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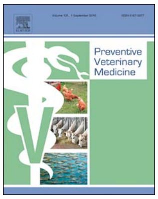

Combining network analysis with epidemiological data to inform risk-based surveillance: Application to hepatitis E virus (HEV) in pigs

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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).