly contaminated truck loading pigs in the farm for an outgoing shipment is therefore extremely unlikely. Unlike Sintayehu et al. (2017) regarding bovine tuberculosis, our statistical model did not show any significant effect of a herd's betweenness on within-herd HEV seroprevalence. Production units with high betweenness centrality play a key role in the spread of disease throughout the network since they can build so-called bridges between distinct network components. Since we explored the role of centrality metrics in HEV occurrence in farms, and not in their ability to transmit HEV to other farms, the lack of an effect for betweenness was also expected. Ingoing and outgoing contact chain values were not found to have a significant effect on HEV seroprevalence either. Again, as we did not investigate a farm's potential for spreading HEV, the lack of a link between OCC and HEV seroprevalence is coherent. An association between ICC and HEV seroprevalence could have been expected. This kind of association has indeed been demonstrated in other studies, but Frössling et al. (2012) showed that this link was pathogen-dependent: indeed, high ICC was found to be a risk factor in the occurrence of bovine coronavirus but not for bovine respiratory syncytial virus.

To the best of our knowledge, the exposure of a geographical area to a pathogen due to animal movements has never been quantified. The choice of the departmental level for our study was policy-oriented; indeed, French *départements* are local administrative areas and surveillance programmes are often designed and implemented on this scale. Due to the low precision of HEV farm-level prevalence data in quite a few *départements*, the distribution of the risk of exposure was large in these *départements* and the results in these *départements* therefore lack precision. Nevertheless, the outputs of the procedure used to assess the risk of HEV exposure were stabilised thanks to a high number of simulations. Given the form of the risk distribution, the median appeared the most appropriate metric for the risk of exposure. High variability in the median risk of exposure to HEV was observed depending on the French *département*, confirming the relevance of designing targeted and differentiated surveillance strategies based on the area's risk level. Moreover, the discrepancy between the departmental observed prevalence figures and the departmental risk levels provides justification for monitoring not only highly prevalent areas but also those having at-risk movements coming from infected areas.

Confounding factors may bias our results. Indeed, we had limited data regarding farm and *département* characteristics. For instance, no detailed data was available regarding farm size, pig density or farm management practices, but we checked that farm type (breeding, farrowing-to-finishing, etc.) was not a confounding factor. Several research teams have recently developed farm-level risk scores based on animal movements. For instance, Schärrer et al. (2015) introduced a cumulative score taking several parameters into account, including the ICC, the number of animals per incoming movement, the type of pasture and the number of weeks per year with movements. Another study proposed a method for calculating a disease-specific relative ratio for the increased probability of infection due to the introduction of animals (Frössling et al., 2014). Ribeiro-Lima et al. (2015) also identified farms with a higher risk of bovine tuberculosis infection using a model based on a risk score at movement level. A further stage in our study could be to build a farm-level risk score including both risk factors linked to pig movements and other farm-specific risk factors for HEV that have previously been identified (Walachowski et al., 2014). Such a score would make it possible to target only high-risk farms for more effective surveillance.

5. Conclusion

Combining network analysis with epidemiological data demonstrated that direct network connectivity and farm centrality in the network are related to the within-herd HEV seroprevalence level and that some areas are more at risk for HEV due to their pig movements. More generally, the methods we proposed prove that farm- or area-level parameters derived from animal movements can support the risk-based selection of farms for surveillance programmes or the implementation of differentiated surveillance strategies depending on the area's movement characteristics. Therefore, risk-based epidemiological approaches benefiting from network analysis should be promoted.

Author contributions

MS and MA performed the statistical analyses. MS drafted the manuscript. NR initiated and supervised the project. All the co-authors revised the manuscript and approved the final submitted version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.prevetmed.2017.11.015.

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Ce qu'il faut retenir

Le couplage de méthodes d'analyse de réseau avec des données épidémiologiques a montré que la connectivité directe des élevages et leur centralité de proximité dans le réseau sont associées à la séroprévalence du HEV intra-élevage et que certaines aires géographiques sont plus à risque vis-à-vis du HEV du fait de leur approvisionnement depuis des zones infectées. Si cette approche a mis en évidence des associations statistiques entre mouvements et prévalence HEV, elle ne permet pas de décrire de manière fine et dynamique la diffusion du HEV à l'échelle nationale, d'expliquer les facteurs de la propagation et la persistance virale dans la filière de production porcine, ni de tester des mesures de lutte sur un territoire. C'est dans cet objectif qu'un modèle dynamique inter-troupeaux, couplant la dynamique infectieuse du HEV circulant dans un élevage avec les échanges de porcs, a été développé.

Take home message

Combining network analysis methods with epidemiological data has shown that farms' direct connections as well as their closeness centrality in the network are associated with high HEV on-farm seroprevalence, and that some areas are at greater risk regarding HEV due to their supply from infected regions. While this approach has highlighted statistical associations between pig movements and HEV prevalence, it does not allow for a detailed and dynamic description of the spread of HEV at the national level, or an explanation of the factors of spread and viral persistence in the pig production chain, or the testing of control measures in a territory. It is with this objective in mind that a between-herd dynamic model, coupling the infectious dynamics of HEV circulating on a farm with pig exchanges, has been developed.

PARTIE 3.2. Un modèle inter-troupeaux pour comprendre la propagation et la persistance du virus de l'hépatite E dans la filière porcine

L'article précédemment présenté, ainsi que l'étude réalisée par Nantel-Fortier *et al.* (2016), suggèrent un **probable rôle des mouvements d'animaux** dans la diffusion du HEV entre des élevages de porcs mais, à notre connaissance, aucune équipe de recherche n'a à ce jour développé de modèle permettant d'évaluer et de comprendre la circulation du HEV entre des élevages en prenant en compte la dynamique virale intra-élevage et la dynamique démographique liée aux échanges d'animaux vivants. Dans ce contexte, l'objectif de l'étude présentée ci-après a été de développer une **approche de modélisation multi-échelles** afin de décrire et d'expliquer les conditions de la diffusion et de la persistance du HEV dans une communauté d'élevages français et d'évaluer la prévalence d'animaux positifs à l'abattoir sous différentes conditions. Pour ce faire, un modèle stochastique a été développé en couplant le modèle intra-élevage décrit dans le chapitre II (Salines *et al.*, 2019d) avec les données de mouvements de porcs sur la période 2012-2015 présentées au début du présent chapitre III (Salines *et al.*, 2017b). Ce modèle a aussi été utilisé pour évaluer différents **scenarii d'introduction** du HEV dans la communauté ainsi que l'**effet d'un assainissement de la population** vis-à-vis des pathogènes intercurrents (virus du SDRP, PCV2 par exemple).

Ce travail a donné lieu à une collaboration avec l'équipe d'épidémiologie du *Swedish Veterinary Institute* (Dr Stefan Widgren, SVA, Uppsala, Suède) et à une mission de trois mois sur place.

Les résultats de ce travail de modélisation sont présentés dans le projet de publication ci-dessous qui sera soumis dans une revue internationale à comité de lecture.

Publication 9 (Draft)

Salines M., Andraud M., Rose N., Widgren S. A between-herd data-driven stochastic model to explore the spatio-temporal spread of hepatitis E virus in the French pig production network. In prep.

A between-herd data-driven stochastic model to explore the spatio-temporal spread of hepatitis E virus in the French pig production network

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Abstract: Hepatitis E virus is a zoonotic pathogen for which pigs are recognized as the major reservoir in industrialised countries. A multiscale model was developed to assess the HEV transmission and persistence pattern in the pig production sector through an integrative approach taking into account within-farm dynamics and animal movements based on actual data. Within-farm dynamics included both demographic and epidemiological processes. Direct contact and environmental transmission routes were considered along with the possible co-infection with immunomodulating viruses (IMVs) known to modify HEV infection dynamics. Movements were limited to 3,017 herds forming the largest community on the swine commercial network in France and data from the national pig movement database were used to build the contact matrix. Between-herd transmission was modelled by coupling within-herd and network dynamics using the SimInf package. Different introduction scenarios were tested as well as a decrease in the prevalence of IMV-infected farms. After introduction of a single infected gilt, the model showed that the transmission pathway as well as the prevalence of HEV-infected pigs at slaughter age were affected by the type of the index farm, the health status of the population and the type of the infected farms. These outcomes could help design HEV control strategies at a territorial scale based on the assessment of the farms' and network's risk.

Keywords: between-herd model; hepatitis E virus; interactions; multi-scale modelling; public health

1. Introduction

Hepatitis E virus (HEV) is a non-enveloped single-stranded RNA virus frequently leading to asymptomatic infections in humans, but also causing acute or chronic hepatitis - depending, inter alia, on the patient's immune status (Emerson and Purcell, 2003; Kamar et al., 2011). If genotypes 1 and 2 are exclusively human viruses mainly present 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). In particular, HEV-3 is highly prevalent in European swine populations (Salines et al., 2017a), e.g. in the French pig production sector, where around 65% of farms have been found to host at least one HEV seropositive pig (Rose et al., 2011). A number of locally acquired cases have been linked to the consumption of raw or undercooked pork products, especially those containing liver in high proportion (Yazaki et al., 2003; Holub et al., 2009; Colson et al., 2012; Moal et al., 2012; Motte et al., 2012; Trmal et al., 2012; Chalupa et al., 2014; Garbuglia et al., 2015; Riveiro-Barciela et al., 2015; Guillois et al., 2016). In that way, hepatitis E is recognised as a foodborne zoonosis with domestic pigs being the major reservoir in Western countries (Pavio et al., 2017).

The risk of slaughtering HEV-positive pigs, and thus to enter contaminated products into the food chain, is strongly related to HEV dynamics in pig herds. Observational and experimental studies have evidenced several risk factors affecting HEV behaviour on pig farms, such as husbandry practices in terms of hygiene, biosecurity and rearing conditions (Walachowski et al., 2014), piglet's sex and sow's parity (Salines et al., 2019b). The protection conferred by maternally-derived antibodies (MDAs) was also shown to impact HEV dynamics (Andraud et al., 2014; Crotta et al., 2018). Moreover, pigs exhibited chronic hepatitis when co-infected with immunomodulating viruses (IMVs), e.g. porcine reproductive and respiratory syndrome virus (PRRSV) or porcine circovirus type 2 (PCV2) (Salines et al., 2015; Salines et al., 2019a; Salines et al., 2019b). Recently, we have developed a stochastic individual-based model representing HEV spread and persistence on a farrow-to-finish pig farm in which pigs may be co-infected with IMVs (Salines et al., 2019c). This model gave insights on HEV spread and persistence and evidenced or confirmed several risk factors, e.g. the type of housing for gestating sows, cross-fostering and mingling practices and health status regarding the IMVs. However, this model only explored HEV dynamics in a single and isolated farrow-to-finish herd, without taking into consideration animal trade with other holdings, although pig movements are likely to play a pivotal role in HEV dynamics in the pig production sector . For instance, Nantel-Fortier et al. (2016) reported the presence of HEV inside and outside farm buildings, on trucks and in slaughterhouse yards, thus suggesting viral transmission between farms and throughout the production network. Recently, we have also shown, by combining French network indicators with epidemiological data, that the in-degree and ingoing closeness of farms were associated with high HEV within-farm seroprevalence (Salines et al., 2018).

To represent infection spread at a regional or national scale, multi-scale models can be designed by coupling infection dynamics within herds together with interactions between interconnected herds. Such approaches have already been developed, particularly to explore the transmission of bacterial diseases between cattle farms (Brooks-Pollock et al., 2014; Beaunee et al., 2015; Widgren et al., 2016b; Widgren et al., 2018) or pig herds (Schulz et al., 2018). Several approaches have been recently used to implement such models that may be computationally challenging (Bui et al., 2016; Widgren et al., 2016a; Picault et al., 2017). In particular, the SimInf package developed in R software is recognized as an efficient and flexible modelling framework for fast event-based epidemiological simulations of infectious disease spread (Widgren et al., 2016a). It makes it possible to integrate within-herd infection dynamics as a continuous-time Markov process and demographic data as scheduled events. Thus, using the SimInf framework, the aims of our study were: *(i)* to model the spatio-temporal spread of HEV in a cluster of highly connected French pig farms, real pig movement data and HEV within-herd epidemiological dynamics being incorporated; *(ii)* to investigate different introduction and control scenarios.

2. Materials and methods

2.1. Population dynamics model

2.1.1. Farms' structure: type, facilities, populations, management system

Eight farm types are considered: nucleus (*SEL*), multiplication (*MU*), farrow-to-finish (*FF*), farrowing (*FA*), farrowing post-weaning (*FPW*), post-weaning (*PW*), post-weaning finishing

(*PWF*) and finishing (*FI*) farms. All farms (within each type) were assumed to have the same structure and size(Figure 1), accounting for one to four sectors, depending on their type (Table 1): gestation, farrowing, post-weaning (i.e. nursery) and finishing sectors. Each of the sectors is divided into rooms, including themselves several pens. Two populations are considered: breeding sows and growing pigs. Depending on its type, a farm can host one or both populations (Table 1).

Figure 1. Farm structure, facilities and populations considered.

Farms can be composed of one to four sectors depending on their type: gestation, farrowing, post-weaning and finishing sectors (coloured squares). Each sector is divided into rooms (dashed lines), that are composed of pens (white squares). Two populations are considered: breeding sows (red triangles) and growing pigs (blue dots).

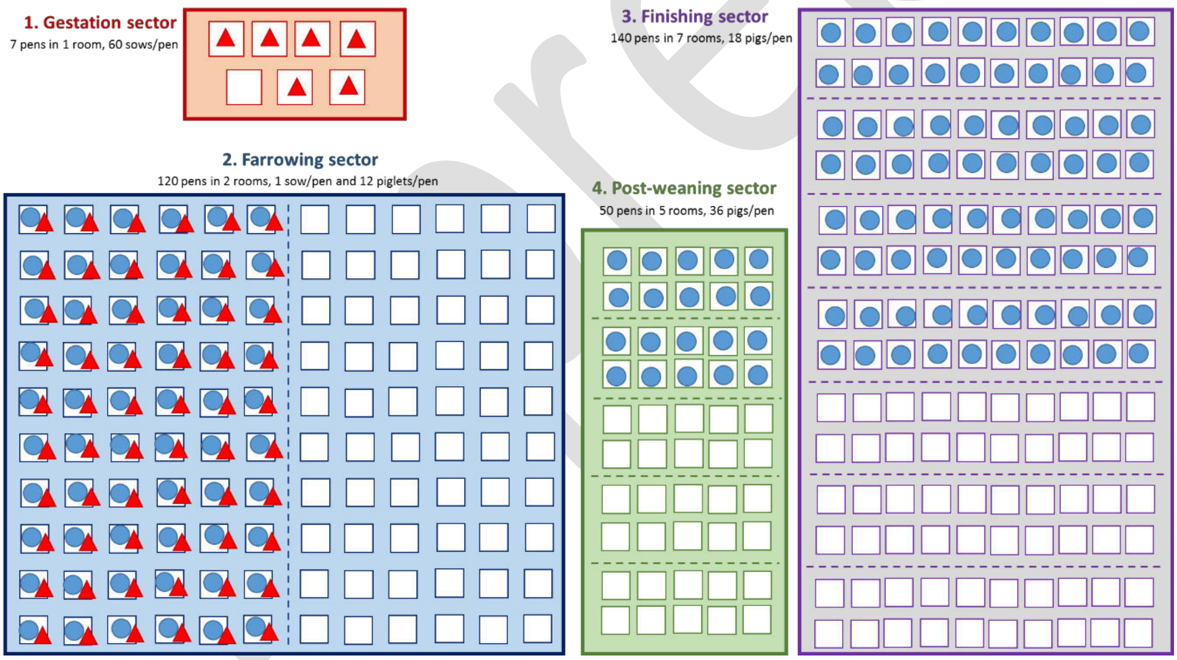


Table 1. Types of sectors, animal populations and events per farm depending on the farm type

Farms are composed of one to four sectors, depending on their type: nucleus (*SEL*), multiplication (*MU*), farrow-to-finish (*FF*), farrowing (*FA*), farrowing post-weaning (*FPW*), post-weaning (*PW*), post-weaning finishing (*PWF*) and finishing (*FI*) farms. They can rear one or two populations (breeding sows, growing pigs). Six types of events can occur depending on the farm type: movement of sows from gestation to farrowing sector (*ges-fa*); piglet birth (*birth*); movement of sows from farrowing back to gestation sector (*fa-ges*); movement of piglets from farrowing to post-weaning sector (*fa-pw*); movement of growing pigs from post-weaning to finishing sector (*pw-fi*); movement of growing pigs leaving the finishing sector (*fi*).

		Farm type							
		SEL	**MU**	**FF**	**FA**	**FPW**	**PW**	**PWF**	**FI**
Sectors	**Gestation**	x	x	x	x	x			
	Farrowing	x	x	x	x	x			
	Post-weaning	x	x	x		x	x	x	
	Finishing	x	x	x				x	x
Animal populations	**Breeding sows**	x	x	x	x				
	Growing pigs	x	x	x	x	x	x	x	x
Events	***ges-fa***	x	x	x	x	x			
	birth	x	x	x	x	x			
	fa-ges	x	x	x	x	x			
	fa-pw	x	x	x	x	x			
	pw-fi	x	x	x		x	x	x	
	fi	x	x	x				x	x

Animals evolve in a sequential way through the above-mentioned facilities: the breeding sows in the gestation and farrowing sectors; the growing pigs in the farrowing, post-weaning and finishing sectors. Thus, the two populations physically interact in the farrowing sector only. The farms are managed according to a batch-rearing system (BRS), meaning that the herd population is divided into sets of individuals from the same physiological stage, called batches. For instance, for farms rearing sows, the reproductive cycles of sows belonging to a given batch are synchronised so that all breeding events occur at the same time for all sows. Consequently, a given batch of sows gives birth to piglets simultaneously, these contemporary piglets forming a group of growing pigs also constituting a batch. The batches are managed with an all-in-all-out strategy, i.e. all animals from a batch leave a facility simultaneously and enter an empty room at once. In the model, all farms are considered to be managed with a 7-batch rearing system (i.e. a 3-week interval management system), with parameters being detailed in Table 2.

Table 2. Parameters governing the population dynamics model in a 7-batch rearing system.

FA: farrowing farms, *FPW*: farrowing post-weaning farms, *SEL*: nucleus farms, *MU*: multiplication farms, *FF*: farrow-to-finish farms

Parameter description (unit)	**Value**
Duration of a sow reproductive cycle (days)	142
- Duration in gestating room (days)	107
- Duration in farrowing room (days)	35

Duration of a growing pig cycle (days)	180	
- Duration in farrowing room (days)	28	
- Duration in post-weaning room (days)	86	
- Duration in finishing room (days)	94	
Interval between two successive batches (days)	21	
Annual renewal rate of sow herds (%)	40	
Number of animals:	*In FA and FPW*	*In SEL, MU and FF*
- Total number of sows	420	210
- Number of sows per batch	60	30
- Number of piglets per litter	12	
- Number of piglets per batch	720	360

2.1.2. Population dynamics processes

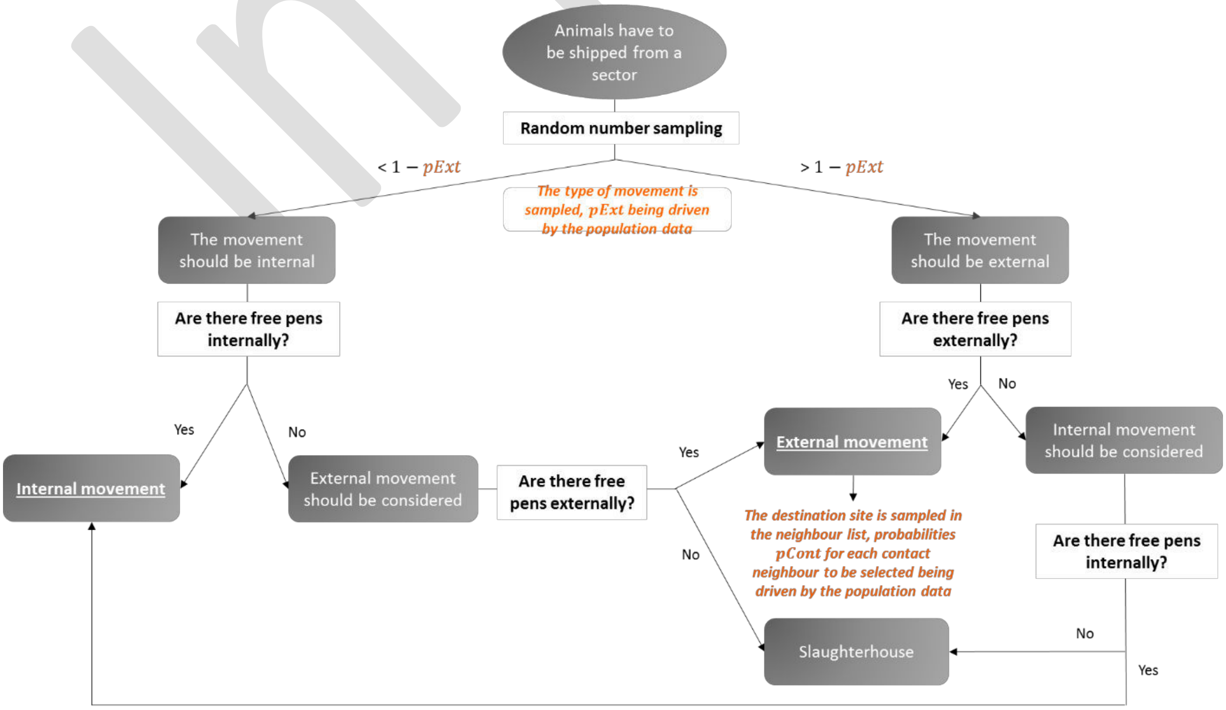
<u>*Life cycle of breeding sows and growing pigs.*</u> After 107 days in the gestation sector (i.e. seven days before farrowing), sows from a batch are transferred into the farrowing sector (one sow per pen) where they give birth to 12 piglets each (Table 2). Dams remain with their litter for four weeks until weaning. At the end of the lactation period, sows are moved back to the gestation sector to begin a new reproductive cycle, when piglets are moved to an empty nursery room (36 pigs per pen, three litters being gathered in one pen). Piglets stay in the nursery sector until 86 days of age when they are moved to a finishing room (18 pigs per pen, i.e. 1.5 litter per pen). When they are 180 day old (i.e. after 94 days in the finishing sector), they are sent to the slaughterhouse. Every 21 days, five replacement gilts are introduced in herds rearing sows and five sows are culled.

<u>*Implementation of population events.*</u> Six types of events can occur in the population depending on the farm type (Table 1): movement of sows from gestation to farrowing sector (*ges-fa*); piglet birth (*birth*); movement of sows from farrowing back to gestation sector (*fa-ges*); simultaneous movement of piglets from farrowing to post-weaning sector (*fa-pw*); movement of growing pigs from post-weaning to finishing sector (*pw-fi*); movement of growing pigs leaving the finishing sector (*fi*). Event times are determined deterministically by the different cycle durations as explained above. The number of animals to be moved are also fixed by the production system, as described above (Table 2, Figure 1). The three first types of events (corresponding to the sow reproductive cycle: *ges-fa*, *birth*, *fa-ges*) are always internal (i.e. the animals remain in the same farm), when the three others (corresponding to movements of growing pigs: *fa-pw*, *pw-fi*, *fi*) can be either internal or external (i.e. the animals are shipped to another site). Selecting the pens of destination is a two-step process detailed in Figure 2. First, the type of movement (internal or external) is selected with probability $pExt$ that the animals

are shipped to another farm, derived from real movement data (section 2.1.3). In case of external movement, the destination site is sampled among the set of possible destination farm from the movement database (see below). When leaving the finishing sector (*fi* event), two possible pathways were considered for growing pigs: *(i)* animals leaving *FF*, *PWF* and *FI* farms are sent to the slaughterhouse; *(ii)* a fraction of females is used for the renewal of the sow population either on the same farm (i.e. self-renewal, in *SEL* farms) or on another farm (in cases of animals reared in *SEL* and *MU* farms), and the others are sent to the slaughterhouse. Again, the choice of the destination of finishing events is driven by the population data presented in the following section.

Figure 2. Selection process of the movements' destinations.

Each time animals have to be shipped from a sector, as defined by the production cycle, the type of event (i.e. internal versus external) is determined according to the probability $pExt$ that is the probability that animals are shipped externally, as defined by the population data. In cases of no free pens found internally (resp. externally), external (resp. internal) movement is considered. If all pens (internally and in contact farms) are full, animals are sent to slaughterhouse. If animals are shipped externally, the destination site is sampled in the contact neighbours of the farm of origin, the probability $pCont$ of a destination farm to be sampled being defined in the population data.

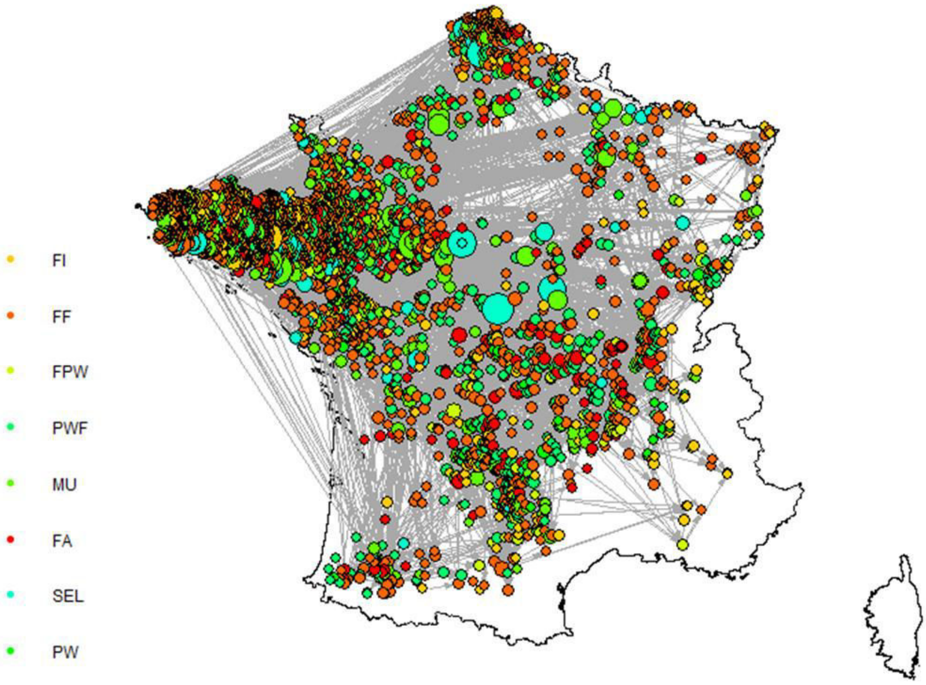


2.1.3. *Data on animal movements between farms*

Dataset. French pig movement data recorded during the period 1st June 2012 to 31st December 2014 were used to drive the population demographics in the model. The data originated from the National Swine Identification Database (BDporc). The dataset, described in detail in Salines et al. (2017b), contained 21,446 farms and 2,382,510 between-farm movement records. Briefly, the main features of all swine holdings in mainland France (continental France and Corsica) were included in the database: identification number (ID), type of holding, type of farming activity, farm size and location. Movements of pigs were reported at the batch level with the following information: farm IDs where animals were loaded or unloaded, round number and chronological sequence of the operations forming the round, batch size and animal category. First, as described in Salines et al. (2017b), a one-mode directed network was built, with holdings being considered as nodes, and movements between two nodes as links. In this network, called Animal Introduction Model in Salines et al. (2017b), in-between movements forming a round were replaced by direct movements between holdings, i.e. intermediate transit movements of a truck through a farm without unloading any animal were neglected. The analysis of the network revealed the existence of communities, defined as subsets of nodes in which there are significantly more links than expected by chance - i.e. groups of highly connected farms (Infomap algorithm (Rosvall et al., 2009)). This approach evidenced a large community including 3,017 farms (Figure 3), among them 55 *SEL*, 210 *MU*, 1,375 *FF*, 86 *FA*, 62 *FPW*, 8 *PW*, 546 *PWF* and 675 *FI* farms. In this community, around 78,000 movements occurred over the study period. Data derived from this community were used to feed SimInf population dynamics sub-model. To achieve this task, we first defined a standard herd size, structure and batch-rearing system to all herds, corresponding to the average characteristics over all the community. Within-farm movements were scheduled following the evolution of the animals through their life- or reproductive-cycles. Who-to-Whom (site-to-site) contact probabilities were then evaluated over the study period to represent the external movements, with a rescaling step to take into account the difference between the standard and the actual herd sizes.

Figure 3. Largest community in the pig movement network in France (2012-2014), derived from Salines et al. (2017b).

Using Infomap algorithm, a large community including 3,017 farm was identified in the French pig movement network (data from 2012 to 2014). Farm and movement data from this community was used as input population data in the present model. The size of the dots is proportional to the total degree of the holding, the colours are related to the farm type. *FI*: finishing farm, *FF*: farrow-to-finish farm, *FPW*: farrowing post-weaning farm, *PWF*: post-weaning finishing farm, *MU*: multiplication farm, *FA*: farrowing farm, *SEL*: nucleus farm, *PW*: post-weaning farm.



Calculation of the probability for a movement to be external. For each farm i in the community, the probabilities $pExt_i^{fa-pw}$, $pExt_i^{pw-fi}$ and $pExt_i^{fi}$ that the corresponding possibly external movements (*fa-pw*, *pw-fi* and *fi*, respectively) are actually external have been calculated. For *FA* farms, *fa-pw* movements are always external, so that:

$$pExt_i^{fa-pw} = 1$$

Similarly, *pw-fi* movements are always external for *FPW* and *PW* farms, leading to:

$$pExt_i^{pw-fi} = 1$$

for these two farm types.

For the other farm types, one may assume that, for an average-sized farm as designed in the population model, the total number of animals shipped over the study period from a sector a to a sector b is:

$$n_{average}^{a,b} = \frac{n_{days}}{BBI} \times n_{batch}^{pigs}$$

where n_{days} is the total number of days over the study period, BBI the number of days between two successive batches (i.e. between-batch interval) and n_{batch}^{pigs} the average number of pigs per batch.

Denoting $R_{average}^{i}$ the ratio between the actual size of a farm i as recorded in the population data and the average size of the farm i as designed in the population model, the expected number of animals shipped by the farm i from a sector a to a sector b over the study period can be expressed as:

$$nExp_{i}^{a,b} = n_{average}^{a,b} \times R_{average}^{i}$$

Let $nObs_{i}^{a,b}$ denote the observed number of animals shipped externally by a farm i from a sector a to the sector b of another farm (as recorded in the population data). Then, the probability that the movement from a sector a of a farm i to a sector b is external is:

$$pExt_{i}^{a,b} = \frac{nObs_{i}^{a,b}}{nExp_{i}^{a,b}}$$

Calculation of the contact probability associated to each neighbour. For each external movement from a sector a of a farm i to an external sector b, the probability that the movement is directed to a contact farm j is calculated by:

$$pCont_{i,j}^{a,b} = \frac{n_{i,j}^{a,b}}{n_{i}^{a}},$$

where $n_{i,j}^{a,b}$ is the number of animals shipped from the sector a of the farm i to the sector b of the contact farm j over the study period, as observed in the population data, and n_{i}^{a} is the total number of animals shipped externally from the sector a of the farm i over the study period, again as observed in the population data.

- *Final structure of input data.* Finally, 11 variables were used to describe each of the 3,017 farms and to drive the population dynamics: farm ID, farm type, and nine variables corresponding to the contact matrix with contact probabilities associated to each sector of each farm.

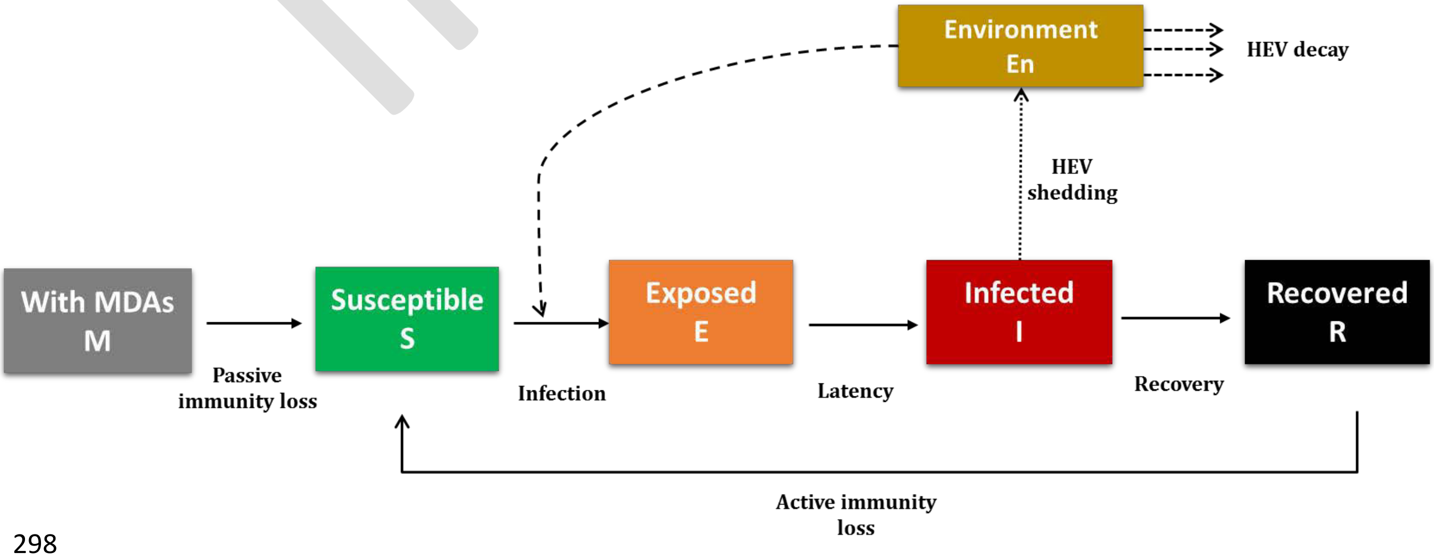
2.2. Epidemiological model

2.2.1. Epidemiological process

As described in Salines et al. (2019c), an MSEIR – Maternally Immune (M), Susceptible (S), Exposed (E), Infectious (I) and Recovered (R) – model including an environmental compartment was considered to describe HEV infection dynamics taking those factors into account (Figure 4). Briefly, new-born piglets born from immune sows acquire anti-HEV maternally-derived antibodies by colostrum intake (health state M), providing complete but temporary protection towards infection. Susceptible (S) pigs can then be infected, entering the exposed (E) state. HEV transmission occurs through faecal-oral route, either by direct contact with an infectious pig or by ingestion of viable virus in the contaminated environment in the pen or the neighbourhood (Bouwknegt et al., 2008; Bouwknegt et al., 2011). After the latency period, the infectious animal (I) shed 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 of empty pens (Andraud et al., 2013). Recovered pigs (R) lose their immunity over time, assuming a gamma-distribution for antibody waning, and eventually revert to full susceptibility (S). Transitions between epidemiological statuses occur stochastically.

Figure 4. HEV infection process as represented with a MSEIRS model.

The epidemiological model has been built as a MSEIR – Maternally Immune (M), Susceptible (S), Exposed (E), Infectious (I) and Recovered (R) – model including an environmental compartment. MDAs: maternally-derived antibodies.



2.2.2. Forces of HEV infection and HEV infection process

As described in Salines et al. (2019c), HEV force of infection takes two components into account: a within-pen and a between-pen force of infection. Briefly, one infectious pig can infect its pen mates by direct contact or indirectly through its contaminated faeces accumulated in the environment, leading to the following within-pen force of infection:

$$\lambda_{\mathrm{p}}^{\mathrm{HEV,wp}}(t) = \frac{\beta_{HEV}\times I_p^{HEV}(t)+\beta_E^{wp}\times Q_p\times Q_{ing}}{N_p(t)}, \qquad \mathbf{(1)}$$

where $N_p(t)$ and I_p correspond to the total number of animals and the number of infected animals in the pen p at the time t, respectively. β_{HEV} denotes the individual HEV transmission rate. 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(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 is the HEV quantity accumulated in the pen p, calculated as follows:

$$Q_p\ (t) = Q_p\ (t-1)\times(1-\varepsilon_1)\times(1-\varepsilon_2)+\frac{w_{HEV}\times I_p^{HEV}(t)}{N_p(t)}, \qquad \mathbf{(2)}$$

where w_{HEV} is the quantity of HEV particles shed in the environment by an infectious pig per gram of faeces. $\varepsilon_1$and ε_2 are the daily proportion of faeces passing through the slatted floor and the daily HEV mortality rate, respectively. 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.

Moreover, 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 the adjacent pen. Thus, the between-adjacent-pen force of infection of a pen p is equal to the sum of the weighted force of infection of its two neighbours.

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

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

Finally, the infection process is event-driven owing to Gillespie algorithm with transition rates as described in Table 3.

Table 3. Transition rates for each health state transition as illustrated in Figure 4.

λ is the global force of infection as described in equations (1) and (3), ρ is the latency rate for exposed animals E, γ is the recovery rate for infectious animals I, σ and μ denote the maternal and active immunity waning respectively.

Health state transition		Transition ate
Passive immunity waning	M → S	$\sigma \times M$
Infection	S → E	$\left(\lambda_{\mathrm{p}}^{\mathrm{HEV,wp}} + \lambda_{\mathrm{p}}^{\mathrm{HEV,bap}}\right) \times S$
Latency	E → I	$\rho \times E$
Recovery	I → R	$\gamma \times I$
Active immunity waning	R → S	$\mu \times R$

2.2.3. Epidemiological parameters

All parameters involved in the infectious process are fully described in Table 4 along with their definition and the origin of the input values. Since HEV dynamics has been shown to be strongly affected by co-infections with immunomodulating viruses such as PRRSV or PCV2 (Salines et al., 2015; Salines et al., 2019a; Salines et al., 2019c), some epidemiological parameters of the model depend on the farm's status regarding IMVs.

Table 4. Epidemiological parameters governing the HEV infection dynamics in cases of IMV-free or IMV-positive farms.

IMV: immunomodulating virus

Notation	Parameter description (unit)	Value		Reference
		IMV-free farms	IMV-positive farms	
D_{HEV}^{M}	Duration of maternal immunity (days)	45		Andraud et al. (2014)
D_{HEV}^{E}	Latency duration (days)	7.4	13.1	Andraud et al. (2013) Salines et al. (2015)
β_{HEV}	Direct transmission rate (pigs/day)	0.15	0.70	
β_{E}^{wp}	Within-pen environmental transmission rate (g/ge/day)	2.10^{-6}	$6.6.10^{-6}$	
β_{E}^{bap}	Between adjacent pen environmental transmission rate (g/ge/day)	2.10^{-8}	$6.6.10^{-8}$	
w	Quantity of HEV particles shed in faeces (ge/g/day)	10^{4}	10^{6}	
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		Expert opinion

ε_2	HEV decay rate in the environment (/day)	0.08		Johne et al. (2016)
ε_3	Faeces removal rate by cleaning	0.98		Expert opinion
D_{HEV}^{I}	Infectious period (days)	9.7	48.6	Andraud et al. (2013) Salines et al. (2015)
D_{HEV}^{R}	Duration of active immunity (days)	185		Expert opinion

2.3. Initialisation and simulations

At the beginning of a simulation, all herds rearing sows (i.e. *SEL*, *MU*, *FF*, *FA* and *FPW*) were composed of seven batches of sows, all being in the susceptible health state; the other farms were empty. At the end of the first year, i.e. after a period of population's initialisation, one HEV exposed gilt was introduced in a farm when a replacement event happens. The index farm was sampled according to different criteria depending on the scenario tested (see below). We assumed no subsequent introduction of HEV infected animals on the index farm. Simulations were run for five years after HEV introduction. One hundred simulations were run for each tested scenario. The number of animals in each epidemiological state in every pen of every farm was recorded four times a year.

2.4. Assessment of characteristics related to HEV spread in the network and evaluation of potential scenarios

2.4.1. Outcomes

Within-farm HEV dynamics was described by reporting within-herd HEV prevalence in sows and growing pigs on the index farm and HEV on-farm persistence five years post-introduction. Three outcomes were then selected to assess HEV spread in the network and evaluate the risk of HEV introduction into the food chain: *(i)* the proportion of HEV positive farms over the study period, i.e. the proportion of farms having at least one HEV-infected animal; *(ii)* the time at which farms got infected; *(iii)* the proportion of HEV-positive pigs sent to the slaughterhouse over the study period.

2.4.2. *Scenarios*

Eight different scenarios were run, as described in Table 5 to explore the impact of the type of the farm of introduction (*SEL*, *MU*, *FF* or *FA*) and of decreasing IMV prevalence in the community (going from 100% to 60% of IMV-positive FF farms) on the outcomes.

Table 5. Description of the different scenarios (S) of the HEV between-herd model.

IMV: immunomodulating virus, *SEL*: nucleus farm, *MU*: multiplication farm, *FF*: farrow-to-finish farm, *FA*: farrowing farm.

Proportion of IMV-free FF farms	**Type of the index farm**			
	***SEL* with** $pExt_i^{fi} > 0.1$	***MU* with** $pExt_i^{fi} > 0.1$	***FF* with more than 5 different contacts**	***FA* with more than 5 different contacts**
0	S1	S2	S3	S4
0.4	S5	S6	S7	S8

2.4.3. *Statistical models*

Three statistical models were built:

- A logistic regression was performed to compare the proportion of HEV-infected farms in the community depending on the type of the index farm and on the proportion of IMV-free FF farms in the community.
- A cox-proportional hazard model was used to assess the influence of four variables on farms' HEV positivity, with the simulation being included as a frailty effect. The four explanatory variables were: *(i)* at the population scale: the type of the index farm and the proportion of IMV-free FF farms; *(ii)* at the individual farm scale: the farm type and the IMV-status (positive or negative). The effect of the interaction between the farm type and the farm IMV-status was also evaluated.
- A generalised estimating equation (GEE) logistic regression was used to compare HEV prevalence in pigs slaughtered in the community depending on the type of the index farm and on the proportion of IMV-free FF farms in the community. The simulation was included as a repeated statement in the model to take into account the non-independence of the proportions of positive pigs for the different farms in a given simulation.

Statistics were performed using SAS 9.1. software (functions *proc logistic*, *proc genmod* and *proc phreg*).

3. Results

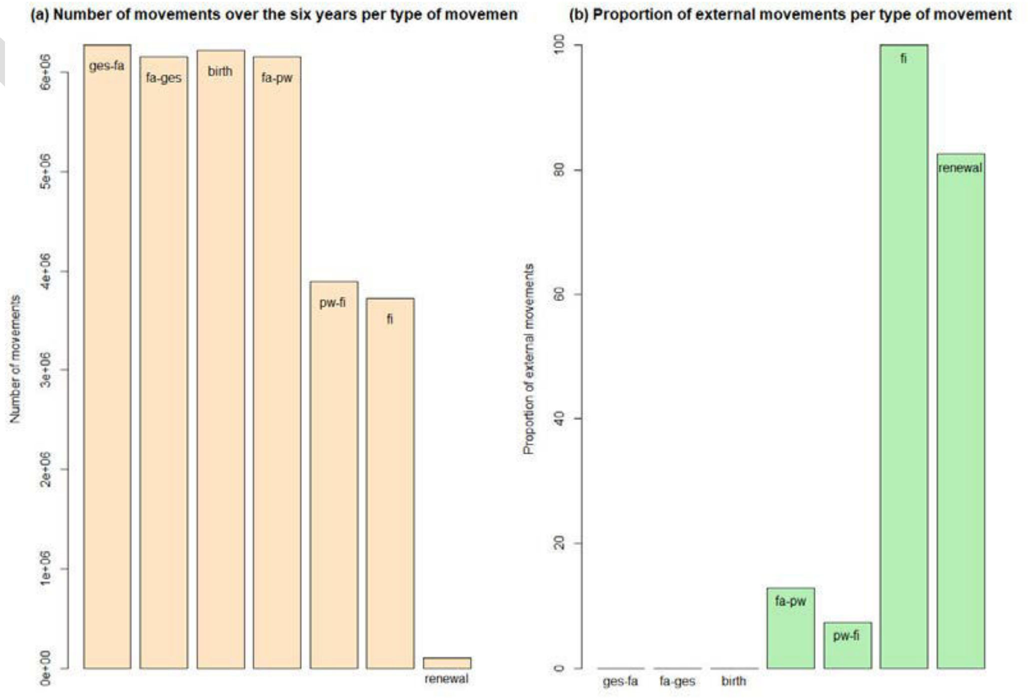
3.1. Descriptive results of the population and epidemiological dynamics

3.1.1. Demographics

At the end of the study period, an average of 406,560 sows and 5,456,799 pigs were present in the community which is consistent with the expected number of pigs on 3,017 farms. A total of 32,629,140 movements occurred over the six years (Supplementary File 1). Among them, 15.3% were between-farm movements when the others were within-herd (i.e. between-sector). More precisely, 12.9%, 7.4% of *fa-pw* and *pw-fi* movements were external, respectively.

Supplementary File 1. Simulated network description: number of movements (a) and proportion of external movements (b) per type of movement

ges-fa: movements from the gestation to the farrowing sector; *fa-ges*: movements from the farrowing to the gestation sector; *fa-pw*: movements from the farrowing to the post-weaning sector; *fi*: movements from the finishing sector to the slaughterhouse.

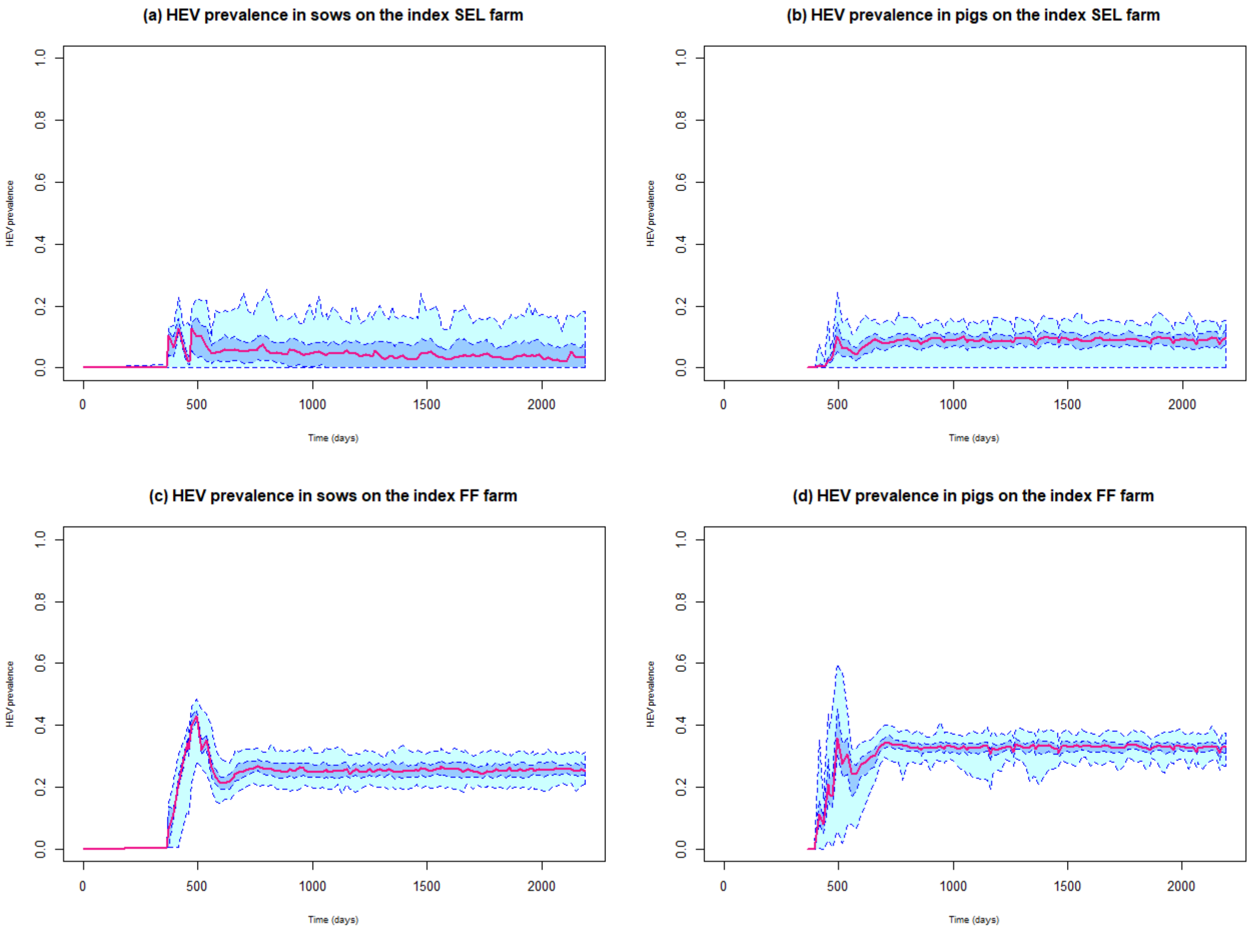


3.1.2. *HEV dynamics on the index farm*

After the introduction of an HEV-infected gilt in the gestation 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 (Supplementary File 2). 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. HEV prevalence levels were lower on *SEL* and *MU* farms than on *FF* and *FA* farms (Supplementary File 2).

Supplementary File 2. HEV prevalence in sows and growing pigs (median, 50% and 95%) on the index farm in case of HEV introduction on a nucleus (a and b) or farrow-to-finish (c and d) farm (Scenarios S1 and S3).

Pink line: median; dark blue area: 50%; light blue area: 95%; SEL: nucleus farm; FF: farrow-to-finish farm

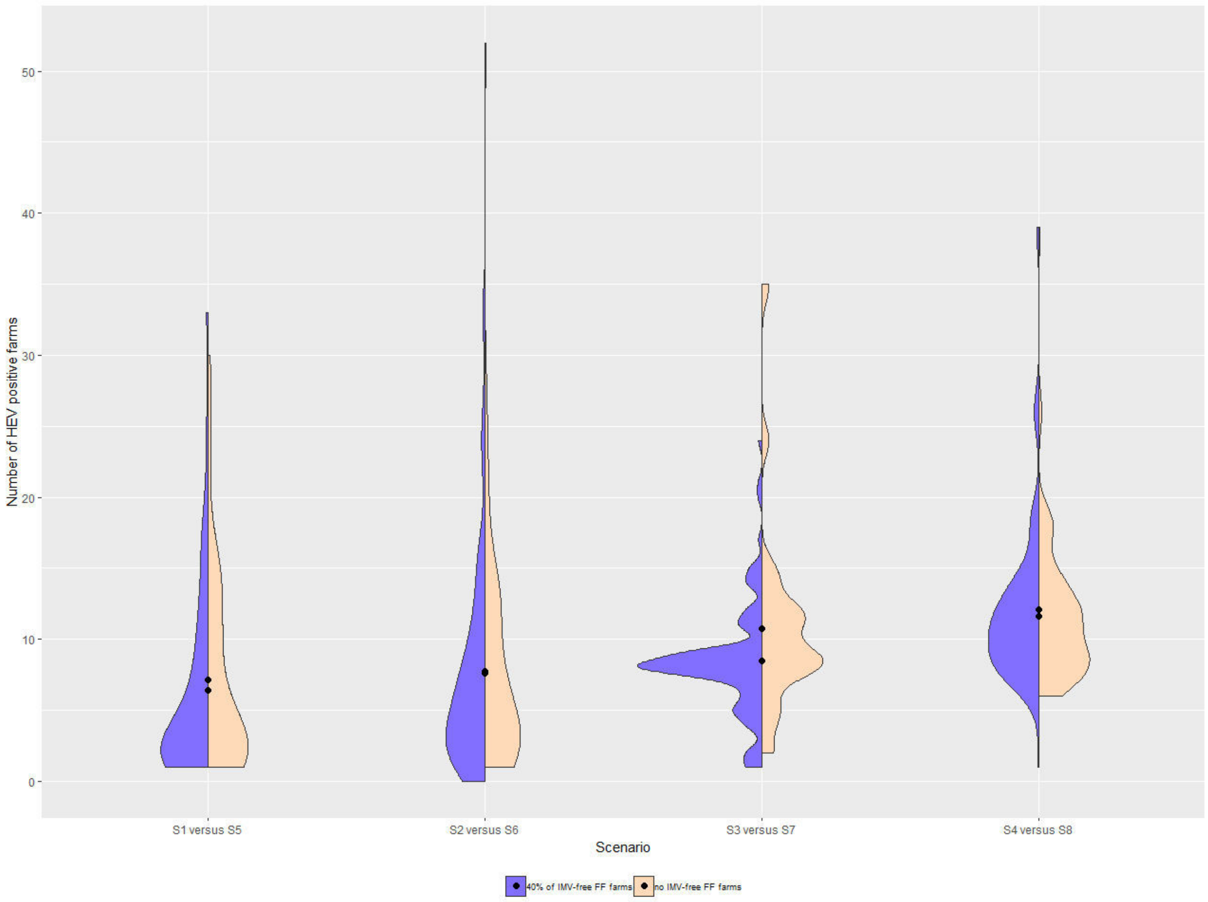


3.2. Factors affecting HEV spread in the community

The distribution of the number of HEV positive farms in the eight tested scenarios is presented in Figure 5. The maximum number of positive farms was 52, with on average nine farms getting infected. In case of *FA* index farm, at least six farms were infected when all *FF* farms were IMV-positive. The minimal number of infected farms fell to one when the proportion of IMV-positive herds was reduced to 60%.

Figure 5. Distribution of the number of HEV positive farms depending on the scenario

S: scenario; FF: farrow-to-finish pig farm.



As shown in Table 6, the proportion of HEV-positive farms over the study period was affected both by the type of the index farm, with a higher proportion of infected farms in case of HEV introduction on a *MU*, *FF*, *FA* farm compared to on a *SEL* farm (Odds Ratio = 1.14 [1.06-1.23], OR = 1.42 [1.33-1.52] and OR = 1.76 [1.65-1.88], respectively), and by the proportion of IMV-free *FF* farms in the community (OR = 0.93 [0.89-0.97] when the prevalence of IMV-positive farms was 60% compared to 100%).

Table 6. Effect of the index farm and of the IMV situation in the community on the farm-level prevalence over the study period

Summary statistics obtained thanks to a multivariate logistic regression.

Variable	Modality	Results of the multivariate model Odds Ratio [95% CI]	 p-value
Type of the index farm		Chi² = 335.58	**p < 0.01**
	SEL	-	-
	MU	1.14 [1.06-1.23]	p < 0.01
	FF	1.42 [1.33-1.52]	p < 0.01
	FA	1.76 [1.65-1.88]	p < 0.01
Proportion of IMV-free FF farms		Chi² = 10.11	**p < 0.01**
	0	-	-
	0.4	0.93 [0.89-0.97]	p < 0.01

As shown in Table 7, farms got infected earlier in case of HEV introduction on a *FF* or *FA* farm (Hazard Ratio = 1.49 [1.30-1.71] and HR = 1.75 [1.53-2.00], respectively) compared to an introduction on a *SEL* farm. The farm type was also associated with the time to HEV infection with earlier infection of *PWF* farms compared to the other farm types (HR = 1.25 [1.08-1.45]). The proportion of IMV free farms did not significantly influence the time to infection.

Table 7. Effect of population and farm features on the farms' time to HEV infection

Summary statistics obtained thanks to a cox-proportional hazard model with the simulation being included as a frailty effect.

	Variable	Modality	Results of the multivariate model Hazard Ratio [95% CI]	 p-value
Population features	**Type of the index farm**		Chi² = 93.41	**p < 0.01**
		SEL	-	-
		MU	1.05 [0.91-1.21]	p > 0.20
		FF	1.49 [1.30-1.71]	p < 0.01
		FA	1.75 [1.53-2.00]	p < 0.01
	Proportion of IMV-free FF farms		Chi² = 0.39	p > 0.10
		0	-	-
		0.4	0.97 [0.88-1.07]	p > 0.10
Farm features	**Farm type**		Chi² = 2544.42	**p < 0.01**
		SEL	-	-
		MU	0.60 [0.51-0.70]	p < 0.01
		FF	0.22 [0.19-0.25]	p < 0.01
		FA	0.83 [0.69-0.99]	p < 0.05

	FPW	0.27 [0.21-0.36]	p < 0.01
	PW	1.20 [0.85-1.70]	p > 0.20
	PWF	1.25 [1.08-1.45]	p < 0.01
	FI	0.77 [0.66-0.89]	p < 0.01
Farm's IMV status		Chi² = 0.15	p > 0.20
	positive	-	-
	negative	1.02 [0.92-1.13]	p > 0.20

3.3. Factors affecting the risk of slaughtering HEV-positive pigs

The type of the index farm was associated with the proportion of HEV-positive pigs slaughtered ($p < 0.01$). HEV introduction in a *MU*, *FF* or *FA* farm led to a higher risk of having HEV-positive livers entering the food chain compared to the HEV introduction on a nucleus farm (OR = 2.07 [1.69-2.55], OR = 2.23 [1.85-2.70] and OR = 4.41 [3.79-5.28], respectively; Table 8). Reducing the prevalence of IMV-infected *FF* farms was associated with a lower risk of slaughtering HEV-positive pigs (OR = 0.88 [0.79-0.98], Table 8).

Table 8. Effect of the type of the index farm and of the IMV situation in the community on the proportion of HEV-positive pigs sent to the slaughterhouse

Summary statistics obtained thanks to a generalised estimating equation (GEE) logistic regression model with the simulation being included as a repeated statement.

Variable	Modality	Results of the multivariate model	
		Odds Ratio [95% CI]	**p-value**
Type of the index farm		Chi² = 375.80	**p < 0.01**
	SEL	-	-
	MU	2.07 [1.69-2.55]	p < 0.01
	FF	2.23 [1.85-2.70]	p < 0.01
	FA	4.47 [3.79-5.28]	p < 0.01
Proportion of IMV-free FF farms		Chi² = 5.53	**p < 0.05**
	0	-	-
	0.4	0.88 [0.79-0.98]	p < 0.05

4. Discussion and conclusions

Though previous studies have shown the potential role of pig trade in the spread of HEV (Nantel-Fortier et al., 2016; Salines et al., 2018), they did not make it possible to describe HEV diffusion at the territory scale in a dynamic and precise way, or to explain the reasons for HEV spread and persistence in the pig production sector, or to assess the efficacy of HEV control measures in the country. This is the reason why the present study reports on the design of a between-herd HEV model that combines HEV within-farm dynamics with pig trade network. For this model, the chosen level of representation was the pen. Indeed, it made it possible to mimic HEV within-farm dynamics consistently with HEV behaviour described in Salines et al. (2019c). Moreover, the pen scale appeared as the most relevant one to represent the within-pen environmental accumulation and transmission of HEV, that has been previously evidenced as a pivotal transmission pathway (Andraud et al., 2013). HEV epidemiological parameters were estimated from several experimental trials (Andraud et al., 2013; Andraud et al., 2014; Salines et al., 2015). The majority of them differed according to the animal's health status regarding the IMV: expanded latency and infectious periods, higher transmission rates for IMV-positive animals than for IMV-negative ones. Nucleus and multiplication farms were considered free from immunomodulating viruses consistently with health situations of these farm types in France (as stated in the health charter of pig producers, available online[1]). All or part of production farms were considered IMV-positive, depending on the scenarios tested. In the case of an IMV-infected farm, the HEV epidemiological parameters were the same for all animals, meaning that all HEV infected animals were considered co-infected with the IMV. By doing so, the frequency of co-infection was over-estimated, as well as all HEV outcomes.

Regarding the population structure, the 3,017 represented farms corresponded to French farms belonging to a single community as described in the analysis of the French network of pig movements (Salines et al., 2017b). These farms have therefore preferential trade relationships likely to favour spread of pathogens. All farms were composed of a given number of pens, grouped into rooms, themselves grouped into sectors. The farm size was standardized for all farms within a farm type, which is one of the limitations of the model since the size seems to be a risk factor as regards HEV (Di Bartolo et al., 2008; Li et al., 2009; Jinshan et al., 2010; Hinjoy et al., 2013; Walachowski et al., 2014); this point would require future improvements to fit real data better. The within-farm demographics was deterministically driven by the time pigs should stay in each sector, related to the batch-management system. Again, the batch-management system was the same for all farms (seven batches, i.e. three weeks interval) which could be upgraded in the future to make it possible to explore the effect of the batch-management system, which was shown to affect HEV on-farm persistence (Salines et al.,

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[1] https://www.ifip.asso.fr/fr/content/eqs-naissance-d%E2%80%99une-charte-sanitaire-dans-la-fili%C3%A8re-g%C3%A9n%C3%A9tique-fran%C3%A7aise

2019c). The between-farm demographics was derived from real data recorded in the national pig movement database from 2012 to 2015. These data were incorporated in the model in the form of a contact matrix with probabilities *(i)* for internal or external transfer *(ii)* and, in the latter case, for transfer to a given neighbour. By doing so, possible temporal evolutions of the pig movement network were not taken into account, but the descriptive analysis we had previously performed showed a stable structure of the network over the study period (Salines et al., 2017b).

When introduced on an IMV-positive *FF* farm, HEV spread in an enzootic way, first in the reproductive herd before affecting piglets and growing pigs. Though the prevalence levels observed in this model were higher than in the within-herd model previously built (Salines et al., 2019c) probably in relation with the co-infection of all animals, the overall HEV behaviour was consistent with the published data (Salines et al., 2019b). HEV prevalence was lower on *SEL* and *MU* farms compared to *FF* farms, which could be explained by their IMV-free status as described in Salines et al. (2019c). Our analysis showed that the number of contaminated farms in the community over the study period was affected by the type of the index farm, with an introduction on a *MU*, *FF* and *FA* farm being more risky than on a *SEL* farm, with an increasing number of positive farms from *MU* to *FA* index farms. This could be explained *(i)* by the different contact patterns between these four farm types, with *FA* farms sending pigs regularly and at age at which they are likely to be HEV-positive; *(ii)* by their different health status regarding the IMV, with *SEL* and *MU* farms being IMV-free when *FF* and *FA* farms were IMV-positive, thus having a higher HEV prevalence and long-lasting persistence. The influence of IMVs was confirmed by the fact that improving the population health status (i.e. decreasing the prevalence of IMV-positive *FF* farms) led to a reduced number of HEV-positive farms over the study period, which highlights again the role of intercurrent pathogens in the HEV dynamics. An interesting outcome is that the dynamics of HEV spread was affected by the farm type (both the type of the index farm and the type of the infected farm) but not by the IMV-related variables. Indeed, the introduction on a *FF* or on a *FA* farm led to a quicker contamination of other farms, which could again be explained by the riskier contact patterns of these farms. Moreover, all farm types were likely to be infected later, except *PWF* farms which got HEV infected earlier because they are frequent receivers of pigs at a risky age of infection. The non-significant results for *PW* farms was probably related to the lack of statistical power given the low number of *PW* farms in the community (only eight). In addition, if *SEL* farms send animals frequently, they send less animals than *FA*, *PW* and *PWF* farms and at a less risky age regarding HEV, the prevalence being low at late fattening stage. Considered together, these results show that at an individual scale, the farm's susceptibility to HEV infection was more related to its frequency of animals' introduction than to its own health situation but that on a collective scale, HEV spread on a breeding community was linked both to the population health status and to the contact patterns. Finally, our analyses evidenced that the risk of slaughtering HEV-positive pigs was related to the type of the index farm, with a 4-times higher risk in the case of introduction on a *FA* farm, and to the population health status, with a lower risk when the prevalence of IMV-positive *FF* farms was decreased.

This model developed at a territory scale, has revealed differences in HEV spatial diffusion patterns related to the introduction pathway, the health status of the pig population, and the type of the exposed farms. If *SEL* and *MU* farms are often considered as the riskiest herds in the pig production sector due to large contact chains, the HEV case highlights that contact patterns have to be considered together with farms' health status regarding immunomodulating pathogens. It appears therefore essential that *SEL* and *MU* farms preserve their IMV-free status, when production farms implement eradication or control programmes of IMVs. Our model can be viewed as an experimental one, with theoretical results that cannot be directly extrapolated to the natural conditions. However, if not relevant from an absolute point of view, they make it possible to compare different scenarios and to identify the riskiest elements. As such, these outcomes can support surveillance strategies by helping target farms having a dense contact network and poor health situation. Our study also gives insight on the HEV diffusion pathway in a HEV-free farming community, which could be structured to provide processing companies with safe livers for the production of raw pork products. Further developments of the model would also make it possible to modify the network structure while simulations are running. This could be particularly useful to simulate trade restriction measures or trade reorganisation, which could occur in the case of the introduction of a regulated disease, an epidemic peak or a modification of the producers' supply network. Incorporating intermediate loading operations could also make it possible to take into account a possible environmental transmission with trucks acting as mechanical vector. These results could also be used as inputs in other studies, e.g. in a quantitative microbiological risk assessment aiming at assessing the risk of consumers to be exposed to HEV. Finally, designing multi-scale models combining complex within-farm dynamics with animal demographics appears particularly relevant to deal with such multifaceted public health issues. Thus, this kind of research approach should be fostered in the future to have a comprehensive and detailed view of pathogen dynamics on a territory scale and support decision-making.

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Authors' contributions

MS and SW designed the mathematical model, implemented the model in the SimInf R package and performed the simulations. MS drafted the manuscript. All authors participated in data analysis and interpretation and in the manuscript writing. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that they have no competing interests.

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Ce qu'il faut retenir

A partir d'une approche innovante de modélisation multi-échelles, le modèle développé a apporté de nouveaux éléments dans la compréhension de la dynamique de l'infection par le HEV dans une communauté d'élevages. Il a permis de mettre en évidence l'influence du type d'élevage d'introduction, du type d'élevage exposé et du statut sanitaire de la population vis-à-vis des pathogènes intercurrents. Ce travail pourrait ainsi contribuer au développement d'une stratégie de surveillance et de maîtrise du risque HEV dans la filière porcine fondée sur le risque que présentent les élevages, en combinant les éléments apportés par les deux approches de modélisation intra- et inter-troupeaux présentés dans les chapitres II et III.

Take home message

Based on an innovative multi-scale modelling approach, the model developed has brought new elements to the understanding of the dynamics of HEV infection in a pig farming community. It highlighted the influence of the type of introduction farm, the type of exposed farm and the health status of the population with respect to intercurrent pathogens. This work could thus contribute to the development of a strategy for monitoring and controlling HEV risk in the pig sector based on the risk posed by pig herds, by combining the factors provided by the two approaches of within- and between-herd modelling presented in Chapters II and III.