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Dynamics of livestock-associated methicillin resistant *Staphylococcus aureus* in pig movement networks: Insight from mathematical modeling and French data

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ABSTRACT

Livestock-associated methicillin resistant *Staphylococcus aureus* (LA-MRSA) colonizes livestock animals worldwide, especially pigs and calves. Although frequently carried asymptomatically, LA-MRSA can cause severe infections in humans. It is therefore important to better understand LA-MRSA spreading dynamics within pig farms and over pig movement networks, and to compare different strategies of control and surveillance. For this purpose, we propose a stochastic meta-population model of LA-MRSA spread along the French pig movement network (n = 10,542 farms), combining within- and between-farm dynamics, based on detailed data on breeding practices and pig movements between holdings. We calibrate the model using French epidemiological data. We then identify farm-level factors associated with the spreading potential of LA-MRSA in the network. We also show that, assuming control measures applied in a limited (n = 100) number of farms, targeting farms depending on their centrality in the network is the only way to significantly reduce LA-MRSA global prevalence. Finally, we investigate the scenario of emergence of a new LA-MRSA strain, and find that the farms with the highest indegree would be the best sentinels for a targeted surveillance of such a strain's introduction.

1. Introduction

Livestock farms are often at high epidemiological risk, in particular farms with a dense animal population (Meadows et al., 2018). Disease spread control in livestock populations is a challenge for animal health and welfare (Broom and Corke, 2002), as well as for farmers in terms of economic and livelihood loss due to productivity drops (Food and Agriculture Organization, 2017). It may also be a concern for human health in the case of zoonotic diseases (Jones et al., 2008). In this context, over recent years, the worldwide spread of antimicrobial-resistant bacteria among livestock has emerged as a major threat that needs to be accounted for to fully understand the global increase of antimicrobial resistance in a one-health perspective (Laxminarayan et al., 2013; Nadimpalli et al., 2018; Puyvelde et al., 2017).

Livestock-associated strains of methicillin-resistant *Staphylococcus aureus* (LA-MRSA) have been identified since the 2000's in farm animals, especially pigs and veal calves, as well as in humans in occupational contact with livestock, in several European countries (Armand-Lefevre et al., 2005; Nadimpalli et al., 2016; Voss et al., 2005; Weese, 2010). *Staphylococcus aureus* is a Gram-positive bacterium carried asymptomatically by a large portion of human populations (Williams, 1963), and is a frequent cause of opportunistic diseases such as skin and soft tissue infections (Wertheim et al., 2005). Methicillin-resistant *S. aureus* (MRSA), that are multi-resistant to antibiotics including most β-lactams, were originally found in human populations in hospitals as sources of nosocomial infections, and then in the human community

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(Chambers and DeLeo, 2009). LA-MRSA strains, mostly belonging to the ST398 subtype in Europe (Weese, 2010), were found able to spread to human populations not in direct contact with farm animals (Kinross et al., 2017; Larsen et al., 2017; van der Mee-Marquet et al., 2011). As pigs are suspected to act as a reservoir for LA-MRSA (Crombé et al., 2013), understanding the spread dynamics of LA-MRSA within and between pig farms is key to being able to design proper surveillance and control measures. In particular, the major impact of pig movements on the spread dynamics of LA-MRSA between farms has been underlined (Broens et al., 2011; Espinosa-Gongora et al., 2012; Sieber et al., 2018).

Over the last decade, a few mathematical models have been proposed to study the spread of LA-MRSA, within a single pig herd (Sørensen et al., 2017; Sørensen et al., 2018), at the scale of a pig movement network (Ciccolini et al., 2012; Schulz et al., 2018; Schulz et al., 2019) and from a single pig farm to humans (Porphyre et al., 2012). These models allowed to explore the implementation of control interventions based on reduced antimicrobial use, reduced mixing of pigs within and between farms, improved biosecurity, movements restrictions, as well as voluntary eradication of pigs. Porphyre et al. (2012) estimated the risk of transmission to human populations even beyond farm communities if such farm-level control measures were not implemented. Finally, it was shown that a description of LA-MRSA spread at both the within- and between-herd scales is necessary when assessing control strategies (Crombé et al., 2013; Schulz et al., 2018).

Here, we propose a novel model of MRSA spread in pigs, that combines within- and between-herd epidemiological and demographic dynamics. This model is based on data from a real pig movement network at a country level and is applied to the French situation. Using the model, we aim to identify farm-related factors associated with extensive spread of LA-MRSA over the network. Additionally, we assess the effect of farm-level control measures on the network spread of LA-MRSA. Finally we aim to optimize sentinel farms selection when designing active surveillance of a new strain in the network.

2. Methods

2.1. Definitions

In the remainder of the text, the term “MRSA” will always refer to LA-MRSA. The term “sows” will always refer to the breeding sows aimed at farrowing. The term “gilt” will refer to young sows destined to replace older sows for farrowing. Several types of pig farms are defined, depending on the purpose of the farms (breeding or production) and the rearing stage at which they raise pigs (Fig. 1). Breeding farms, including nucleus (SEL) and multiplier (MU) farms, are defined as farms exporting breeding sows (28-week old gilts). Other farms, including farrowing (FA), farrowing-post-weaning (FPW), post-weaning (PW), post-weaning-finishing (PWF), finishing (FI) and farrowing-to-finishing (FF) farms, are production farms and aim at producing pigs that will be slaughtered when they are 28 weeks old. Breeding farms include a breeding herd composed of sows aimed at producing new piglets. This is also the case for some production farms: types FA, FPW and FF. The fattening herd is composed of pigs raised to be sent to slaughterhouse, or, in the case of breeding farms, exported to other farms for renewing their breeding herd (see Supplementary Material SM1, Figure S1).

2.2. Data on the French pig industry

The National Swine Identification Database (BDPORC) has recorded pig movements in France since 2010, allowing to reconstruct the network of French pig farms, which was described previously (Salines et al., 2017). This network was shown to be stable over time, with similar active nodes, network properties and connected components (Salines et al., 2017). Here, we used time-aggregated data from BDPORC for the full year 2014: the characteristics of all pig farms, including their type of activity – i.e. the age of pigs they raise (Fig. 1) – and size (Fig. 2a); and all pig movements reported at the batch level between all pairs of farms in 2014 (Fig. 2b). The total database recorded 13,124,032 pigs moved and included 20,688 sites, including breeding and production farms as defined in Section 2.1, small farms (defined as farms rearing less than 80 pigs), wild boar farms, boar stations, trade operators and slaughterhouses. However, because we aimed to study the spread of MRSA between farms through pig movements only, the database was screened and filtered to exclude types of holdings from which there were no or very little pig movements to other farms (small farms, boar stations, wild boar farms, trade operators and slaughterhouses) (Salines et al., 2017), individual farms for which no movement was recorded (i.e. inactive nodes), and types of movements that were rare and not consistent with farm types (e.g. fattening pig movements from finishing to multiplier farms). This resulted in 10,542 farms, which is consistent with the number of active nodes in the French pig industry identified in Salines et al. (2017). After filtering, 12,124,527 (92.4 % of the total recorded movements) pig movements were included.

2.3. Network analysis

In our analyses, we calculated several centrality indicators for farms within the network: outdegree, indegree, outflux, influx, betweenness, closeness, coreness and eigenvector centrality. The outdegree of farm A is the number of farms to which farm A exports pigs. The indegree of farm A is the number of farms from which farm A imports pigs. The outflux is defined as the number of pigs exported by farm A to other farms. The betweenness is the number of directed geodesics – i.e. directed shortest paths between each pair of nodes – going through farm A. Definitions for all these indicators are provided in the SM2. For the network we study, these indicators’ values have already been described in an earlier study (Salines et al., 2017).

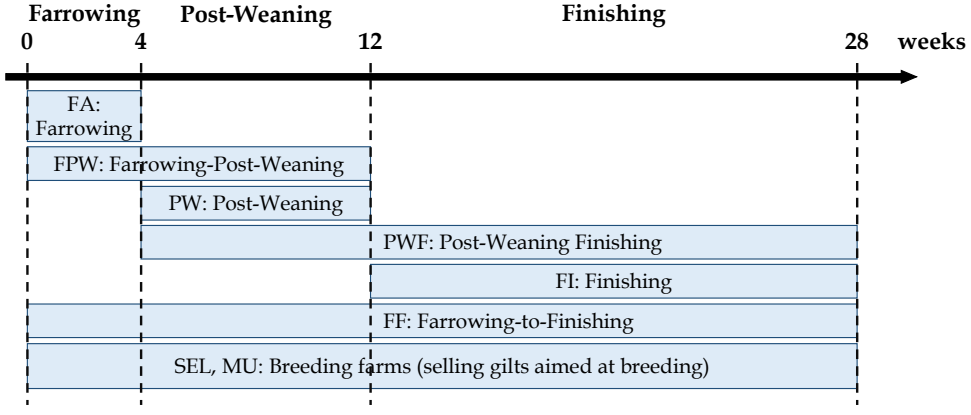


Fig. 1. Types of pig farms. Each type (or category) of farms raises pigs over one or several production steps: the Farrowing step (piglets aged 0–4 weeks old), the Post-Weaning step (4–12 weeks old) and the Finishing step (12–28 weeks old). For instance, PWF (Post-Weaning Finishing) farms raise pigs aged 4–28 weeks old, over Post-Weaning and Finishing production steps.

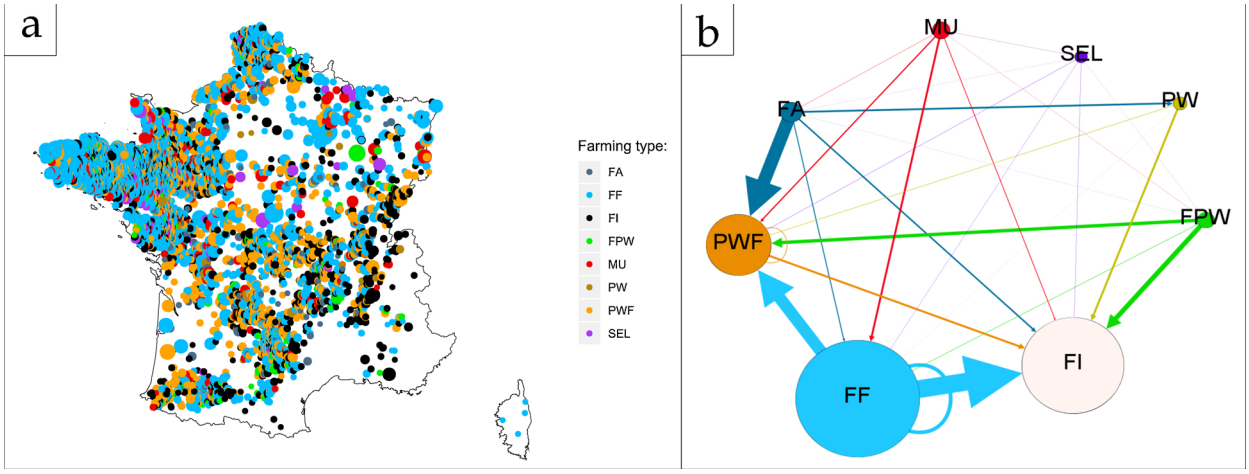


Fig. 2. Characteristics of the French pig movement network. a) Map of French pig farms in 2014. Dot colour represents the farm type (FA Farrowing, FF Farrowing-to-Finishing, FI Finishing, FPW Farrowing-Post-Weaning, MU Multiplier, PW Post-Weaning, PWF Post-Weaning Finishing, SEL Nucleus), and dot size is proportional to the number of pigs on site. b) Weighted oriented network of pig movements between farm types. Node size is proportional to the number of farms of the corresponding type; arrow size is proportional to the number of pig movements between the two farm types.

2.4. Dynamic model description

We built a discrete dynamic stochastic model of the spread of MRSA within pig farms and between them over a connected network. Two distinct processes were modelled both within and between herds: MRSA colonization and transmission dynamics on the one hand, and pig demographics on the second hand. Model parameters are summarized in Table 1, along with their assumed values.

2.4.1. Demographic model

Demographic processes were modelled deterministically, at both the within-farm and between-farm levels.

The model formalized both breeding and fattening herds within farms (Fig. 3a and SM1). The within-farm structure divided farms into four sectors: the gestation sector (GS), farrowing sector (FAS), post-weaning sector (PWS) and finishing sector (FIS). GS and FAS housed breeding sows. FAS, PWS and FIS housed fattening pigs of increasing age. Sectors were divided again into rooms: 4 rooms in GS, 1 in FAS, 2 in PWS and 4 in FIS (Fig. 3a).

We modelled a 7-batch rearing system, the most common pig management system in France (IFIP, 2016), based on a 4-week cycle for pig movements. Each room in the FAS, PWS and FIS sectors housed a single batch, resulting in seven batches of fattening pigs in total. Therefore, piglets stayed four weeks in the FAS with their mother, then 8 weeks in the PWS, and finally 16 weeks in the FIS. In total, the production cycle for fattening pigs was assumed to last for 28 weeks (Fig. 1), and farm size was supposed to be constant over time.

Pig movements between farms directly replayed the pig movement network described above: for each movement, the receiving and sending herds were extracted directly from the database. Two types of pig movements between farms were possible every four weeks. On the one hand, gilts were transferred from breeding farms to replace a proportion P_{rep} of breeding sows in production farms. P_{rep} was assumed to be on average equal to 3.19 %, based on 2014 French data in which 41.5 % of sows in a sow herd were shown to be replaced over the entire year (Badouard and Calvar, 2015). Self-renewal of sows was also possible: in this case, the replacing gilts were randomly chosen among 28-week old pigs within their own farm's finishing sector (FIS4 in Fig. 3a).

On the second hand, batches of fattening pigs could be moved between farms at two ages corresponding to two production steps: 4 weeks old (right after weaning), or 12 weeks old (for finishing). The proportion $P_{exp,farm}$ of exported pigs from a given batch depended on the farm category. For instance, 100 % of 4-week old piglets were exported from Farrowing farms, because these farms do not raise older pigs. Conversely, Farrowing-to-Finishing farms were assumed to export 12-week old pigs only. For each farm and at each production step, the number of pigs exported was computed from the network data and $P_{exp,\ farm}$. When the exportation proportion could not directly be set to 0 % or 100 %, it was computed as follows based on the BDPORC data:

$$P_{exp,farm} = \frac{Number\ of\ pigs\ of\ a\ batch\ exported}{Number\ of\ pigs\ in\ a\ batch} = \frac{\frac{Number\ of\ pigs\ exported\ in\ 2014}{Number\ of\ 4-week\ periods\ in\ a\ year}}{\frac{Number\ of\ fattening\ pigs\ in\ the\ farm\ in\ 2014}{Number\ of\ batches}} = \frac{\frac{Number\ of\ pigs\ exported\ in\ 2014}{13}}{\frac{Number\ of\ fattening\ pigs\ in\ the\ farm\ in\ 2014}{7}}$$

In this formula, we assumed that, for a given farm, the proportion of exported pigs in a batch is constant over all exportation rounds occurring every four weeks. This proportion was calculated from the number of pigs exported in 2014 and the number of fattening pigs on farm recorded for each farm in the BDPORC database.

The week of the first movement for each farm was randomly drawn among the four first weeks of simulations. The 4-week periodicity of pig movements was therefore shifted among farms, so that they did not occur at the same time in all farms.

The resulting contact matrices between farm categories are consistent with data published by the French pig industry on piglets' movements between categories of farms (Roguet and Laugé, 2009). More details on the between-farm model, including contact matrices between farm categories, are available from the SM1.

2.4.2. Epidemiological model

Pig-to-pig MRSA transmission was modelled at the within-farm scale, through a discrete time stochastic Susceptible-Colonized-Susceptible (SCS) model (Fig. 3b). Transmission could only occur within the same farm sector. Thus, the only way for MRSA to spread between farms was through movements of colonized pigs. Pigs were assumed not to change MRSA status during their between-farm transportation.

For any week t, the susceptible (i.e. non-colonized) and colonized

Table 1
Model parameters and their assumed values.

Variable	Description	Value	Source
N_f	Number of farms in the network	10,542	BDPORC
N_b	Number of farms in the network housing breeding sows	5102	BDPORC
D_{prod}	Duration of a full production cycle	28 weeks	(Badouard and Calvar, 2015)
β	Transmission rate of LA-MRSA between two pigs (baseline)	0.26 $week^{-1}$	Calibrated
d	Average LA-MRSA colonization duration in pigs (baseline)	4.3 weeks	(Gibbons et al., 2013)
C_{STP}	Sow-to-piglets contamination probability	1	(Moodley et al., 2011)
P_{exp}	Proportion of fattening pigs exported at the end of each production step (4 weeks or 12 weeks of age)	farm-specific	BDPORC
P_{rep}	Proportion of sows replaced by gilts every four weeks	3.19 %	(Badouard and Calvar, 2015)
P_{farms}	Proportion of farms contaminated by MRSA at $t = 0$	5 %	(Jouy et al., 2008; Madec and Haenni, 2010)
$P_{col\ farms}$	Mean proportion of pigs colonized by MRSA in contaminated farms at $t = 0$	16 %	(Jouy et al., 2008; Madec and Haenni, 2010)
$P_{col\ total}$	Global proportion of pigs colonized by MRSA at $t = 0$	5 % * 16 % = 0.8 %	(Jouy et al., 2008; Madec and Haenni, 2010)

pig populations within a given farm sector U at week $t + 1$ were calculated as follows:

$$S_U(t+1) = S_U(t) - \Delta SC_U(t) + \Delta CS_U(t)$$

$$C_U(t+1) = C_U(t) + \Delta SC_U(t) - \Delta CS_U(t)$$

where $S_U(t)$ is the number of susceptible pigs in sector U at week t, and $C_U(t)$ the number of colonized pigs in sector U at week t. $\Delta SC_U(t)$ and $\Delta CS_U(t)$ represent respectively the flux from S_U to C_U state, and from C_U to S_U state, at week t. As in Daley and Gani (1999), they were drawn from binomial distributions as follows:

$$\Delta SC_U(t) \sim Bin\left(S_U(t); 1 - e^{-\beta \frac{C_U(t)}{S_U(t)+C_U(t)}}\right)$$

$$\Delta CS_U(t) \sim Bin\left(C_U(t); 1 - e^{-\frac{1}{d}}\right)$$

where β is the MRSA transmission rate between pigs of the same sector (assumed constant across all ages and all farms), which may also account for indirect transmission through the sector environment, and d is the average duration of MRSA colonization of a pig before natural clearance (decolonization). In previous experimental work (Gibbons et al., 2013), MRSA was shown to persist in half of colonized pigs for at least 30 days (d = 4.3 weeks).

In farrowing sectors, because of close proximity between a sow and its piglets, we assumed that piglets had the same MRSA status (colonized or susceptible) as their mother, based on published experimental data (Moodley et al., 2011). This status was assumed to be maintained during the entire farrowing step in both the sow and its piglets, due to constant recontamination occurring between them.

2.5. Model simulations

All simulations and analyses were performed using R version 3.4.3 "Kite-Eating Tree" and packages *mc2d*, *parallel*, *igraph*, *Hmisc* and *mratios*. Simulations were generated using discrete time steps of one week.

We first initialized the network as MRSA-free and ran the model until the pig herd populations stabilized, which took in average 32 weeks of simulation. We then studied the spread of MRSA over the network using two distinct scenarios.

2.5.1. The "realistic scenario"

In scenario 1, the "realistic scenario", we used data from a cross-sectional study led by the French Agency for Food Safety in 2007 to assess MRSA carriage in pigs in France (Jouy et al., 2008; Madec and Haenni, 2010). In this study, 5 % of pig farms were found to be MRSA-positive (i.e. housing at least one MRSA-positive pig), and 0.8 % of sampled pigs were MRSA-positive. To simulate this situation, at $t = 0$, we randomly selected 5 % of the farms to be MRSA-positive. In these farms, we set 16 % of randomly selected pigs of all ages as MRSA colonized, to result in 0.8 % of total prevalence in pigs.

Scenario 1 was used for calibrating β, and for assessing the impact of targeted control measures in an endemic situation. In this scenario, due to stochasticity, 300 repetitions of the model were simulated, as this value was found to be enough to hold stable the mean and variance of model outputs, namely the percentage of farms contaminated (PFC), the total prevalence in pigs and the prevalence of pigs heading for slaughterhouse.

2.5.2. The "introduction scenario"

In scenario 2, the "introduction scenario", we assumed an initial MRSA-free situation and simulated the introduction of a single MRSA-positive group of gilts in a single given farm (the seed). At $t = 0$, we set 3.19 % (that is P_{rep}, the portion of sows replaced by gilts every four weeks in our model, see Table 1 of the breeding herd of the seed farm as MRSA-colonized, among sows entering gestation. This MRSA introduction process was repeated in simulations starting from each of the

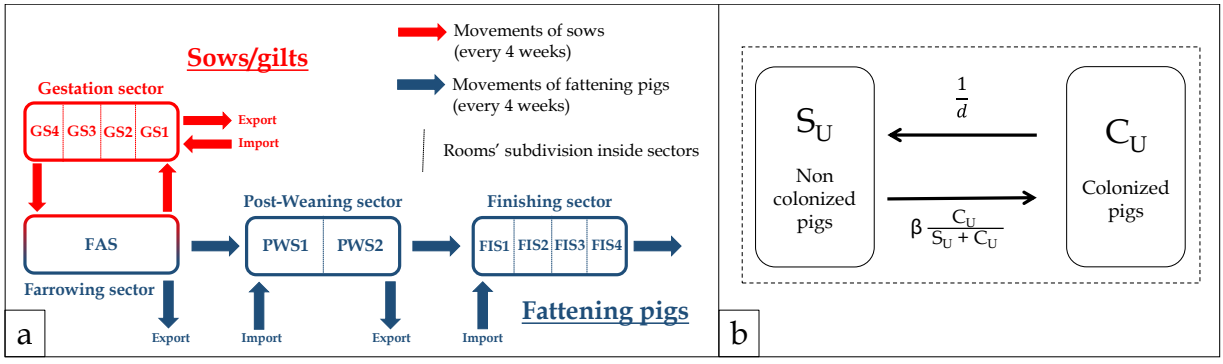


Fig. 3. Mathematical model components. a) Demographic model at the within-farm scale. Each farm is divided into four sectors (GS, FAS, PWS, FIS), divided again into rooms (resp. 4, 1, 2 and 4). b) Epidemiological model within a given farm sector. S_U (resp. C_U) is the number of non-colonized (resp. colonized) pigs in the sector.

5102 farms housing breeding sows.

Scenario 2 was used for identifying factors associated with the spreading potential of farms, and for selecting efficient sentinel farms to detect the dissemination of a new MRSA strain over the pig movement network. In this scenario, for each seed farm, 50 stochastic repetitions were simulated, this number being sufficient to hold model outputs' mean and variance stable.

2.6. Model and data analysis

2.6.1. Model calibration

We calibrated the value of the transmission rate, β, using scenario 1. We aimed to select the value of β minimizing residuals between the mean predicted prevalence in pigs of all farm sectors at steady state (among all simulations, accounting for both within- and between-herd dynamics), and the reported carriage of 0.8 % (Jouy et al., 2008; Madec and Haenni, 2010).

2.6.2. Analysing the spreading potential of seed farms

We performed a multivariate analysis to assess the relationship between the spreading potential of the seed farm in scenario 2 and the seed's characteristics. Spreading potential was measured through the percentage of farms contaminated (PFC) at $t = 52$ weeks (one year) predicted with this scenario. Investigated characteristics were the seed's breeding herd size, production herd size, farming category (breeding farm, i.e. Multiplier or Nucleus, VS production farm), and eight network centrality indicators: outdegree, indegree, betweenness, eigenvector centrality, closeness, coreness, outflux and influx.

The variables associated with the PFC in univariate linear regression with a p-value < 0.2 were selected for the multivariate analysis. Variable selection in the multivariate linear models was performed using a stepwise selection procedure algorithm, using Akaike's information criterion (AIC). We checked the multicollinearity among explanatory variables selected in the multivariate analysis by computing the Variance Inflation Factors (VIF). In case variables showed a VIF > 10, they were excluded from the multivariate model, and the stepwise algorithm and VIF checking procedure was repeated without them.

We illustrated more specifically the association between PFC and the seed farm's outdegree and category.

2.6.3. Assessing the impact of targeted control measures

Assuming that efficient within-farm control measures to reduce MRSA spread exist, one may need to identify which farms should be targeted preferentially, through a program supporting specific farmers to implement them for instance. In this part, we used our model to determine the types of farms in which these measures should be selectively applied to enhance their effectiveness at the national production level. We compared the impact of farm-level control measures targeting 100 farms with either the highest indegree, the highest outdegree, the highest outflux or the highest betweenness, with that of the same control measures implemented in 100 random farms. As in Sørensen et al. (2018), we assumed that control measures reduced the transmission parameter β in farms. In the "realistic" scenario 1, once the prevalence had plateaued, at $t = 208$ weeks, we reduced the transmission parameter in the 100 selected farms (targeted or randomly selected). Two levels of reduction were assessed: 25 % (leading to $\beta = 0.19$/week) and 50 % (leading to $\beta = 0.13$/week), and compared to the "no action" baseline value $\beta = 0.26$/week. We investigated the total prevalence of MRSA colonization in pigs of all ages and the PFC at different times after the introduction of the control measures.

2.6.4. Sentinel selection for targeted surveillance

We used our model to seek the best method to select sentinel farms to perform targeted surveillance of incursions of a new MRSA strain in the network, based on "introduction" scenario 2 simulating outbreaks starting from all farms housing sows. We ranked farms in priority lists: for instance, if for economic or practical reasons, only N farms can be monitored regularly, which should be the first N farms to be monitored to obtain the most efficient surveillance? We investigated three criteria for surveillance efficiency: the percentage of MRSA incursions detected, the time before MRSA detection, and the PFC at detection (that is, the outbreak size at detection). As in Holme (2018), we calculated the Kendall correlation (Kendall, 1938) between these three criteria. We compared 10 distinct methods of targeted sentinel selection (Holme, 2018; Bajardi et al., 2012; Ciccolini et al., 2014; Schirdewahn et al., 2017) to a random selection of sentinels. The first eight of these methods were simply based on sorting farms by decreasing values for network centrality measures (see SM2 for definitions): outdegree, indegree, betweenness, eigenvector centrality, closeness, coreness, outflux and influx (Holme, 2018; Ciccolini et al., 2014). The 9th method was the "Invasion paths" method, described in (Bajardi et al., 2012; Schirdewahn et al., 2017). The principle of this method is to cluster farms based on the similarity of the paths that would potentially take pathogens in the oriented network (details of the method are provided in SM3). In the last method, we set a priority list by selecting farms that maximized alternatively the following criteria: 1) the best farm in terms of percentage of detected incursions, 2) the best in terms of time before detection, 3) the 2nd best in terms of percentage of detected incursions, etc. We called this the "Alternated method". For all these methods, we assessed the surveillance efficiency depending on three numbers of sentinels monitored: 30, 60 and 120 sentinel farms.

2.7. Sensitivity analysis

We tested the sensitivity of our results to changes in the values of parameters β and d.

First, we kept the reference value $d = 4.3$ weeks (Table 1) and investigated the behaviour of the model under a range of values for β, from 0.1 to 0.7. Under scenario 1, we computed the evolution over time of (i) the number of farms contaminated by MRSA, (ii) the number of farms that were decontaminated after a period of contamination, and (iii) the number of farms that were never contaminated.

Second, we assessed how sensitive our predictions were to a different initial hypothesis on carriage duration. Assuming respectively $d = 3$ weeks and $d = 5$ weeks, we recalibrated β (as in section 2.6.1). We performed with these sets of parameters the analysis described in 2.6.3, i.e. reducing the value of β by 25 % or 50 % after 208 weeks in 100 farms either chosen at random, with the highest outdegree, or with the highest indegree.

3. Results

3.1. Model calibration and baseline predictions

Under "realistic" scenario 1, for values of $\beta < 0.3$/week, a non-null steady-state for the PFC and the national prevalence in pigs could not be reached, due to local extinctions in farms (SM4). Irrespective of the value of β, the prevalence plateaued during the 4th year of simulation, before a slow and steady decrease (SM4). Hence, we selected the value minimizing residuals between the predicted prevalence in pigs of all farm sectors, and the observed carriage of 0.8 %, between $t = 156$ weeks and $t = 208$ weeks (i.e. in the 4th year of simulation). The calibrated baseline value of the transmission parameter is $\beta = 0.26$/week. Simulations show that with this transmission parameter value, the predicted prevalence of MRSA in pigs in scenario 1 remains close to 0.8 % for more than 8 years of simulations (SM4).

Model simulations showed high stochasticity at the farm level, with frequent extinctions and transmissions. As an illustration, Fig. 4 depicts the predicted prevalence of MRSA colonization among the pigs from four selected farms in our model under the "introduction" scenario 2, as a function of time (Fig. 4a), as well as pig movements between these

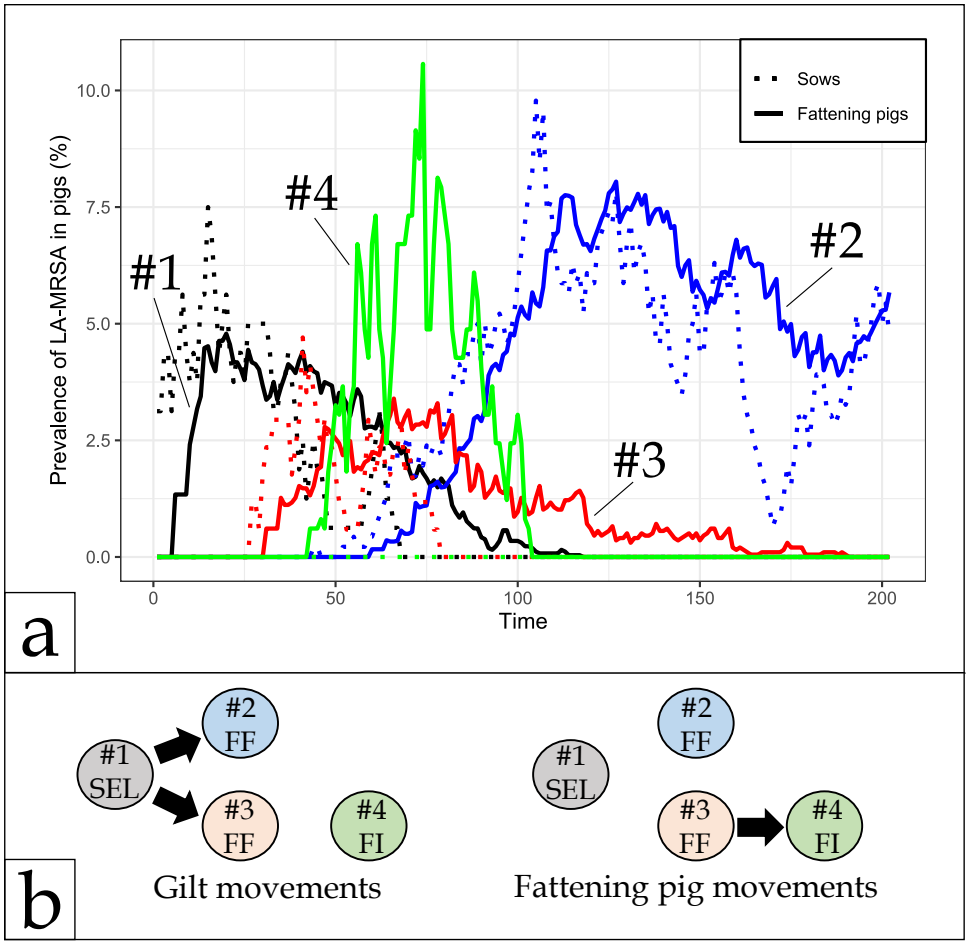


Fig. 4. Illustration of model simulations. MRSA spread in four farms in our model based on a single stochastic simulation: a nucleus farm (SEL), where MRSA was seeded, and three production farms (2 farrowing-to-finishing farms (FF) and a finishing farm (FI)). a) Time changes in MRSA prevalence in the breeding (dotted line) and fattening (solid line) herd of each farm. b) Pig movements between the four farms, according to the database, differentiating gilt and fattening pig movements.

same farms (Fig. 4b).

Farm #1 (a Nucleus farm) was the seed farm in this simulation: 3.19 % of its breeding herd was contaminated at initialization. Farms #2 and 3 (Farrowing-to-Finishing farms) were first contaminated through importation of colonized gilts. Then, MRSA reached their fattening herd. Farm #4 (a finishing farm) was however contaminated through importation of fattening pigs. Due to stochasticity, extinction was observed in some farms (SM4).

3.2. Factors associated with the spreading potential of seed farms

Being a breeding farm (as opposed to a production farm), as well as higher values of production herd size, outdegree, betweenness, closeness, coreness and outflux, were significantly associated with a higher spreading potential ($p < 0.0001$) (SM5). A higher value of indegree was significantly associated with a lower spreading potential ($p < 0.0001$) (SM5). In the final multivariate linear model, all VIF were < 2.5, showing a limited multicollinearity among explanatory variables.

As an illustration, Fig. 5 highlights the effect of the seed's farming category and outdegree on two indicators after one year: the PFC and the prevalence of MRSA in pigs heading for slaughterhouse, just before transportation. Irrespective of the seed farm, the outbreak size in this scenario remained limited: the average proportion of farms contaminated after one year was 0.03 % (SD: 0.05) (n = 3.3 farms), and the maximum was 0.62 % (n = 65.3 farms). Moreover, after one year, the average percentage of pigs colonized by MRSA sent to slaughterhouse was 9.6×10^{-4} % per week (SD: 1.0×10^{-3}), and the maximum was 0.01 % per week (Fig. 5).

Regarding the effect of the seed's outdegree, we compared the spreading potential of the 10 % of seed farms with the highest outdegree (category " > = 11") with that of other seed farms (category " < 11") (Fig. 5a). The PFC predicted one year after MRSA introduction significantly increased with the seed farm's outdegree (Welch t-tests between categories " < 11" and " > = 11", $p < 0.0001$). It also depended on the seed farm's category, with higher PFC predicted when MRSA was seeded in breeding farms (with no statistical difference between nucleus and multiplier farms), and lower PFC when MRSA was seeded in production farms (Welch *t*-test, $p < 0.0001$) (Fig. 5b). Among production farms, MRSA introduction in a farrowing farm led to a higher PFC than introduction in a farrowing-post-weaning farm (Welch *t*-test, $p < 0.0001$), and the lowest PFC was predicted when the seed farm was a farrowing-to-finishing farm (Welch *t*-tests between categories "FF", and "FA" or "FPW", both $p < 0.0001$).

One year after MRSA introduction, the predicted prevalence among pigs at slaughter age also significantly increased with the seed farm's outdegree (Welch t-tests between categories " < 11" and " > = 11", $p < 0.0001$) (Fig. 5a). It was significantly lower when the seed farm was a farrowing-to-finishing farm (Welch *t*-tests between categories "FF", and all others, all $p < 0.0001$). Introducing MRSA in a Multiplier farm led to a higher prevalence among pigs heading to slaughterhouse than in a Farrowing farm (Welch *t*-test, $p < 0.01$) (Fig. 5b).

The proportion of each farm category within the contaminated farms depended on seed farm's characteristics (Fig. 5a and b), and could

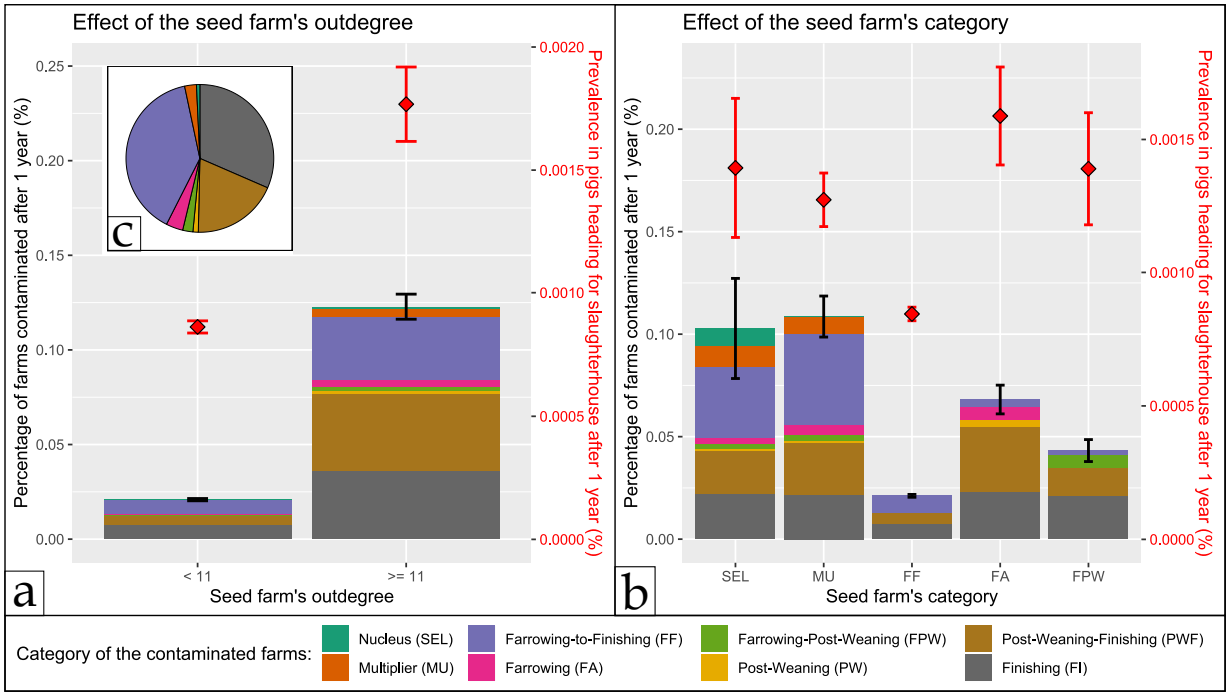


Fig. 5. Impact of seed farm characteristics on its spreading potential. Using the "introduction" scenario 2, the effect of the seed farm's outdegree (a), and category (b), on two outputs after one year is depicted: the proportion of farms contaminated (PFC, left axis, bar graphs) and the national prevalence of MRSA in pigs heading for slaughterhouse (right axis, red diamonds dots). We also show in which proportions the different categories of farms (including the seed farm) are contaminated. Intervals are 95 % confidence intervals of the one-sample t-test on the mean of the output (PFC and prevalence at slaughter age) for farms of a given category or outdegree. c) Proportions of the different farm categories in the network (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

highly vary from the proportions of farm categories in the network (Fig. 5c). In particular, seeding MRSA in a Nucleus farm led to a proportion of Multiplier farms among contaminated farms about four times higher than the proportion of Multiplier farms in the network (10.0 % against 2.6 %). On the contrary, whereas Farrowing-to-Finishing farms represented 39.2 % of farms in the network, they were only 5.6 % – i.e. a 7-fold decrease – among contaminated farms when the seed farm was a Farrowing farm.

3.3. Impact of targeted farms when implementing control measures

Based on "realistic" scenario 1, Fig. 6 compares the impact of

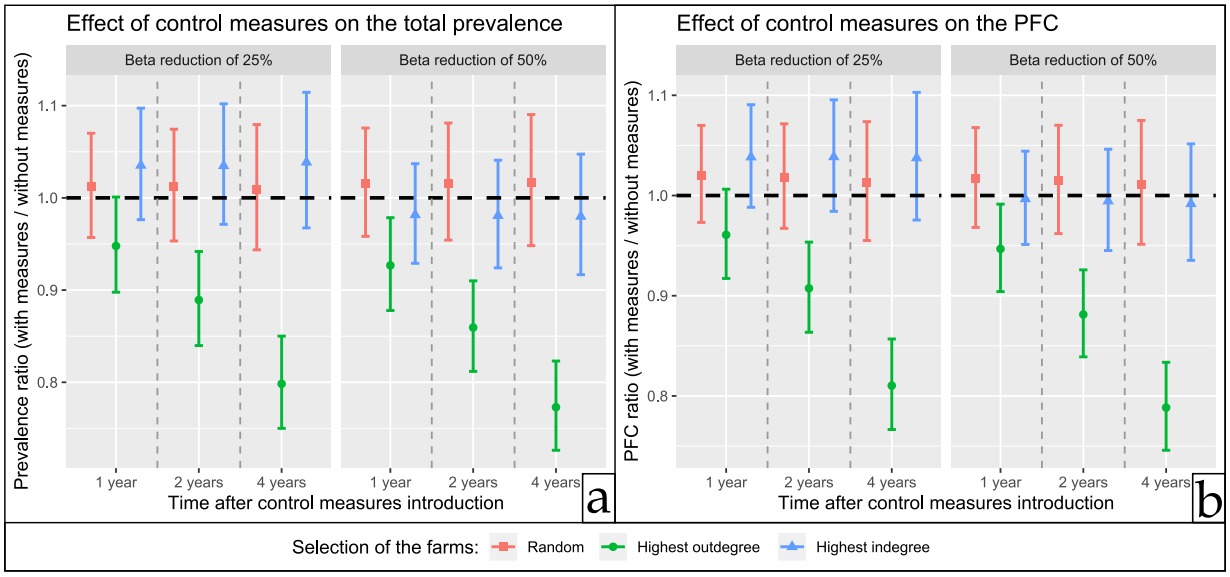


Fig. 6. Impact of targeted control measures. Impact of control measures implemented in 100 farms selected at random, in the 100 farms with the highest outdegree or in the 100 farms with the highest indegree. The ratio "Output value with control measures / Output value without control measures" is depicted at different times (1, 2 and 4 years after control measures implementation) for two model outputs: (a) Total prevalence in pigs and (b) Percentage of Farms Contaminated (PFC). "Realistic" scenario 1 was simulated. Two levels of control measure intensity are considered: reducing the transmission parameter β by 25 % or 50 %. Intervals are Fiellers 95 % confidence intervals of the *t*-test for the ratio of two means: the mean values of outputs of 300 model iterations for the case control measures are applied VS the case control measures are not applied.

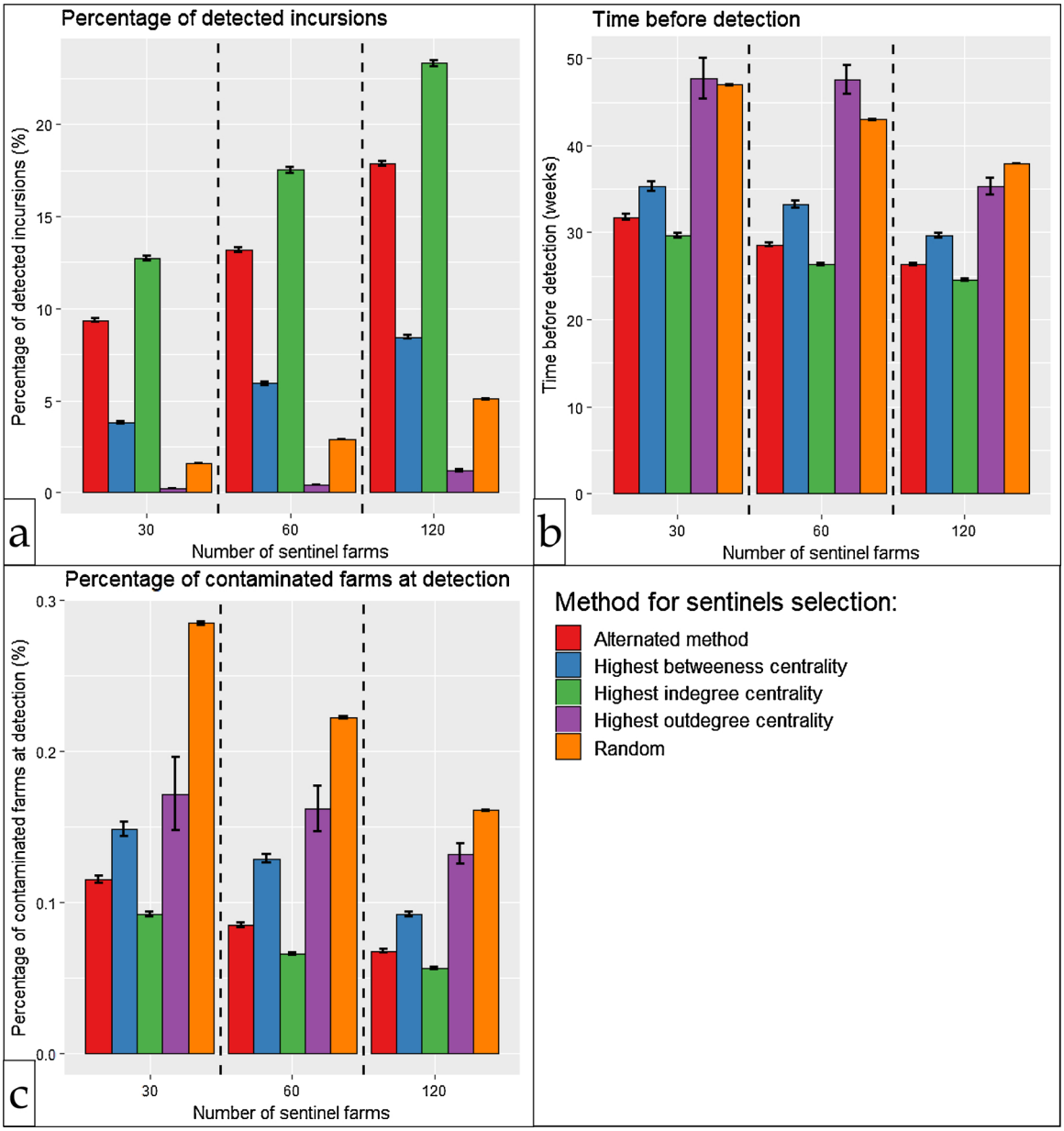


Fig. 7. Comparison of the efficiency of several methods for sentinel selection. Three efficiency criteria are depicted: Percentage of MRSA incursions detected (a), Time before detection (b), and Percentage of farms contaminated (PFC) at detection (c). Several sizes of sentinel sets were tested: 30, 60 and 120 sentinel farms. For each set of sentinel farms, the surveillance performance was assessed based on the average of model simulations of MRSA introduction starting from all farms housing breeding sows in the network (scenario 2). Intervals are 95 % confidence intervals of the *t*-test. 100 different sets of sentinels were considered with the "Random" choice method.

applying farm-level control measures – i.e. reducing the transmission parameter β by 25 % or 50 % – in 100 farms, either chosen randomly, targeting the ones with the highest outdegree, or the ones with the highest indegree. Irrespective of the assumed intensity of control measures (amount of β reduction), the delay after their implementation and the model output considered, control measures implemented in random farms and in the farms with the highest indegree had no significant impact on MRSA spread (ratio *t*-test comparing model predictions with and without control measures, $p > 0.05$). On the contrary, a 25 % (resp. 50 %) β reduction in highest outdegree farms significantly decreased MRSA prevalence, as soon as two (resp. one) years after the implementation of control measures ($p < 0.01$) (Fig. 6a). In this case, the impact of control measures increased with time passed since their implementation. For instance, a 25 % reduction of within-farm MRSA transmission in highest outdegree farms led to an 11.1 % (Fiellers 95 % confidence interval (CI) [5.8 % ; 16.0 %]) reduction in the predicted overall MRSA prevalence 2 years after control measures implementation, and to a 20.2 % (Fiellers 95 % CI [15.0 % ; 25.0 %]) reduction after 4 years, compared to the "no action" baseline case. Similar results were obtained regarding the PFC (Fig. 6b). Comparable results were also obtained when considering the 100 farms with the highest betweenness or the 100 farms with the highest outflux as targets for the implementation of within-farm control measures (SM6).

3.4. Impact of sentinel farm selection for targeted surveillance

Fig. 7 compares the performance of several methods for sentinel farm selection, in terms of three criteria for surveillance efficiency: the

percentage of detected incursions (Fig. 7a), to be maximized, and the time before detection (Fig. 7b) and the PFC at detection (Fig. 7c), to be minimized.

Irrespective of the selection method, all three efficiency criteria improved when the number of sentinel farms increased. For instance, with the highest indegree method, a 4-fold increase in the number of sentinels (from 30 to 120) multiplied the percentage of detected incursions by 1.8 (from 12.7% to 23.3%), and allowed to detect the incursion 5.1 weeks earlier (from 29.7 to 24.6 weeks).

For all efficiency criteria, the best method for sentinel selection was the one based on the highest indegree, and the second best was the "Alternated method". For instance, monitoring the 120 farms with the highest indegree allowed to detect an incursion after 24.6 weeks on average (95 % prediction interval [10.0 ; 73.0]), 13.4 weeks earlier than when sentinels were chosen at random; upon detection, the average PFC was 0.06 % (95 % prediction interval [0.01 % ; 0.28 %]) (n = 6.0 farms), 2.8-fold less than when sentinels were chosen at random. Other sentinel selection methods that proved less performant than the highest indegree on all three criteria are displayed in SM7.

3.5. Sensitivity analyses

The model's behaviour under scenario 1 for several values of β, keeping the reference value for d, is displayed in SM4 (Fig S3). For $\beta < 0.26$, no MRSA carriage was left in the whole network after less than 200 weeks. For all tested values of $\beta > 0.26$, the PFC plateaued around the same value (25%–30%).

SM8 presents the results of the sensitivity analysis performed on d. For $d = 3$ weeks (resp. $d = 5$ weeks), the recalibrated value of β was 0.38 (resp. 0.23). This conducted to a time-evolution of the PFC identical to that observed with the reference values of d and β (SM8, Fig S7), showing that the invasion path of MRSA in the network was not sensitive to the initial hypothesis on carriage duration. As obtained with the reference values (Fig. 6), introducing control measures – i.e. reducing β by 25 % or 50 % – in 100 random farms or in the 100 farms with the highest indegree did not significantly reduce the global prevalence compared to the "no action" baseline case, for both tested values of d (SM8, Fig S8 & S9). On the contrary, introducing control measures in the 100 farms with the highest outdegree led to a significant reduction of MRSA prevalence for both tested values of d (SM8, Fig S8 & S9), as was found with the reference values (Fig. 6).

4. Discussion

Pig movements between farms are believed to be one of the main factors of MRSA dynamics in the pig industry (Sieber et al., 2018). Moreover, recent modelling work underlined the importance of considering within-farm dynamics when studying between-farm spread of MRSA (Schulz et al., 2018). In this study, we propose a mathematical model combining the within-farm and the between-farm levels to simulate the spread of MRSA in an intensive pig production system such as the French pig industry. We highlight the importance of individual and network-based farm characteristics on their role in the global MRSA epidemic. We compare several scenarios to target within-farm control measures implementation, and to identify pertinent sentinel farms for MRSA surveillance.

4.1. Main findings

The "introduction" scenario we proposed in our analyses, in which MRSA is introduced in the network through a single seed farm, is not realistic, in the sense that it leads to a maximum PFC of 0.62 % (n = 65 farms), far from the 5 % observed in France in 2007 (Jouy et al., 2008; Madec and Haenni, 2010). This reflects the fact that MRSA was probably introduced in French pig farms through several distinct farms, and on repeated occasions over time, probably as was shown in Denmark (Sieber et al., 2018). However, this scenario is still useful for two main reasons. First, it allowed us to investigate the specific spreading potential of different farm types. Second, it may realistically simulate the situation where a hypothetical new MRSA strain would arrive in the network, and propose criteria for sentinel surveillance of such incursions.

We found that MRSA spread in the pig industry largely depends on the characteristics of the farm in which it is first introduced, namely its size, category and its centrality in the network. Outbreaks originating from breeding farms (Multiplier or Nucleus) or from farms with high outdegree led to a significantly higher proportion of farms contaminated (PFC) than outbreaks originating from production farms (Farrowing, Farrowing-to-Finishing or Farrowing-Post-Weaning) and from farms with lower outdegree (Fig. 5). Results regarding the prevalence in pigs heading for slaughterhouse are less clear (Fig. 5). This may be due to the low predicted prevalence values in pigs at slaughter age.

One strategy to set up global infectious diseases surveillance over the network is to choose sentinel nodes that are closely monitored. The choice of these sentinel farms is however challenging as, depending on this choice, the reactivity in sending the alert can vary. We proposed and assessed several methods to help select sentinel farms that may be used in a surveillance system. Because disease surveillance in livestock meets limitations as only a sample of the total pig industry can be regularly monitored, for costs reasons, we simulated the monitoring of 30–120 sentinel farms only. There was a high Kendall's correlation coefficient value between the three surveillance efficiency criteria we considered (Percentage of detected incursions VS Time before detection: 0.81 ($p < 0.0001$); Percentage of detected incursions VS Number of contaminated farms at detection: 0.71 ($p < 0.0001$); Time before detection VS Number of contaminated farms at detection: 0.82 ($p < 0.0001$)). This justifies why we tested the "Alternated method" for sentinel selection. Indeed, these correlations can lead to difficulty in optimizing simultaneously the percentage of detected incursions, the time before detection and the outbreak size (PFC) at detection, as evidenced by earlier work (Holme, 2018). This alternated method of sentinel selection proved to be rather efficient (Fig. 7). However, we found that the sentinel selection method based on choosing the farms with the highest indegree was even more efficient, irrespective of the chosen criteria and the number of sentinel farms monitored.

Different types of control measures of MRSA spread within farms have been suggested (Sørensen et al., 2018; Catry et al., 2010; Dorado-García et al., 2015). Earlier studies (Schulz et al., 2019) have suggested that the implementation of within-farm control measures could have an effect on the global pig movement network. In the hypothesis where efficient within-farm control measures were available, we showed that targeting certain categories of farms may increase their effectiveness at the network level. For the same "cost", that is, the same amount of control interventions implemented to decrease MRSA's within-herd transmission (e.g. a hypothetical program to enhance biosecurity in farms (Sørensen et al., 2018)), our results suggest that it is more efficient to target pig farms sending pigs to the highest number of other farms (highest outdegree), pig farms exporting the highest number of pigs (highest outflux), or pig farms with the highest betweenness, than random farms (Fig. 6 and SM6). On the contrary, targeting farms with the highest indegree was shown not to be more efficient than targeting random farms (Fig. 6). This suggests that the farms monitored to detect a hypothetical introduction (which should be those with the highest indegree) should not be the same than the ones targeted for within-farm control measures implementation once detection has occurred.

Consistently with previous findings (Ciccolini et al., 2012), our simulations also confirm that MRSA would be hard to eradicate in the pig industry. Indeed, in our simulations, the obtained reduction in total prevalence after 4 years is only 23 %, even when reducing transmission by 50 % in 100 well-targeted farms (with the highest outdegree), and assuming no other MRSA introduction occurs meanwhile in the farms' network.

Finally, it should be noted that MRSA prevalence in the French pig industry may have increased since the latest carriage study (Jouy et al., 2008; Madec and Haenni, 2010). However, although the actual prevalence levels we predict may not reflect the current situation regarding MRSA in France, this does not impact the validity of the qualitative results we obtained, in particular in terms of farm selection for control strategy implementation or for surveillance.

4.2. Main study limitations

This study has several limitations.

First, our model simplified the pig movements recorded in 2014 in France by excluding some types of holdings and inconsistent movements (see section 2.2). Nevertheless, the model reconstructed 92.4 % of recorded pig movements, and the contact matrix between farm categories (SM1) was consistent with published descriptions of the French pig industry (Roguet and Laugé, 2009). Therefore, these simplifications should not have a major impact on our findings.

Second, our calibrated value of the transmission parameter β – 0.26/week – was seven times lower than the value estimated in a previous study (Broens et al., 2012a), which was 0.21/day to 0.42/day. However, in our model, β accounted for global transmission of MRSA among a whole pig sector, which may also include transmission between pigs not in direct contact, although located in the same sector, whereas (Broens et al., 2012a) only accounted for direct contacts between pigs. This could partly explain this lower value, along with the fact β was calibrated to reproduce a low observed carriage in France. What is more, in another study performed by the same team (Broens et al., 2012b), the parameter calculated for transmission from other pig pens and the environment in the absence of antibiotics was 0.039/day, which is close to our calibrated value of 0.26/week (i.e. 0.037/day). In addition, our model does not account for routes of MRSA spread beyond transmission within farm sectors and colonized pig movements. Indeed, we considered that pig farm sectors were spatially distinct enough, and the biosecurity on farm strong enough, for transmission to occur within sectors only, and not between sectors. In Sørensen et al., (2017), the authors followed a comparable reasoning, as they assumed the between-stable transmission rate was only 2 % of the between-pen transmission rate. Yet, MRSA may also spread between farm sectors through the global farm environment, farmers or contaminated fomites, as well as between farms via humans in contact with pigs (e.g. veterinarians). Taking these routes into account, additionally to the movements of MRSA-positive pigs from other farms or from other sectors of the same farm, would have led to a potentially faster spread of MRSA. In future work, it may be interesting to investigate between-sector transmission by collecting longitudinal data at the farm level.

The local extinctions we observed in some farms were likely due to the low value of our transmission parameter β, together with our model's stochasticity and its within-farm structure, leading to smaller populations in contact (within sectors). While observed data suggest that pig farms can remain MRSA-positive for long time periods, such spontaneous extinctions have also been documented (Van der Wolf et al., 2011).

The effect of variations of β on the model's predictions are shown, for scenario 1, in SM4. Lower values of β led to global extinctions of MRSA in the network after less than 200 weeks: in this case, it was pointless to assess the efficiency of control measures and surveillance measures. With higher values of β, local extinctions were scarcer, but the PFC still capped around 25–30 %, irrespective of the value of β. This may be explained by the oriented structure of the network which led MRSA to follow the same invasion paths, and not to spread in more farms, irrespective of its spreading potential (i.e. transmission parameter and carriage duration).

Furthermore, we chose not to take into account age differences in the transmission parameter, due to the limited carriage data available that did not allow us to calibrate several values for the transmission parameters. Provided age-specific MRSA prevalence data becomes available, this might prove an interesting addition to the model. Similarly, we did not take into account farm type differences, for instance due to variations in biosecurity levels. A lower transmission parameter in breeding farms could decrease the difference of PFC induced by introducing MRSA in breeding farms VS production farms. In contrast, a higher transmission rate in breeding farms could increase this difference.

Third, we chose to select a value of MRSA colonization duration d – 30 days – based on biological data (Gibbons et al., 2013), although other values were found in the literature, such as 17.4 days in Broens et al. (2012a). The value we used was obtained from MRSA CC5 (Gibbons et al., 2013), whereas CC398 seems to be predominant in France (Madec and Haenni, 2010). However, we showed in a sensitivity analysis that changing this initial hypothesis did not qualitatively affect our results. In addition, we did not consider persistent carriage, while it may have the effect of preventing extinctions of MRSA.

Fourth, we assumed that piglets had the same colonization status as their mother, based on Moodley et al. (2011), even though other experimental results (Verhegghe et al., 2013) suggested that the association between sow and piglets colonization status may not be so direct. Using a probabilistic approach on the piglets' colonization status would have potentially decreased the number of animals entering the production cycle while colonized by MRSA, and therefore the prevalence and PFC.

Finally, other network centrality indicators such as ingoing and outgoing contact chains which enable assessing indirect contacts, could have been considered (Nöremark et al., 2011). However, we explored eight different centrality indicators over the network, including the eigenvector centrality, which also allows to explore indirect contacts, by taking a higher value when the node is connected to other well connected nodes (Mekonnen et al., 2019).

4.3. Perspectives and veterinary public health implications

Our results show that increasing the number of sentinel farms improves the surveillance efficiency, but more in-depth cost-effectiveness analyses would be useful to investigate what would be the most cost-efficient number of sentinel farms, regarding surveillance costs and veterinary public health objectives. It would also be interesting to compare a surveillance led in farms, versus a surveillance led at the slaughterhouse level. The hypothetical within-farm control measures we discussed may also have different implementation costs depending on farm size or category. Besides, the impact of potential control measures and surveillance on farm productivity and daily work, as well as on animal health and welfare, should always be carefully assessed before their implementation.

Furthermore, our findings in terms of MRSA prevalence among pigs sent to slaughterhouses should not be interpreted directly in terms of contamination by MRSA of pork products intended for human consumption. Indeed, from the moment pigs leave the farm to the consumer's fork, many factors, during transport, in the slaughterhouse and during food processing, are susceptible to affect the bacterial load in pork (Lassok and Tenhagen, 2013). In the future, these limitations should be addressed in a detailed risk assessment study to evaluate the risks for human health ensuing from the pig MRSA epidemic.

4.4. Conclusions

In conclusion, we show here how, using a multi-scale model of MRSA spread in a pig movement network, criteria may be proposed to select which farms could be used as sentinels in a surveillance system, as well as which farms to apply control measures in. More thorough cost-effectiveness analyses, accounting for actual economic costs related to different types of control or monitoring interventions, would be necessary in the French context, similar to what was done recently in

Denmark (Olsen et al., 2018). However, this work has the potential to help better understand MRSA spread in intensive pig production systems similar to the French one in terms of global structure and batch management (Relun et al., 2016). What is more, the methodology we proposed could also be applied to other asymptomatic bacteria or viruses circulating in pigs or other farm animal networks.

Authors' contribution

JB, MA, CC, PG, LO and LT conceptualized the project. LO and LT supervised the project. MA prepared, analysed and provided the dataset. JB, LO and LT designed the model and performed the statistical analysis. JB developed the model. MA and CC provided expertise on the pig industry and advice on the model. All authors approved the latest version of this article.

Declaration of Competing Interest

LO received research funding from Pfizer through their research unit on an unrelated project. LO received consulting fees from WHO for work on antimicrobial resistance in South East Asia.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.epidem.2020.100389.

References

Armand-Lefevre, L., Ruimy, R., Andremont, A., 2005. Clonal comparison of Staphylococcus aureus isolates from healthy pig farmers, human controls, and pigs. Emerg Infect Dis 11 (5), 711–714. https://doi.org/10.3201/eid1105.040866.

Badouard, B., Calvar, C., 2015. Résultats Porcs Bretagne 2014. IFIP, CRAB, UGPVB 6 pages. June.

Bajardi, P., Barrat, A., Savini, L., Colizza, V., 2012. Optimizing surveillance for livestock disease spreading through animal movements. J. R. Soc. Interface 9 (76), 2814–2825. https://doi.org/10.1098/rsif.2012.0289.

Broens, E.M., Graat, E.A.M., van der, Wolf P.J., et al., 2011. MRSA CC398 in the pig production chain. Prev. Vet. Med. 98 (2), 182–189. https://doi.org/10.1016/j.prevetmed.2010.10.010.

Broens, E.M., Graat, E.A.M., van de Giessen, A.W., Broekhuizen-Stins, M.J., de Jong, M.C.M., 2012a. Quantification of transmission of livestock-associated methicillin resistant Staphylococcus aureus in pigs. Vet. Microbiol. 155 (2–4), 381–388. https://doi.org/10.1016/j.vetmic.2011.09.010.

Broens, E.M., Espinosa-Gongora, C., Graat, E.A., et al., 2012b. Longitudinal study on transmission of MRSA CC398 within pig herds. BMC Vet. Res. 8, 58. https://doi.org/10.1186/1746-6148-8-58.

Broom, D.M., Corke, M.J., 2002. Effects of disease on farm animal welfare. Acta Vet Brno, AVB 71 (1), 133–136. https://doi.org/10.2754/avb200271010133.

Catry, B., Duijkeren, E.V., Pomba, M.C., et al., 2010. Reflection paper on MRSA in food-producing and companion animals: epidemiology and control options for human and animal health. Epidemiol. Infect. 138 (5), 626–644. https://doi.org/10.1017/S0950268810000014.

Chambers, H.F., DeLeo, F.R., 2009. Waves of resistance: staphylococcus aureus in the antibiotic era. Nat. Rev. Microbiol. 7 (9), 629–641. https://doi.org/10.1038/nrmicro2200.

Ciccolini, M., Dahl, J., Chase-Topping, M.E., Woolhouse, M.E.J., 2012. Disease transmission on fragmented contact networks: livestock-associated Methicillin-resistant Staphylococcus aureus in the Danish pig-industry. Epidemics 4 (4), 171–178. https://doi.org/10.1016/j.epidem.2012.09.001.

Ciccolini, M., Donker, T., Grundmann, H., Bonten, M.J.M., Woolhouse, M.E.J., 2014. Efficient surveillance for healthcare-associated infections spreading between hospitals. Proc. Natl. Acad. Sci. U. S. A. 111 (6), 2271–2276. https://doi.org/10.1073/pnas.1308062111.

Crombé, F., Argudín, M.A., Vanderhaeghen, W., Hermans, K., Haesebrouck, F., Butaye, P., 2013. Transmission dynamics of methicillin-resistant Staphylococcus aureus in pigs. Front. Microbiol. 4. https://doi.org/10.3389/fmicb.2013.00057.

Daley, D.J., Gani, J., 1999. Epidemic Modelling: An Introduction. Cambridge University Press, Cambridge; New York.

Dorado-García, A., Dohmen, W., Bos, M.E.H., et al., 2015. Dose-response relationship between antimicrobial drugs and livestock-associated MRSA in pig Farming1. Emerg. Infect. Dis. 21 (6), 950–959. https://doi.org/10.3201/eid2106.140706.

Espinosa-Gongora, C., Broens, E.M., Moodley, A., Nielsen, J.P., Guardabassi, L., 2012. Transmission of MRSA CC398 strains between pig farms related by trade of animals. Vet. Rec. 170 (22), 564. https://doi.org/10.1136/vr.100704.

Food and Agriculture Organization, 2017. Economic Analysis of Animal Diseases. Food & Agriculture Organization of the United Nations.

Gibbons, J.F., Markey, B.K., Jahns, H., et al., 2013. Investigation of the persistence and transmission of MRSA CC 5 in pigs following intra-nasal inoculation. Vet. Microbiol. 162 (2-4), 771–778. https://doi.org/10.1016/j.vetmic.2012.10.001.

Holme, P., 2018. Objective measures for sentinel surveillance in network epidemiology. arXiv. 180310637 [physics, q-bio]. March. http://arxiv.org/abs/1803.10637 Accessed June 19, 2018.

IFIP, 2016. Les conduites s'adaptent aux tailles d'élevages et aux besoins d'organisation. Tech Porc 30, 19–20.

Jones, K.E., Patel, N.G., Levy, M.A., et al., 2008. Global trends in emerging infectious diseases. Nature 451 (7181), 990. https://doi.org/10.1038/nature06536.

Jouy, E., Le Roux, A., Tocqueville, V., et al., 2008. Prévalence du portage de SARM par les porcs à l'abattoir. Comptes-Rendus Du Congrès RICAI. Paris.

Kendall, M.G., 1938. A new measure of rank correlation. Biometrika 30 (1-2), 81–93. https://doi.org/10.1093/biomet/30.1-2.81.

Kinross, P., Petersen, A., Skov, R., et al., 2017. Livestock-associated meticillin-resistant Staphylococcus aureus (MRSA) among human MRSA isolates, European Union/European Economic Area countries, 2013. Eurosurveillance 22 (44), 16–00696. https://doi.org/10.2807/1560-7917.ES.2017.22.44.16-00696.

Larsen, J., Petersen, A., Larsen, A.R., et al., 2017. Emergence of livestock-associated methicillin-resistant Staphylococcus aureus bloodstream infections in Denmark. Clin. Infect. Dis. 65 (7), 1072–1076. https://doi.org/10.1093/cid/cix504.

Lassok, B., Tenhagen, B.-A., 2013. From pig to pork: methicillin-resistant Staphylococcus aureus in the pork production chain. J. Food Prot. 76 (6), 1095–1108. https://doi.org/10.4315/0362-028X.JFP-12-341.

Laxminarayan, R., Duse, A., Wattal, C., et al., 2013. Antibiotic resistance—the need for global solutions. Lancet Infect. Dis. 13 (12), 1057–1098. https://doi.org/10.1016/S1473-3099(13)70318-9.

Madec, J.-Y., Haenni, M., 2010. Les Staphylocoques dorés résistants à la méthicilline (SARM) chez les animaux en France: prévalence et résistances associées. Bulletin de l'Académie vétérinaire de France (1), 275. https://doi.org/10.4267/2042/48061.

Meadows, A.J., Mundt, C.C., Keeling, M.J., Tildesley, M.J., 2018. Disentangling the influence of livestock vs. farm density on livestock disease epidemics. Ecosphere 9 (7), e02294. https://doi.org/10.1002/ecs2.2294.

Mekonnen, G.A., Ameni, G., Wood, J.L.N., Berg, S., Conlan, A.J.K., The ETHICOBOTS consortium, 2019. Network analysis of dairy cattle movement and associations with bovine tuberculosis spread and control in emerging dairy belts of Ethiopia. BMC Vet. Res. 15 (1), 262. https://doi.org/10.1186/s12917-019-1962-1.

Moodley, A., Latronico, F., Guardabassi, L., 2011. Experimental colonization of pigs with methicillin-resistant Staphylococcus aureus (MRSA): insights into the colonization and transmission of livestock-associated MRSA. Epidemiol. Infect. 139 (10), 1594–1600. https://doi.org/10.1017/S0950268810002888.

Nadimpalli, M., Delarocque-Astagneau, E., Love, D.C., et al., 2018. Combating global antibiotic resistance: emerging one health concerns in lower- and middle-income countries. Clin. Infect. Dis. 66 (6), 963–969. https://doi.org/10.1093/cid/cix879.

Nadimpalli, M., Stewart, J.R., Pierce, E., et al., 2016. Livestock-associated, antibiotic-resistant Staphylococcus aureus nasal carriage and recent skin and Soft tissue infection among industrial hog operation workers. PLoS One 11 (11). https://doi.org/10.1371/journal.pone.0165713.

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 (2), 78–90. https://doi.org/10.1016/j.prevetmed.2010.12.009.

Olsen, J.V., Calvo-Artavia, F.F., Sandøe, P., Toft, N., 2018. Modeling the cost of eradicating livestock-associated methicillin-resistant staphylococcus aureus in countries with a high proportion of positive herds. Prev. Vet. Med. 158, 97–105. https://doi.org/10.1016/j.prevetmed.2018.07.010.

Porphyre, T., Giotis, E.S., Lloyd, D.H., Stärk, K.D.C., 2012. A metapopulation model to assess the capacity of spread of meticillin-resistant Staphylococcus aureus ST398 in humans. PLoS One 7 (10), e47504. https://doi.org/10.1371/journal.pone.0047504.

Puyvelde, S.V., Deborggraeve, S., Jacobs, J., 2017. Why the antibiotic resistance crisis requires a one Health approach. Lancet Infect. Dis. 0 (0). https://doi.org/10.1016/S1473-3099(17)30704-1.

Relun, A., Grosbois, V., Sánchez-Vizcaíno, J.M., et al., 2016. Spatial and functional organization of pig trade in different european production systems: implications for disease prevention and control. Front. Vet. Sci. 3. https://doi.org/10.3389/fvets.2016.00004.

Roguet, C., Laugé, V., 2009. La production et les flux de porcelets en France: volumes,

acteurs et prix. Techni porc 32 (1).
Salines, M., Andraud, M., Rose, N., 2017. Pig movements in France: designing network models fitting the transmission route of pathogens. PLoS One 12 (10). https://doi.org/10.1371/journal.pone.0185858.
Schirdewahn, F., Colizza, V., Lentz, H.H.K., Koher, A., Belik, V., Hövel, P., 2017. Surveillance for outbreak detection in livestock-trade networks. Temporal Network Epidemiology. Theoretical Biology. Springer, Singapore, pp. 215–240. https://doi.org/10.1007/978-981-10-5287-3_10.
Schulz, J., Boklund, A., Toft, N., Halasa, T., 2018. Drivers for livestock-associated methicillin-resistant Staphylococcus aureus spread among danish pig herds - a simulation study. Sci. Rep. 8 (1), 16962. https://doi.org/10.1038/s41598-018-34951-1.
Schulz, J., Boklund, A., Toft, N., Halasa, T., 2019. Effects of control measures on the spread of LA-MRSA among Danish pig herds between 2006 and 2015 – a simulation study. Sci. Rep. 9 (1), 691. https://doi.org/10.1038/s41598-018-37075-8.
Sieber, R.N., Skov, R.L., Nielsen, J., et al., 2018. Drivers and dynamics of methicillin-resistant livestock-associated Staphylococcus aureus CC398 in pigs and humans in Denmark. mBio 9 (6). https://doi.org/10.1128/mBio.02142-18.
Sørensen, A.I.V., Rosendal, T., Widgren, S., Halasa, T., 2018. Mechanistic modelling of interventions against spread of livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) within a Danish farrow-to-finish pig herd. PLoS One 13 (7). https://doi.org/10.1371/journal.pone.0200563.
Sørensen, A.I.V., Toft, N., Boklund, A., et al., 2017. A mechanistic model for spread of livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) within a pig herd. PLoS One 12 (11), e0188429. https://doi.org/10.1371/journal.pone.0188429.
van der Mee-Marquet, N., François, P., Domelier-Valentin, A.-S., et al., 2011. Emergence of unusual bloodstream infections associated with pig-borne–Like Staphylococcus aureus ST398 in France. Clin. Infect. Dis. 52 (1), 152–153. https://doi.org/10.1093/cid/ciq053.
Van der Wolf, P., Broens, E., Köck, R., Graat, E., 2011. A longitudinal study on the persistence of livestock associated-MRSA in swine herds. In: Proceedings of SafePork 2011. January.
Verhegghe, M., Pletinckx, L.J., Crombé, F., et al., 2013. Cohort study for the presence of livestock-associated MRSA in piglets: effect of sow status at farrowing and determination of the piglet colonization age. Vet. Microbiol. 162 (2-4), 679–686. https://doi.org/10.1016/j.vetmic.2012.09.014.
Voss, A., Loeffen, F., Bakker, J., Klaassen, C., Wulf, M., 2005. Methicillin-resistant Staphylococcus aureus in pig farming. Emerg. Infect. Dis. 11 (12), 1965–1966. https://doi.org/10.3201/eid1112.050428.
Weese, J.S., 2010. Methicillin-resistant Staphylococcus aureus in animals. ILAR J. 51 (3), 233–244.
Wertheim, H.F., Melles, D.C., Vos, M.C., et al., 2005. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect. Dis. 5 (12), 751–762. https://doi.org/10.1016/S1473-3099(05)70295-4.
Williams, R.E.O., 1963. Healthy carriage of Staphylococcus aureus: its prevalence and importance. Bacteriol. Rev. 27 (1), 56–71.