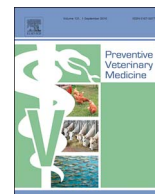




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## Combining network analysis with epidemiological data to inform risk-based surveillance: Application to hepatitis E virus (HEV) in pigs



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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; Beaune 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*<sup>1</sup> 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<sup>®</sup> by Adaltis (Ingen, France) adapted to pig serum.

### 2.3. Statistical analyses

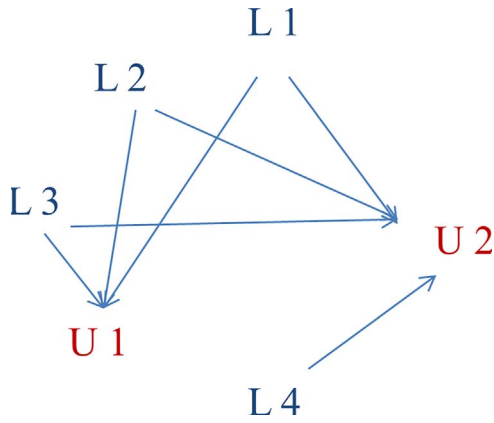
#### 2.3.1. Farm centrality indicators and within-farm HEV seroprevalence

**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.

<sup>1</sup> 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.

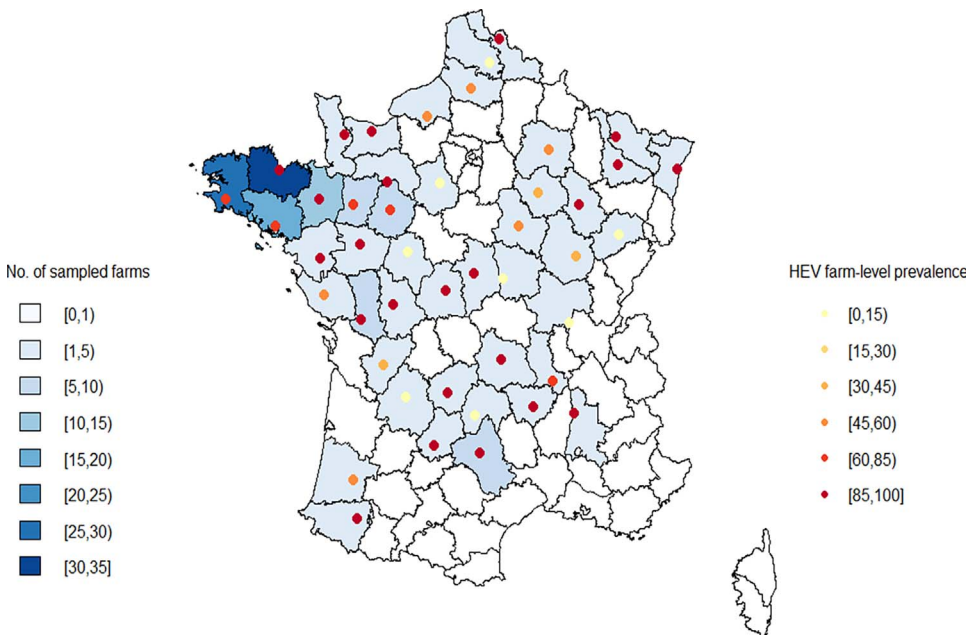
2.4. Indicator of risk of exposure to HEV of French départements

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



**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.

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  $2.17 \cdot 10^{-9}$  and  $2.18 \cdot 10^{-9}$ , 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

**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 <sup>-9</sup>		–	–	–	–
> 2.176.10 <sup>-9</sup>		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 <sup>-9</sup>		–	–	–	–
> 2.175.10 <sup>-9</sup>		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



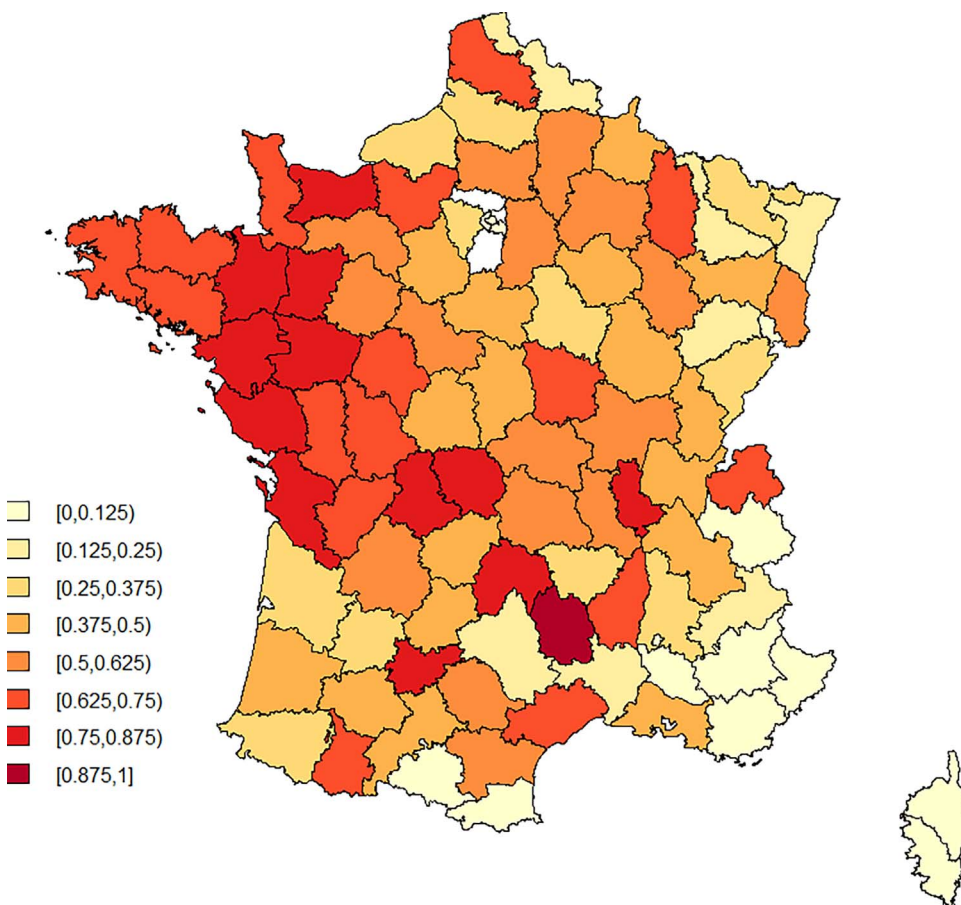


Fig. 3. Median risk of French départements being exposed to HEV through external incoming pig movements (10,000 simulations). An indicator of the risk of a French département being exposed to HEV was calculated as the number of infected movements it had received from source départements divided by its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

## References

- Adlhoch, C., Avellon, A., Baylis, S.A., Ciccaglione, A.R., Couturier, E., de Sousa, R., Epstein, J., Ethelberg, S., Faber, M., Feher, A., Ijaz, S., Lange, H., Mandakova, Z., Mellou, K., Mozalevskis, A., Rimhanen-Finne, R., Rizzi, V., Said, B., Sundqvist, L., Thornton, L., Tosti, M.E., van Pelt, W., Aspinall, E., Domanovic, D., Severi, E., Takkinen, J., Dalton, H.R., 2016. Hepatitis E virus: assessment of the epidemiological situation in humans in Europe, 2014/15. *J. Clin. Virol.: Off. Publ. Pan Am. Soc. Clin. Virol.* 82, 9–16.
- Beaune, G., Vergu, E., Ezanno, P., 2015. Modelling of paratuberculosis spread between dairy cattle farms at a regional scale. *Vet. Res.* 46, 111.
- Bigras-Poulin, M., Thompson, R.A., Chriel, M., Mortensen, S., Greiner, M., 2006. Network analysis of Danish cattle industry trade patterns as an evaluation of risk potential for disease spread. *Prev. Vet. Med.* 76, 11–39.
- Bigras-Poulin, M., Barfod, K., Mortensen, S., Greiner, M., 2007. Relationship of trade patterns of the Danish swine industry animal movements network to potential disease spread. *Prev. Vet. Med.* 80, 143–165.
- Buttner, K., Krieter, J., Traulsen, A., Traulsen, I., 2013. Static network analysis of a pork supply chain in Northern Germany-characterisation of the potential spread of infectious diseases via animal movements. *Prev. Vet. Med.* 110, 418–428.
- Buttner, K., Krieter, J., Traulsen, I., 2015. Characterization of contact structures for the spread of infectious diseases in a pork supply chain in northern Germany by dynamic network analysis of yearly and monthly networks. *Transbound. Emerg. Dis.* 62, 188–199.
- Colson, P., Borentain, P., Queyriaux, B., Kaba, M., Moal, V., Gallian, P., Heyries, L., Raoult, D., Gerolami, R., 2010. Pig liver sausage as a source of hepatitis E virus transmission to humans. *J. Infect. Dis.* 202, 825–834.
- Dalton, H.R., Bendall, R., Ijaz, S., Banks, M., 2008. Hepatitis E: an emerging infection in developed countries. *Lancet Infect. Dis.* 8, 698–709.
- Dorjee, S., Revie, C.W., Poljak, Z., McNab, W.B., Sanchez, J., 2013. Network analysis of swine shipments in Ontario, Canada, to support disease spread modelling and risk-based disease management. *Prev. Vet. Med.* 112, 118–127.
- EFSA, B.P., Ricci, A., Allende, A., Bolton, D., Chemaly, M., Davies, R., Fernandez Escamez, P.S., Herman, L., Koutsoumanis, K., Lindqvist, R., Nørrung, B., Robertson, L., Ru, G., Sanaa, M., Simmons, M., Skandamis, P., Snary, E., Speybroeck, N., Ter Kuile, B., Threlfall, J., Wahlström, H., Di Bartolo, L., Johne, R., Pavio, N., Rutjes, S., van der Poel, W., Vasickova, P., Hempen, M., Messens, W., Rizzi, V., Latronico, G., Girones, R., 2017. Public health risks associated with hepatitis E virus (HEV) as a food-borne pathogen. *EFSA J.* 15, e04886-n/a.
- Feurer, C., Le Roux, A., Rossel, R., Barnaud, E., Dumarest, M., Garry, P., Pavio, N., 2017. High load of hepatitis E viral RNA in pork livers but absence in pork muscle at French slaughterhouses. *Int. J. Food Microbiol.*
- Frössling, J., Ohlson, A., Bjorkman, C., Hakansson, N., Noremark, M., 2012. Application of network analysis parameters in risk-based surveillance – examples based on cattle trade data and bovine infections in Sweden. *Prev. Vet. Med.* 105, 202–208.
- Frössling, J., Nusinovic, S., Noremark, M., Widgren, S., Lindberg, A., 2014. A novel method to identify herds with an increased probability of disease introduction due to animal trade. *Prev. Vet. Med.* 117, 367–374.
- Green, D.M., Kiss, I.Z., Mitchell, A.P., Kao, R.R., 2008. Estimates for local and movement-based transmission of bovine tuberculosis in British cattle. *Proc. R. Soc. B: Biol. Sci.* 275, 1001–1005.
- Guinat, C., Relun, A., Wall, B., Morris, A., Dixon, L., Pfeiffer, D.U., 2016. Exploring pig trade patterns to inform the design of risk-based disease surveillance and control strategies. *Sci. Rep.* 6, 28429.
- Ihaka, R., Gentleman, Robert, 1996. R: a language for data analysis and graphics. *J. Comput. Gr. Stat.* 5, 299–314.
- Keeling, M., 2005. The implications of network structure for epidemic dynamics. *Theor. Popul. Biol.* 67, 1–8.
- Lee, K., Polson, D., Lowe, E., Main, R., Holtkamp, D., Martinez-Lopez, B., 2017. Unraveling the contact patterns and network structure of pig shipments in the United States and its association with porcine reproductive and respiratory syndrome virus (PRRSV) outbreaks. *Prev. Vet. Med.* 138, 113–123.
- Lindstrom, T., Lewerin, S.S., Wennergren, U., 2012. Influence on disease spread dynamics of herd characteristics in a structured livestock industry. *Journal of the Royal Society. Interface* 9, 1287–1294.
- Lloyd-Smith, J.O., Schreiber, S.J., Kopp, P.E., Getz, W.M., 2005. Superspreading and the effect of individual variation on disease emergence. *Nature* 438, 355–359.
- Martínez-López, B., Perez, A.M., Sánchez-Vizcaíno, J.M., 2009. Combined application of social network and cluster detection analyses for temporal-spatial characterization of animal movements in Salamanca, Spain. *Prev. Vet. Med.* 91, 29–38.
- Martin, V., Zhou, X., Marshall, E., Jia, B., Fusheng, G., FrancoDixon, M.A., DeHaan, N., Pfeiffer, D.U., Soares Magalhães, R.J., Gilbert, M., 2011. Risk-based surveillance for avian influenza control along poultry market chains in South China: the value of social network analysis. *Prev. Vet. Med.* 102, 196–205.
- Moal, V., Gerolami, R., Colson, P., 2012. First human case of co-infection with two different subtypes of hepatitis E virus. *Intervirology* 55, 484–487.
- Motte, A., Roquelaure, B., Galambun, C., Bernard, F., Zandotti, C., Colson, P., 2012. Hepatitis E in three immunocompromised children in southeastern France. *J. Clin. Virol.: Off. Publ. Pan Am. Soc. Clin. Virol.* 53, 162–166.

- Nöremark, M., Håkansson, N., Lewerin, S.S., Lindberg, A., Jonsson, A., 2011. Network analysis of cattle and pig movements in Sweden: measures relevant for disease control and risk based surveillance. *Prev. Vet. Med.* 99, 78–90.
- Nantel-Fortier, N., Letellier, A., Lachapelle, V., Fravallo, P., L'Homme, Y., Brassard, J., 2016. Detection and phylogenetic analysis of the hepatitis e virus in a canadian swine production network. *Food Environ. Virol.* 8 (4), 296–304.
- Natale, F., Giovannini, A., Savini, L., Palma, D., Possenti, L., Fiore, G., Calistri, P., 2009. Network analysis of Italian cattle trade patterns and evaluation of risks for potential disease spread. *Prev. Vet. Med.* 92, 341–350.
- Nicolas, G., Durand, B., Duboz, R., Rakotondravao, R., Chevalier, V., 2013. Description and analysis of the cattle trade network in the Madagascar highlands: potential role in the diffusion of rift valley fever virus. *Acta Trop.* 126, 19–27.
- Ortiz-Pelaez, A., Pfeiffer, D.U., Soares-Magalhães, R.J., Guitian, F.J., 2006. Use of social network analysis to characterize the pattern of animal movements in the initial phases of the 2001 foot and mouth disease (FMD) epidemic in the UK. *Prev. Vet. Med.* 76, 40–55.
- Pavio, N., Meng, X.J., Renou, C., 2010. Zoonotic hepatitis E: animal reservoirs and emerging risks. *Vet. Res.* 41, 46.
- Porphyre, T., McKenzie, J., Stevenson, M.A., 2011. Contact patterns as a risk factor for bovine tuberculosis infection in a free-living adult brushtail possum *Trichosurus vulpecula* population. *Prev. Vet. Med.* 100, 221–230.
- Rautureau, S., Dufour, B., Durand, B., 2012. Structural vulnerability of the French swine industry trade network to the spread of infectious diseases. *Anim.: Int. J. Anim. Biosci.* 6, 1152–1162.
- Reist, M., Jemmi, T., Stark, K.D., 2012. Policy-driven development of cost-effective, risk-based surveillance strategies. *Prev. Vet. Med.* 105, 176–184.
- Relun, A., Grosbois, V., Sánchez-Vizcaíno, J.M., Alexandrov, T., Feliziani, F., Waret-Szkuta, A., Molia, S., Etter, E.M.C., Martínez-López, B., 2016. Spatial and functional organization of pig trade in different european production systems: implications for disease prevention and control. *Front. Vet. Sci.* 3.
- Ribbens, S., Dewulf, J., Koenen, F., Mintiens, K., de Kruif, A., Maes, D., 2009. Type and frequency of contacts between Belgian pig herds. *Prev. Vet. Med.* 88, 57–66.
- Ribeiro-Lima, J., Enns, E.A., Thompson, B., Craft, M.E., Wells, S.J., 2015. From network analysis to risk analysis—An approach to risk-based surveillance for bovine tuberculosis in Minnesota, US. *Prev. Vet. Med.* 118, 328–340.
- Rogan, W.J., Gladen, B., 1978. Estimating prevalence from the results of a screening test. *Am. J. Epidemiol.* 107, 71–76.
- Rose, N., Boutrouille, A., Fablet, C., Madec, F., Eloit, M., Pavio, N., 2010. The use of Bayesian methods for evaluating the performance of a virus-like particles-based ELISA for serology of hepatitis E virus infection in swine. *J. Virol. Methods* 163, 329–335.
- Rose, N., Lunazzi, A., Dorenlor, V., Merbah, T., Eono, F., Eloit, M., Madec, F., Pavio, N., 2011. High prevalence of Hepatitis E virus in French domestic pigs. *Comp. Immunol. Microbiol. Infect. Dis.* 34, 419–427.
- SAS, 2014. SAS, 9.4. Language Reference: Concepts, 3rd ed. SAS Institute Inc., Cary, NC.
- Salines, M., Andraud, M., Rose, N., 2017a. From the epidemiology of hepatitis E virus (HEV) within the swine reservoir to public health risk mitigation strategies: a comprehensive review. *Vet. Res.* 48, 31.
- Salines, M., Andraud, M., Rose, N., 2017b. Pig movements in France: designing network models fitting the transmission route of pathogens. *PLoS One* 12, e0185858.
- Schärrer, S., Widgren, S., Schwermer, H., Lindberg, A., Vidondo, B., Zinsstag, J., Reist, M., 2015. Evaluation of farm-level parameters derived from animal movements for use in risk-based surveillance programmes of cattle in Switzerland. *Vet. Res.* 11, 149.
- Sintayehu, D.W., Prins, H.H., Heitkonig, I.M., de Boer, W.F., 2017. Disease transmission in animal transfer networks. *Prev. Vet. Med.* 137, 36–42.
- Stärk, K.D.C., Regula, G., Hernandez, J., Knopf, L., Fuchs, K., Morris, R.S., Davies, P., 2006. Concepts for risk-based surveillance in the field of veterinary medicine and veterinary public health: review of current approaches. *BMC Health Serv. Res.* 6, 20.
- Thakur, K.K., Sanchez, J., Hurnik, D., Poljak, Z., Opps, S., Revie, C.W., 2015. Development of a network based model to simulate the between-farm transmission of the porcine reproductive and respiratory syndrome virus. *Vet. Microbiol.* 180, 212–222.
- Thakur, K.K., Revie, C.W., Hurnik, D., Poljak, Z., Sanchez, J., 2016. Analysis of swine movement in four canadian regions: network structure and implications for disease spread. *Transbound. Emerg. Dis.* 63, e14–26.
- Walachowski, S., Dorenlor, V., Lefevre, J., Lunazzi, A., Eono, F., Merbah, T., Eveno, E., Pavio, N., Rose, N., 2014. Risk factors associated with the presence of hepatitis E virus in livers and seroprevalence in slaughter-age pigs: a retrospective study of 90 swine farms in France. *Epidemiol. Infect.* 142, 1934–1944.
- Wasserman, S., Faust, K., 1994. *Social Network Analysis: Methods and Applications*.