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Modelling environmentally mediated spread of livestock-associated methicillin-resistant *Staphylococcus aureus* in a pig herd

K.S. Tuominen [a,*], S. Sternberg Lewerin [a], M. Jacobson [b], T. Rosendal [c]

[a] *Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences (SLU), Box 7036, SE-750 07 Uppsala, Sweden*
[b] *Department of Clinical Sciences, Swedish University of Agricultural Sciences (SLU), Box 7054, SE-750 07 Uppsala, Sweden*
[c] *Department of Epidemiology and Disease Control, National Veterinary Institute (SVA), SE-751 89 Uppsala, Sweden*

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ABSTRACT

Infectious disease models are a useful tool to support within-herd disease control strategies. This study presents a stochastic compartment model with environmentally mediated transmission to represent the spread of livestock-associated methicillin-resistant *Staphylococcus aureus* (**LA-MRSA**) in a farrow-to-finish pig herd. The aims of the study were to (1) construct a model of the spread of LA-MRSA that included spread of LA-MRSA through the environment; (2) parameterise the model to fit previously published observational data in order to obtain realistic LA-MRSA transmission rates; (3) and to investigate how changes in the mixing of animals in the farrowing and finishing units may affect the prevalence of LA-MRSA in a herd. The results showed that indirect transmission allowed LA-MRSA to persist in the herd without the assumption of persistently shedding individuals. Reducing the mixing of pigs upon entry to the finishing unit was also shown to lower the LA-MRSA prevalence in the unit if the initial LA-MRSA level in the unit was low, but at high prevalence, no effect of mixing was identified. In the farrowing unit, changing the proportion of piglets that were cross-fostered did not affect the within-herd LA-MRSA prevalence. The study demonstrates that there are several important knowledge gaps regarding the shedding and transmission of LA-MRSA in different animal age groups and further experimental studies are needed. This work also provides a new, robust and flexible model framework for the investigation of control and mitigation strategies for LA-MRSA and other infections in a pig herd.

Implications

Livestock-associated methicillin-resistant *Staphylococcus aureus* bacteria are capable of transmitting between animals and humans. This poses a health risk, especially to those working with pigs and other livestock, but also to the wider community. The study shows that reducing mixing of pigs may reduce the number of livestock-associated methicillin-resistant *Staphylococcus aureus* carriers in the herd. The model presented in this study will be useful for investigating the spread patterns and control strategies of the bacteria in a pig herd, aiming to provide tools to combat the spread. The model is also adaptable for studying other diseases in pig herds.

Introduction

The spread of infectious animal diseases is complex, which poses a challenge when evaluating possible outbreak scenarios and control strategies. This applies to individual herds where investments in internal biosecurity may need to be adapted to herd-specific risks; but it also affects choices made in regional or national responses to disease outbreaks or control programmes for endemic diseases. Mathematical models provide a useful tool to explore outbreak scenarios as well as possible control strategies, when experimental studies are not possible (Heesterbeek et al., 2015). Modelling has been used successfully to gain an understanding of many infectious diseases in animals (Keeling et al., 2001; Ivanek et al., 2004; Halasa et al., 2019).

Staphylococcus aureus is a commensal bacterium and opportunistic pathogen in both humans and animals. Since the introduction of antimicrobial therapies, *S. aureus* has gained resistance against antimicrobial agents, of which the resistance against β-lactams in methicillin-resistant *S. aureus* (**MRSA**) is the most notable (Crombe et al., 2013). The livestock-associated MRSA

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* Corresponding author.
E-mail address: krista.tuominen@slu.se (K.S. Tuominen).

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(**LA-MRSA**) strains belonging to clonal complex CC398 are frequently found in Europe and North America, both in pigs and people in contact with pigs as well as in other livestock species (Vanderhaeghen et al., 2010; Crombe et al., 2013; Hansen et al., 2017). While the zoonotic impact of LA-MRSA in pig herds is a concern in many countries, effective strategies for its control are still lacking. In Sweden, domestic pigs are assumed to be free of LA-MRSA or the prevalence is very low. It has also been deemed worthwhile to attempt to keep LA-MRSA out of the Swedish pig population (Höjgård et al., 2015).

Previous studies have shown that direct transmission (Broens et al., 2012a; Broens et al., 2012b) and indirect transmission via exposure to airborne LA-MRSA within the barn (Rosen et al., 2018) are both important routes of transmission between pigs as well as between humans and pigs (Bos et al., 2016; Feld et al., 2018). However, current knowledge on the effectiveness of environmental interventions is conflicting. A study by Kobusch et al. (2020) suggests that cleaning and disinfection of the barn can be worthwhile to decrease the infectious pressure of LA-MRSA in pig herds, whereas in a Danish study, different disinfection techniques were unsuccessful in reducing the environmental infectious pressure (Bækbo et al., 2019). To properly assess different interventions for reducing the environmental load of LA-MRSA, and consequently the risk of transmission and re-colonisation of the pigs, it is important to incorporate environmental transmission into a disease spread model.

The spread of LA-MRSA within a pig herd has been previously studied in an individual-based model, where the LA-MRSA carriers could be either intermittent or persistent shedders (Sørensen et al., 2017). Individual-based approach has also been used in a between-herd model (Schulz et al., 2018). In another study, within and between-herd dynamics were studied in a stochastic metapopulation model, where the within-herd transmission was modelled at the farm-section level (Bastard et al., 2020). In addition, different intervention and control strategies have been investigated in individual-based models (Sørensen et al., 2018; Schulz et al., 2019) and the spread from pigs to humans in a metapopulation model (Porphyre et al., 2012). The transmission of LA-MRSA through barn air has been previously modelled by Sørensen et al. (2020) to assess the potential hazard to humans, but to the best of our knowledge, a model of LA-MRSA spread that includes the spread among pigs via the environment has not previously been described.

The current study presents a stochastic compartment model of LA-MRSA spread in a pig herd, which incorporates environmentally mediated spread. The model provides a framework for testing the efficacy of potential LA-MRSA surveillance, prevention and control strategies to reduce the prevalence in the herd or to mitigate the spread after an introduction of the disease. It also allows future investigation of environmental interventions, such as cleaning and disinfection of pens, changes to downtime between groups of pigs and other factors that could affect the burden of LA-MRSA in the barn.

The aims of this study were to (1) build and (2) parameterise an efficient and flexible model of the animal movements within a pig herd, which would allow modelling the environmental infectious pressure of LA-MRSA within the herd and the spread of LA-MRSA in a Swedish context. The final aim was to (3) investigate the effects of different animal mixing practices on the LA-MRSA prevalence in the model herd. This study will serve as a basis for further study of the spread of LA-MRSA and intervention strategies to reduce the prevalence and probability of introduction to a herd.

Material and methods

The simulation model was built in the R programming language version 4.0.3 – "Bunny-Wunnies Freak Out" (R Core Team, 2020) with the SimInf package version 8.2.0.9000 (Widgren et al., 2019). SimInf is a framework for discrete event-based epidemiological simulations, where transitions between compartments are modelled as a continuous-time discrete-state Markov chain with the Gillespie stochastic simulation algorithm. The framework incorporates both a stochastic simulation in continuous time and the ability to add scheduled events that can move individuals between compartments in the model at the end of each unit of time. This allows for the precise simulation of movement, birth, ageing and death of animals within a herd, as well as testing the effects of changing pig flows on the within-herd spread.

Disease spread model

In this model, the term 'infected' is used to describe animals that are colonised by LA-MRSA, even though LA-MRSA rarely causes clinical disease in pigs. Therefore, 'infected' should be interpreted as a way of clearly communicating the infectious disease model results rather than as an indication of the state of disease of the pig. The disease spread model is an SIS_E compartment model, where animals move between susceptible (S) and infected (I) states and E represents the LA-MRSA-contaminated environment and farm air (Fig. 1). Animals in the model were also divided into metapopulations (nodes) which were interpreted as pens. Environment, in this context, should be interpreted as every surface and the air in each pen. The infected state was assumed to be transient; the pigs could return to the susceptible state and subsequently become recolonised. Based on previous studies, LA-MRSA prevalence varies by age of the animal (Broens et al., 2011; Broens et al., 2012a; Bangerter et al., 2016), but the underlying reasons for this variation have not been fully clarified. Therefore, the susceptible and infected compartments were further divided into age categories including mature sows and gilts in the reproductive cycle, suckling piglets, growing pigs (from weaning and up to 13 weeks of age) and finishing pigs (from 13 weeks up to slaughter).

LA-MRSA may be transmitted through both direct and indirect transmission, but in the model, these routes of transmission were not separated, since the observations available in the literature were not sufficient to allow for this distinction to be made. Thus, the transmission parameters can be interpreted to represent their combined effect. The approach to include indirect spread via the environment is an improvement over direct-spread models, as it allows LA-MRSA to persist in the environment even when animals are removed from their pens.

The transitions from the susceptible to the infected states were dependent on the environmental infectious pressure in the node (pen), age group specific transmission rates and the number of susceptible individuals in the node as described in Supplementary Material S1. Recovery from infected to susceptible states was driven by the number of infected individuals in the node and the average duration of carriage (17.4 days). The duration of carriage was based on the study by Broens et al. (2012b). The environmental infectious pressure in the transitions was specific for each individual node in the herd, and the transmission rates were specified for the four animal age groups.

To incorporate the indirect transmission in the model, a continuous value representing environmental infectious pressure $\varphi_i(t)$ was stored for each node during the simulation. The level of $\varphi_i(t)$ was updated when the simulated time had progressed by one unit (day). Each infected animal in a node contributed to $\varphi_i(t)$ by shedding one unit of contamination per day, which was assumed to be the same for all age categories. The environmental infectious pressure decayed over time by the daily decay rate ($N_{env} = 0.871$), based

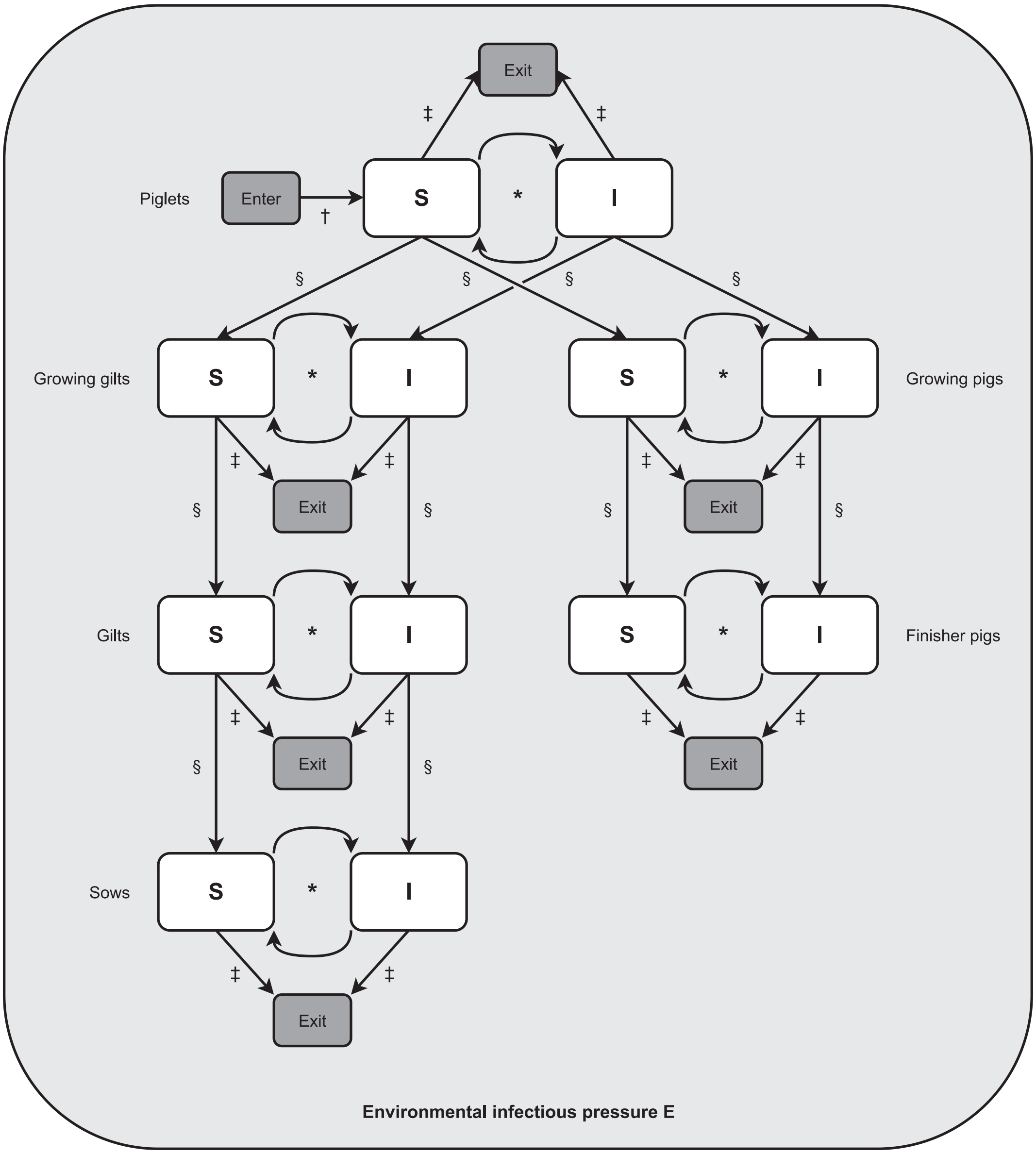

Fig. 1. Conceptual disease spread model for livestock-associated methicillin-resistant *Staphylococcus aureus* in a pig herd. Model has susceptible (S) and infected (I) disease states. Transitions from S to I are dependent on environmental infectious pressure (E). The environmental infectious pressure is specific for each individual node (pen) in the model. The herd consists of six different animal categories which are divided into twelve compartments depending on the animal production phase and disease status. A detailed description of the disease spread model, descriptions of transmission functions and model compartments are presented in Supplementary Figure S1, Supplementary Material S1 and Supplementary Table S1, respectively. *State transitions between S and I states. †Enter events. The birth of piglets into the model is controlled by a Poisson process after sows enter the farrowing room. ‡Exit events. Deaths and culling of animals from the model. §Predetermined scheduled ageing events.

on the reported half-life of LA-MRSA in dust of 5 days (Feld et al., 2018). The level of contamination was determined daily by the amount of existing contamination, the daily decay rate and the shedding from infected animals in the node. This change in the environmental infectious pressure (accumulation and decay) can be expressed as:

$$\frac{d\varphi_i}{dt} = \alpha \sum_j I_{i,j}(t) - \beta(t)\varphi_i(t) \quad (1)$$

where α is the shedding rate per day per infected individual and $I_{i,j}(t)$ is the number of infected individuals in node i and age group j at time t. The parameter $\varphi_i(t)$ is the environmental infectious pressure in node i at time t and $\beta(t)$ is the decay of $\varphi_i(t)$ over one day.

Parameterisation of transmission rates

Transmission rates based on large-scale sampling in Danish and Dutch herds have been presented in a previous study by Broens et al. (2012a). As this study included a transmission rate only for preweaned piglets and a total rate for all pigs in each herd, parameterisation was used to estimate the transmission rates for each different age group in the present model. Having separate animal group transmission rates was seen as justified, as it would help fit the possible age-dependent susceptibility.

The parameterisation was performed using approximate Bayesian computation (**ABC**; Sunnåker et al., 2013) included in the SimInf package. In this method, the simulated LA-MRSA prevalence in the model was compared against expected target values to produce best fitting transmission rates (see Supplementary Material S2). The simulated values were collected from the last year of the model timespan, when LA-MRSA was at a steady state. The target values were obtained from the within-herd prevalences presented by Broens et al. (2012a) and used to obtain separate transmission rates for mature pigs (sows and gilts), suckling piglets, growing pigs and finishing pigs. The within-herd prevalences presented by Broens et al. (2012a) were assumed to be obtained when LA-MRSA was at steady state in the herds. Because the variation of within-herd prevalence in this data was high, i.e. originating from farms with very different prevalence levels, parameterisation was performed against three different target prevalence sets (low, medium and high), which are presented in Table 1.

To find suitable priors for the parameterisation, a preliminary evaluation was done by observing the effect of different transmission rates on LA-MRSA prevalence. Based on these observations, a prior range from 0.1×10^{-3} to 0.3 was used as a starting point for all three target prevalence sets (Table 1). For each generation of the ABC, two hundred accepted particles were acquired. An accepted particle refers to a set of four transmission rates for the respective animal age categories that are considered to produce suitable age-specific prevalences. Particles were accepted if the distance of the model output data was less than the tolerance of the ABC rejection function (Supplementary Material S2), which was reduced stepwise for each generation.

The model output distance was calculated from the sum of the squared differences of the prevalence at each of the time points presented in Table 1 over the last year of each model trajectory, where the model was at a steady state of prevalence. One model trajectory is a single random realisation of the simulated model output, in this case prevalence, over time. The parameterisation process for each target parameter set was halted when the latest produced generation took at least two days to process, or the number of proposed particles exceeded one million. The identified transmission rates obtained through parameterisation were used in the transmission functions, which, together with the recovery functions, are presented in Supplementary Material S1.

Within-herd animal flow

Production statistics for Swedish pig production

The presented model will be used to investigate interventions to control LA-MRSA in a Swedish context and therefore production statistics, such as the average number of piglets born per sow, return to oestrus rate and pig mortality, were obtained from the Winpig production monitoring programme's statistics provided by the Swedish Farm and Animal Health organisation (Farm and Animal Health, 2020a; 2020b). In 2017, the Winpig statistics covered 49% of the Swedish sow population and 14% of the total production of pigs grown for slaughter (Farm and Animal Health, 2019). Values such as group sizes and standard strategies for animal movement and mixing of pigs were obtained by interviewing three Swedish pig experts: one professor in pig medicine and two pig health practitioners.

Herd size and type

The conceptual model of the herd is based on a farrow-to-finish farm, which covers all the production phases in a herd. The herd was set to be closed (no animal influx from outside of the herd) as this is common practice in Sweden. The model was designed to be representative of a farrow-to-finish farm with approximately 500 sows in production.

Farm structure

The hierarchical structure of the farm—including units, sections and pens and the associated animal flow—is presented in Supplementary Figure S2. The herd was conceptually divided into six basic units: breeding, gestation, farrowing, growing, finishing and gilt units. The farrowing, growing and finishing units were further divided into several sections. 'Sections' can be interpreted as wall-separated rooms in a real farm. The growing unit had an additional buffer section, which represented the scenario where slow-growing pigs are moved to a separate room to grow for an extended period before they are moved to the finishing unit. Each section consisted of pens. These pens are nodes in the Siminf nomenclature, and they contained individuals in metapopulations from several model compartments (see section Infectious disease model). The breeding and gestation units consisted of separate pens for sows and gilts. The breeding unit also had separate buffer pens for both sows and gilts, which were a tool to manage the non-pregnant animals that were returning back to breeding.

The sections in the farrowing, growing and finishing units followed the all-in all-out principle, where each section was completely emptied before a new batch of animals entered. Farrowing occurred once a week, where one farrowing section was filled and another one emptied each week. Because of the all-in all-out system, pens that were emptied during a week stayed empty until the start of next production week (downtime period). Breeding, gestation and gilt units, as well as the grower buffer section, functioned as continuous flow, as only some of the pens within the same rooms were emptied and refilled each week. Individual pens in these units followed the all-in all-out principle. Further description of the housing in different production phases is presented in Supplementary Table S2.

Sow production cycle

The sow production cycle in the model was set to 155 days. The time spent in the breeding unit included the days from weaning to

Table 1
Target prevalence values in pigs for parameterisation of low, medium and high prevalence models.[1]

Sampling occasion[2]		Set[3]		
Name	Description	Low (%)	Medium (%)	High (%)
M1 sows	1 week before farrowing	8.0	40.9	84.3
M2 sows	3 days after farrowing	10.4	53.8	91.4
M2 piglets	3 days after birth	12.1	57.5	92.0
M3 sows	3 weeks after farrowing	13.7	67.1	94.1
M3 piglets	3 after birth	12.3	72.8	95.1
M4 growing pigs	6 weeks after birth	22.1	65.2	94.3
M5 growing pigs	10 weeks after birth	15.3	93.2	99.2
M6 finishing pigs	25 weeks after birth	19.0	70.3	94.1

[1] For each sampling occasion reported by Broens et al. (2012a), the 10th, 50th and 90th percentiles of prevalence were calculated and used to represent low, medium and high prevalence farms, respectively. These target values were used to fit age-specific transmission parameters in the disease spread model.
[2] Sampling occasion refers to the sampling moments as described by Broens et al. (2012a).
[3] Target prevalences were calculated from the within-herd prevalences reported by Broens et al. (2012a).

oestrus and the first 27 days of gestation. A pregnancy check was done on the 27th day in the breeding unit, where the probability of pregnancy failure (0.055) was equivalent to the average return-to-oestrus rate in the production statistics (Farm and Animal Health, 2020b). The non-pregnant animals were returned to the breeding buffer pens, and the pregnant animals were moved to the appropriate gestation section. Additionally, sows and gilts had a daily probability of reproductive failure during the first 28 days in gestation which was 0.0029 failures/sow per day, as described in Supplementary Material S3.

To mimic the routine of replacing part of the sow population in the herd, sows were removed from the herd at the time of weaning with a rate of 0.184 per weaned sow (Supplementary Material S3). Those sows and gilts that were found to be non-pregnant during gestation were randomly either returned to the breeding section or removed, where the probability of removal was 0.5. To maintain the target number of mature animals in the herd, the removed animals were replaced by new gilts from the gilt unit.

Pig growing cycle. At the time of farrowing, the sows and gilts were moved from the gestation to the farrowing unit. For simplicity, the farrowing events were set to occur one day later. The litter sizes were sampled from a Poisson distribution (λ = 14.8), based on the average reported number of live piglets born per litter (Farm and Animal Health, 2020b). Following weaning, 5% of the pigs in the section were transferred to the gilt unit and the rest were moved to a growing unit. After the growing period, pigs were moved either to a finisher section or to a grower buffer section. From the finishing unit, pigs were sent to slaughter on three occasions after spending 85, 92 or 99 days in the unit.

Mixing of pigs. As cross-fostering is routinely performed in many pig herds, this was included in the model. In the simulations, a baseline proportion of 10% of the piglets from each pen in the same farrowing section were randomly mixed one day after birth. When pigs in farms are moved from growing to the finishing unit, the slow-growing animals are often moved into a separate grower buffer section, or they might be left in the grower section and mixed with a new batch of growing pigs. In the model, 10% of animals from each grower pen were moved to a grower buffer section, while the rest of the pigs continued to the finishing unit. The pigs that were transferred straight from growing to finishing were mixed one day after the movement. This was implemented by randomly allocating the pigs into new pens. In the grower buffer section, pigs from the same grower section were placed together in the pens. After 23 days, they were merged together with the newest batch of finishing pigs, maintaining the original pen groups in the finishing unit.

Removal of pigs. Pigs can be removed from the herd in three ways: slaughter, euthanasia or death. Removal of animals by slaughter was simulated in the model as described in the Sow production cycle and Pig growing cycle sections. Euthanasia and death were assumed to be part of the mortality rates and were handled together using state transitions and scheduled events. The mortality rates for growing and finishing units were 0.0004 and 0.0002 mortalities per animal per day, respectively. This corresponded to the 2.0 and 1.7% mortalities reported in Swedish production statistics (Farm and Animal Health, 2020a; 2020b). The daily mortality rate for piglets was 0.006, which is based on the reported average total piglet mortality (17.7%) during the suckling period (Farm and Animal Health, 2020b). Calculations for the mortality rates are presented in Supplementary Material S4. Removal of sows and gilts was implemented as scheduled culling events as described in section Sow production cycle. Mortality in sows and gilts was not included in the model.

Model initialisation and run

For the baseline model, the model was run for 3 000 days over a total of 100 trajectories for the low, medium and high transmission parameter sets, where each trajectory is one random realisation of the model. The parameters were sampled from the accepted particles in the last generation of the ABC parameterisation for the corresponding model. In each trajectory, the herd was initiated by adding 22 susceptible gilts to the breeding unit on weekly intervals for a total of 21 weeks. The herd population had stabilised by model day 730. At this time point, the whole herd was infected by moving all animals from the susceptible to infected state from where the LA-MRSA prevalence settled to its steady state over time. The disease was initialised by infecting the entire herd to decrease the probability of disease die-out and to achieve a steady state of infection in all model trajectories.

Effect of mixing of pigs

In addition to the base model simulations, the impact of animal mixing on the LA-MRSA steady state prevalence in the farrowing and finishing units was investigated for all three transmission parameter sets (low, medium, and high). Simulations were completed by sampling parameters from the posterior of the final generation of each model presented in Table 2. In the finishing unit, the mixing of animals was turned off and the LA-MRSA prevalence in the unit was compared to the baseline model's full mixing practice. To investigate the impact of mixing in the farrowing unit (cross-fostering), the baseline LA-MRSA prevalence with 10% mixing of the piglets was compared with two other scenarios, where all piglets were mixed either one or two days after their birth.

Table 2
Parameterised median transmission rates in pigs with associated 95% credible intervals (in parentheses) and model fit values for the final generations of the approximate Bayesian computation (ABC) for the low, medium and high target parameter sets.

	Low set	Medium set	High set
Parameter estimates			
Mature	0.0010 (0.0009–0.0011)	0.0018 (0.0017–0.0020)	0.0071 (0.0065–0.0077)
Piglets	0.0020 (0.0019–0.0021)	0.0051 (0.0047–0.0056)	0.1337 (0.0833–0.2570)
Growing	0.0010 (0.0008–0.0012)	0.0035 (0.0030–0.0041)	0.0200 (0.0158–0.0249)
Finishing	0.0012 (0.0011 –0.0013)	0.0028 (0.0026–0.0030)	0.0140 (0.0124–0.0159)
Model fit			
Final generation tolerance	0.525	6.700	2.135
Proposed particles in final generation	37 586	233 563	1 197 796

Results

Parameterisation of transmission rates

The transmission rates obtained from parameterisation are presented in Fig. 2 and Table 2. The indicators of model fit are also presented in Table 2. The final generation tolerances are a measure of model fit and relate to how closely the model-predicted prevalence matched the targeted observations from the literature (Supplementary Material S2). A difference between the parameter estimates was defined as less than 5% overlap in the posterior density of the parameter distributions, corresponding to a lack of overlap in the 95% credible intervals (**CrI**). In all three parameter sets, the transmission rate for piglets differed from the other three animal groups, but in the high parameter set, the distribution of the identified values was very wide. In the low parameter set, there was no difference between the transmission rates for mature, growing and finishing pigs, whereas in the medium parameter set, the transmission rates differed for all animal groups. In the high set, the transmission rates for growing and finishing pigs overlapped, but the rate for mature pigs differed from the other transmission rates.

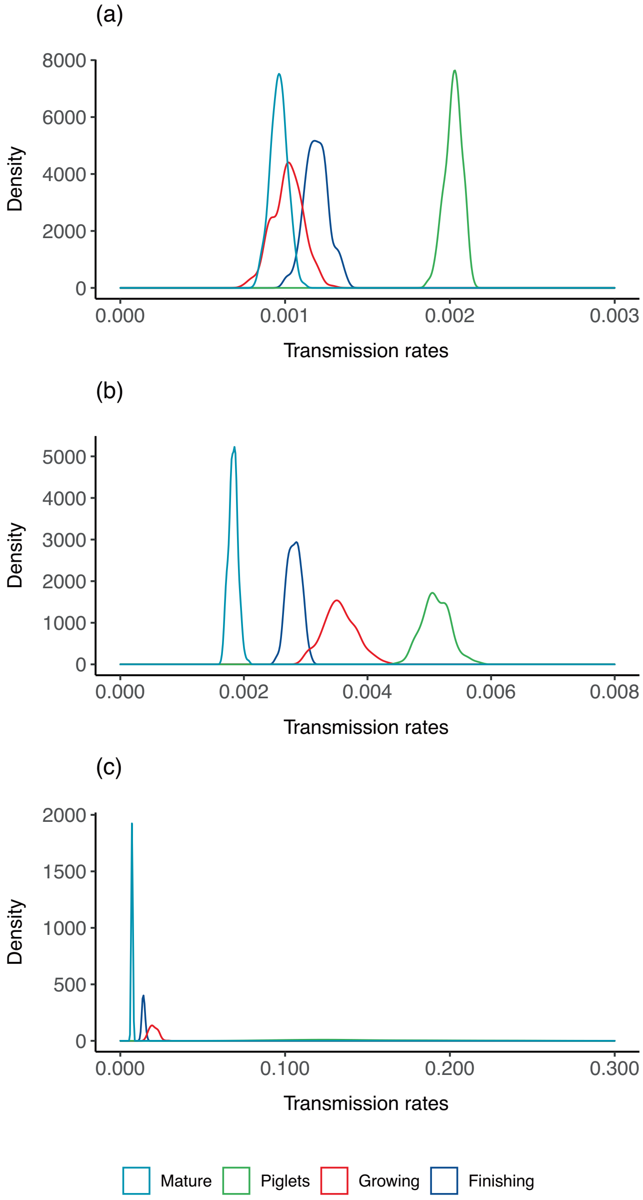

Fig. 2. The posterior densities of the parameterised transmission rates. Parameterisation was performed using approximate Bayesian computation (ABC) to estimate the four transmission rates for each pig age group (Mature, Piglets, Growing and Finishing pigs) against three different target prevalences: low (a), medium (b) and high (c).

Model within-herd prevalence

The model-predicted prevalences for the different animal groups, based on the transmission rates obtained through parameterisation, are presented in Fig. 3. The median prevalences in all three parameter sets for piglets, sows in the farrowing unit, growing pigs, and finishing pigs were similar to the target prevalence values presented in Table 1. The predicted prevalences of other mature animal groups could not be compared to the target prevalence values, as the available values for parameterisation included only sows from one week before farrowing to three weeks after farrowing, whereas Fig. 3 presents the within-herd prevalence for all different production phases of the mature animals.

Validation of the model animal flow

The model's production output was compared to the Swedish pig production statistics (Farm and Animal Health, 2020a; 2020b) to evaluate how well the animal flow reflected normal production. When run over 100 trajectories, the model farm produced on average 12 555 finishing pigs annually for slaughter, whereas an average Swedish farm with the same number of sows produces 13 350 pigs. The target total number of sows and gilts in the sow cycle was set to 500, and the result output is presented in Fig. 4a. The proportion of gilts relative to all breeding animals was 23%. In the production statistics, the proportion is presented as the proportion of gilt litters in the herd, which was on average 24.2%. The model reached a stable population structure within two years (Fig. 4); at this time point, the number of gilts and sows in each breeding cycle and the annual number of slaughtered finisher pigs both stabilised to the levels presented in the section Conceptual herd model.

Effect of mixing of pigs

Mixing of pigs in the finishing unit

When observing the difference in LA-MRSA prevalence between mixing and not mixing animals in the finishing unit, disabling mixing lowered the prevalence in the low transmission parameter set (Fig. 5) when LA-MRSA had reached steady state in the herd. For the low transmission parameter set, the median difference in prevalence between days 1 500 and 3 000 was 8.8% (95% CrI: [2.0–15.7%]). The prevalence was considered to differ because the credible interval did not include zero. This difference is also apparent in the lack of overlap in the 95% credible intervals illustrated in Fig. 5. Using the medium and high parameter sets, no difference in prevalence could be shown between the models with the different mixing scenarios (Supplementary Table S3).

Cross-fostering in the farrowing unit

When assessing the effect of cross-fostering on the transmission of LA-MRSA, no difference in the prevalence could be shown between different cross-fostering scenarios (Supplementary Table S4). This is illustrated by the overlapping credible intervals between different cross-fostering scenarios in Fig. 6. For clarity, as the results of mixing piglets one and two days after the birth were similar, mixing of the piglets two days after birth was excluded from Fig. 6. Complete results for all mixing scenarios are provided in Supplementary Table S5.

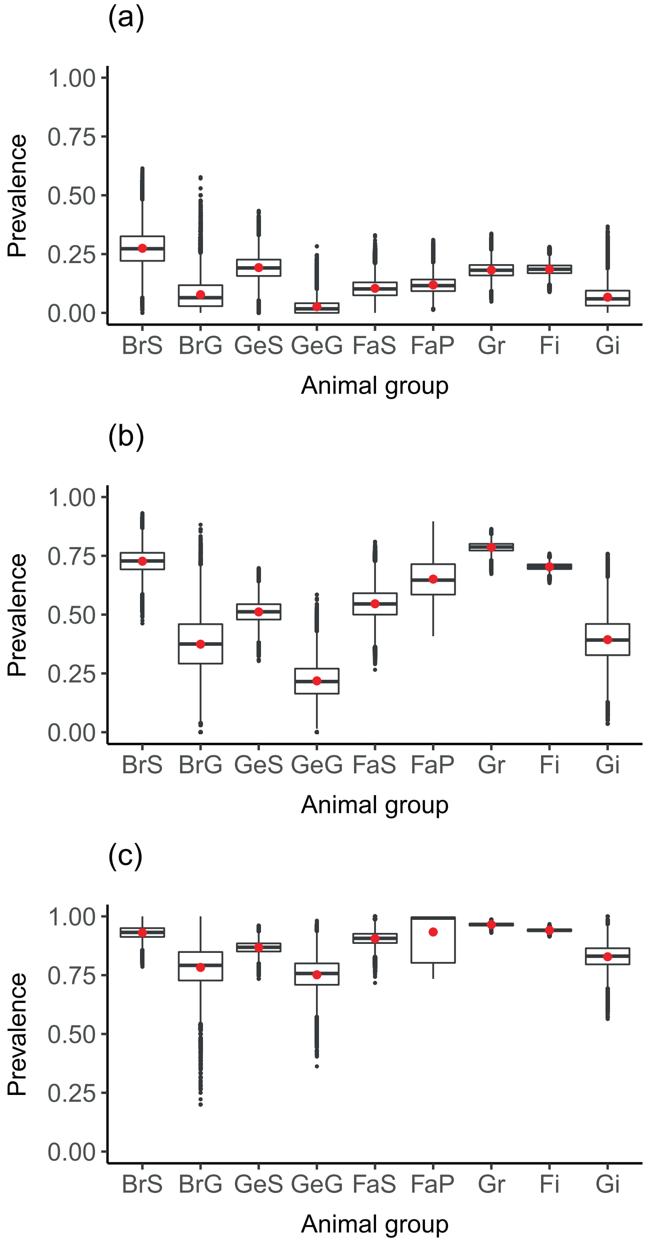

Fig. 3. Model-predicted within-herd livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) prevalence for different pig age groups when using the parameterised transmission rates. The transmission rates were classified into low (a), medium (b) and high (c) sets based on the target prevalences used in parameterisation. The prevalences were obtained over a period of 1 year (days 2 635–3 000) when LA-MRSA was in a steady state in the herd. The model was run over 1 000 trajectories. Mean prevalences are indicated with a red dot. LA-MRSA did not die out in the herd in any of the trajectories. Abbreviations: BrS = Breeding unit, sows; BrG = Breeding unit, gilts; GeS = Gestation unit, sows; GeG = Gestation unit, gilts; FaS = Farrowing unit, sows; FaP = Farrowing unit, piglets; Gr = Growing unit; Fi = Finishing unit; Gi = Gilt unit.

Discussion

Model structure and validation

This study presented a stochastic event-based model for simulating the environmentally mediated spread of LA-MRSA in pig herds in a Swedish context. In the study, the shedding of LA-MRSA was assumed to be intermittent. This differs from a previous modelling study where pigs could be either persistent or intermittent shedders (Sørensen et al., 2017). There is currently no scientific consensus on whether pigs can be persistent shedders of LA-MRSA or if they are being re-exposed to the bacteria either from the environment or by direct contact with other pigs. In humans, different *S. aureus* strains show varying degrees of persistence: persistent carriage of *S. aureus* has been described (Wertheim et al., 2005) but with LA-MRSA CC398, the possibility of re-colonisation with the same strain has not been ruled out (Goerge et al., 2017). Hence, without further experimental studies, it is not possible to ascertain whether the persistent carriage is a reality. As including environmentally mediated indirect transmission allowed LA-MRSA to persist in the herd, adding persistent shedders was not necessary in this modelling approach.

In this study, the entire herd was infected simultaneously for the purpose of finding a steady state of infection in the herd. This could impact the persistence of LA-MRSA as a smaller targeted introduction of the disease would result in a stochastic die-out of the disease from the herd in some cases. It was not known whether the prevalences used in parameterisation were from herds in a steady state with different disease dynamics, or if the sampled herds were from different phases of an epidemic of LA-MRSA. For the purpose of this study, it was assumed that the study herds were in a steady state which justifies the introduction of LA-MRSA into the entire herd simultaneously. Future work will investigate how the probability of LA-MRSA persistence in a pig herd is related to disease introduction intensity or introduction into specific age categories in the herd (e.g. purchased breeding stock).

In the current model, LA-MRSA was transmitted indirectly via the environment described by a single transmission term for each age category. These transmission parameters can be interpreted as the combined indirect and direct transmission that was required to achieve the LA-MRSA prevalences reported in the literature. This approach allowed the inclusion of environmental load in the model, reflecting how the infectious pressure can persist even when animals are not present in the pen. In a model with only direct transmission, the disease could not be perpetuated between animal groups subsequently housed in the same pens. Therefore, investigating environmental intervention strategies, such as cleaning or changing downtime between groups, would not be possible in a model with only direct transmission. One might argue that the inclusion of separate direct and indirect transmission in a spread model of LA-MRSA would be the best representation of the true disease dynamics. However, the reported observations of prevalence would not have allowed for separate parameters to be identified by the parameterisation method.

Based on the model output, the chosen values for animal housing and movements resulted in a realistic representation of a Swedish pig herd when comparing it to the Swedish pig production statistics. However, these statistics include only a portion of all Swedish herds, which limits their representativeness. On the other hand, the herds included in the statistics are mostly larger commercial herds, which are becoming more common while the total number of herds is decreasing in Sweden.

Parameterisation of transmission rates

Approximate Bayesian computation (ABC) was used to estimate the transmission rates for different animal age groups at three different prevalences. The ABC method is easy to implement, and it does not restrict the kind of model that can be fitted. However, ABC is not suitable for comparing models with different structures as increasing model complexity results in better fit without penalisation for the added complexity.

The transmission rates in the current study were estimated to fit previously published observational data by Broens et al. (2012a), which included six farrow-to-finish farms. The low

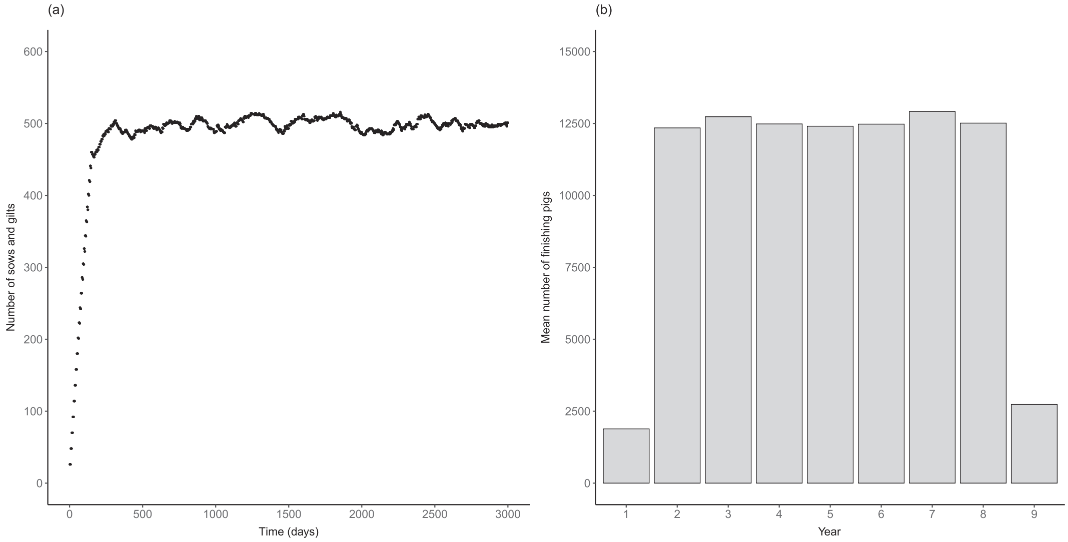

Fig. 4. Model-predicted mean number of sows and gilts in the pig herd over time (a) and the model-predicted mean number of finishing pigs slaughtered per year (b). The year-9 observation of the number of finishing pigs slaughtered included only 80 days. The model was run for 3 000 days and 100 trajectories.

number of farms in the study might limit the representativeness of the data. The within-herd prevalences reported by Broens et al. (2012a) are dependent on the diagnostic sensitivity of the used sampling methods, which was unknown in this case. However, the number of animals sampled in the study was high and several of the reported prevalences were approaching 100%. This would imply that the sensitivity of the sampling and testing methods were nearly perfect in these herds, assuming a test specificity of 100%.

In the current study, the parameterisation was done for three different target prevalence levels, as the within-herd prevalences reported by Broens et al. (2012a) varied between the farms. This could have been caused by either variables that were not included in the data (eg. differences in management practices) or that the herds were in different phases of an LA-MRSA outbreak. The current modelling approach is suitable for the first type of variation. More detailed data, including observations over time from the same herds, would be required to build more accurate models of the dynamics of LA-MRSA.

Based on the transmission rates obtained by the parameterisation, the piglet transmission rate differed from the other three transmission rates in all three (low, medium and high) parameter sets. Therefore, it was evident that a separate rate for preweaned piglets was necessary when aiming to fit the model to the observational data. However, in the high parameter set, the distribution of the fitted transmission rates for piglets was considerably wider than in the other transmission rates, reflecting the difficulty in obtaining a precise value through parameterisation for this rate. This could be driven by the high overall transmission level, where the transmission rate for piglets becomes less influential when the high prevalence of infection in mature animals leaks to the piglets in the farrowing pens. When observing the medium parameter set,

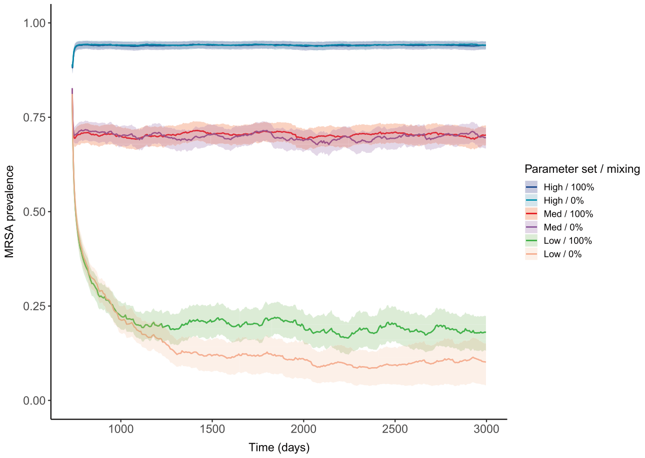

Fig. 5. Model-predicted mean livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) prevalence and associated 95% credible intervals in the finishing unit when 0 or 100% of pigs were mixed one day after arrival to the unit. Prevalence was simulated for three transmission parameter sets (low, medium [med], high). The model was run over 1 000 trajectories and all animals in the herd were infected at day 730 when the herd had reached its steady state. To assess the temporal variation of the production cycle, the mean and the credible intervals were plotted as the rolling mean over a 7-day period.

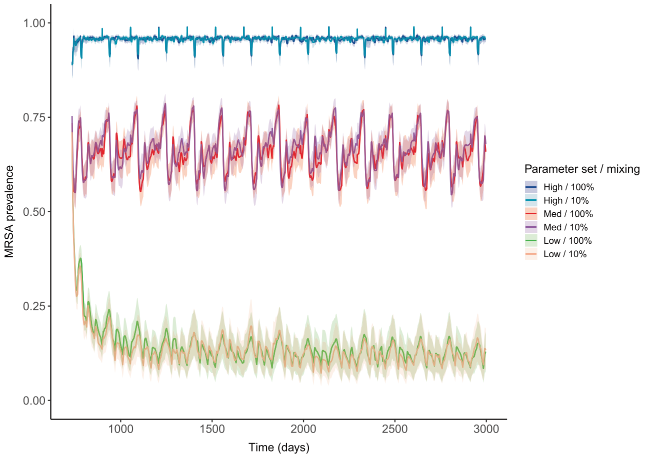

Fig. 6. Model-predicted mean livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) prevalence in the piglets in the farrowing unit and the associated 95% credible intervals when 10 or 100% of the piglets were mixed one day after birth. Prevalence was simulated for three transmission parameter sets (low, medium [med], high). The model was run over 1 000 trajectories and all animals in the herd were infected at day 730 when the herd had reached its steady state. To assess the temporal variation of the production cycle, the mean and the credible intervals were plotted as the rolling mean over a 7-day period.

using separate transmission rates for mature pigs, piglets, growing pigs and finishing pigs was justified, as in this set, the transmission rates for each animal group differed from each other. In the low parameter set, the lack of difference in transmission rates between age groups could be partially explained by the small numerical difference between the low target prevalences.

The model-predicted prevalence for piglets and sows in the farrowing unit and for pigs in growing and finishing units were comparable to the target values used for parameterisation. For other mature pigs (sows and gilts in the breeding, gestation, and gilt units), the model output varied among different animal groups. This could be explained by the limited number of sampling points in the parameterisation data which was focused only on farrowing sows. Interestingly, when model prevalence in sows was observed, all parameter sets indicated that LA-MRSA prevalence was higher in the breeding unit than in the farrowing unit, but the prevalence decreased again in the gestation unit. The higher prevalence in the sow breeding unit could be explained by the high prevalence in the farrowing unit—which is the origin of the animals in the sow breeding unit—and by the larger group sizes in the breeding pens. However, this phenomenon was absent when new gilts were moved from the gilt unit to breeding. This difference between gilts and sows in the breeding unit could be a consequence of the smaller group sizes of gilts, as well as the long gilt growing period prior the arrival to the breeding unit. During the growth period, the new gilts were housed in small fixed groups, which could have slowed down the spread of LA-MRSA. Similar to the sows, the prevalence among gilts decreased when the animals were moved to the gestation unit.

Effect of mixing of pigs

In addition to proposing a model and transmission rates of LA-MRSA in pigs, the effects of mixing pigs on the LA-MRSA prevalence in finishing pigs and cross-fostering piglets in the farrowing unit were investigated. In the finishing unit, removing the mixing of pigs at the time of entry to the unit had an effect on LA-MRSA prevalence when the low transmission parameter set was used. However, a similar effect was not observed with the medium and high parameter sets, and the difference between different mixing practices was smaller in the high than in the medium set. The lack of effect in the high parameter set could be explained by the high proportion of infected individuals entering the finishing unit, which overwhelmed the effect of reduced mixing. This finding indicates that, in circumstances of low disease spread, an intervention of reduced mixing in finishing pigs could be an effective reduction strategy.

In the cross-fostering scenarios, reducing or increasing the proportion of mixed animals did not have an effect on the LA-MRSA prevalence in any of the transmission parameter sets. Interestingly, performing the cross-fostering events one day later gave similar results, even though the piglets had more time to become infected. The lack of effect of both cross-fostering and mixing in finishing units can be linked to the way LA-MRSA is disseminated throughout the pens. If the infected individuals are spread uniformly over the pens in a section before the mixing events occur, mixing all the animals randomly will not substantially change the likelihood of an infected individual being added to pens that were previously free from infection. However, the difference in the effects of mixing between farrowing and finishing units could be explained by the different animal densities as well as different transmission rates due to the suspected higher susceptibility of piglets in the farrowing unit. It is also noteworthy that, unlike mixing in the finishing unit, cross-fostering was not completely turned off in the scenarios but only performed at the level commonly practised in Swedish herds.

Overall aspects

In case of an LA-MRSA outbreak, avoiding mixing in the finishing unit could be beneficial in reducing the prevalence when the LA-MRSA level is low in the herd. The practical importance of the observed reduction in prevalence (8.8%) would require a cost-benefit analysis also assessing the impact on human health. In other model scenarios, reducing the mixing as the only intervention strategy is not sufficient for reducing LA-MRSA prevalence. However, the study focused on the effect of reduced mixing when LA-MRSA had reached its steady state. The effect of the interventions could be different if performed earlier in an outbreak, perhaps even causing fade-out of LA-MRSA in the herd. Future work will investigate the effect of reduced mixing in different phases of an LA-MRSA outbreak or combining the reduced mixing with other interventions, for example, reduced environmental infectious load through thorough cleaning and disinfection.

Overall, further research on LA-MRSA transmission in different age groups and the relative role of indirect transmission are needed to fill the knowledge gaps and produce more accurate modelling results. With more observational data on indirect transmission, the model could be extended with between-pen transmission to simulate the animal contact between adjacent pens. In addition, the knowledge of LA-MRSA half-life in the environment is incomplete as previous knowledge is limited to analyses of dust collected from the barn air.

The advantage of this modelling approach was that including indirect transmission allowed the infection load to persist in the environment after the animals had been moved out from the pen. Using an event-based compartment model also provided a modelling framework that is faster and less resource-intensive than similar individual-based disease models. On the other hand, individual-based models make it possible to follow an individual animal and its status through the model, which is not possible in the current approach where the basic unit is the pen. From a control perspective, however, the status of individual animals is of less interest than the status at the group level or herd level.

This study presents a robust and flexible model with detailed herd representation and transmission through the environment. The model is a useful tool to investigate the effects of LA-MRSA and other infectious diseases in pig herds. The results show that using only transmission through the environment allows LA-MRSA to persist in the herd without assuming the presence of persistent shedders as has been previously suggested. The results also suggest that avoiding mixing of pigs in the finishing unit can reduce LA-MRSA prevalence in the herd when the within-herd prevalence is low. This study emphasises that there are still several substantial knowledge gaps regarding the transmission and shedding of LA-MRSA in pigs.

Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.animal.2021.100450.

Ethics approval

Not applicable.

Data and model availability statement

The model code is publicly available in a GitHub repository: https://github.com/KSTuominen/LA-MRSA. The data that support the study findings are available upon request from the corresponding author.

Author ORCIDs

K.S. Tuominen: https://orcid.org/0000-0002-2223-9376
S. Sternberg Lewerin: https://orcid.org/0000-0001-7907-8377
M. Jacobson: https://orcid.org/0000-0002-8652-6593
T. Rosendal: https://orcid.org/0000-0002-6576-9668

Author contributions

K.S. Tuominen: data curation, investigation, methodology, software, formal analysis, validation, visualization, writing - original draft

S. Sternberg Lewerin: conceptualization, validation, funding acquisition, supervision, writing - review & editing

M. Jacobson: conceptualization, supervision, writing - review & editing

T. Rosendal: conceptualization, data curation, methodology, software, formal analysis, validation, supervision, writing - original draft

Declaration of interest

None.

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