SUPPLEMENTARY INFORMATION

DRIVERS FOR LIVESTOCK-ASSOCIATED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS SPREAD AMONG DANISH PIG HERDS - A SIMULATION STUDY

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Data preparation

Herd information. Holding information data included the holding and herd identification numbers. Several herds could be owned by the same farmer and therefore share an individual holding number, yet have different herd identification numbers. To keep the herds anonymous, new herd identification numbers were generated, and the herd was used as the unit of interest. Herds owned by the same farmer were marked to track the connection between them. The registered numbers of sows, weaners and finishers per year, as well as the herd type were extracted from the CHR.

The VetStat database records herd-level information on prescription-only drugs[1]. These data were used to add an antimicrobial usage index per year. The index was set to 1 if at least one prescription of tetracycline and/or beta-lactam was reported in the VetStat register.

In addition, the number of registered movements to abattoirs for each herd h per year was calculated based on the movement data and this value divided by 365, giving a herd-specific λ_a^h that was used as a parameter to model indirect contacts related to abattoir movements.

Our datasets lacked information on UTM coordinates for some of the herds. This information was updated using a website to calculate the coordinates based on the address of the holdings provided on the CHR website[2] (www.geoplaner.com/).

All herds were categorised according to: (1) herd type (breeding and multiplier herds, production herds, weaner herds, organic and free-range pig herds and hobby herds), (2) the proportion of sows, weaners and finishers registered in the CHR[2], and (3) the type of production (Table S1-S2).

No sows, weaners or finishers were registered in 181 herds in 2007 and 844 herds in 2014[3], but these herds had registered in-coming or out-going movements, and could therefore be considered active. The number of animals was estimated for these herds. For each herd type, the distribution of herds (with registered sows, weaners or finishers) was determined in each combination of categories 1-7 and A-C (Tables S1-S2). In addition, the average number of sows, weaners and finishers registered in these herds in the CHR was calculated for each category combination. To estimate the missing number of animals, a category combination was randomly assigned to herds that had not registered any animals. Based on this combination, the number of sows, weaners and/or finishers was calculated using an exponential distribution with lambda given by the average number of sows, weaners and finishers.

Movement data. Information on the movements of swine was available from the movement database, including the holding and herd identification numbers for both sending and receiving herds, the date of the pig movements and the number of pigs moved. No information was available on the age group (sows, weaners or finishers) of pigs moved.

The age group of pigs moved out of the sending herd and into the receiving herd was estimated based on the herd categories 1-7 and A-C (Tables S1-S4). If no weaners were registered, but were thought to have been moved out of a herd, they were assumed to have been moved directly from the sow section.

Modelling disease spread within a herd

Environment-related recurrence. The probability decreases exponentially over time as follows:

$$f^{envir}(\Delta t) = \exp(-\alpha_{envir} \cdot \Delta t), \tag{1}$$

where Δt is defined as the time difference between the current simulation day and the day when LA-MRSA died out in the respective herd.

Within-herd dynamics. For each individual susceptible animal, the probability of infection $Prob_{C_i}^t$ at each time step t resulting from positive animals within compartment C_i was assumed to be density-dependent and was calculated based on the number of LA-MRSA-positive pigs $I_{C_i}^t$ and the total number of pigs $N_{C_i}^t$ within the individual compartment as follows:

$$Prob_{C_i}^t = 1 - \exp\left(-\frac{\beta_{C_i}^t * I_{C_i}^t}{N_{C_i}^t}\right), \tag{2}$$

where $\beta_{C_i}^t$ is the daily transmission rate of the infection for each compartment C_i, and

$i \in \{sows, weaners, finishers\}$. The probability of infection $Prob_{C_i C_j}^t$ resulting from positive animals from another compartment $C_j \neq C_i$ was calculated as:

$$Prob_{C_i C_j}^t = 1 - \exp\left(-\frac{\beta_{C_i C_j}^t * I_{C_j}^t}{N_{C_j}^t}\right), \tag{3}$$

where $\beta_{C_iC_j}^t$ is the between-compartment transmission rate. The total probability for each individual in compartment C_i was therefore:

$$Prob_{C_i}^t = 1 - (1 - Prob_{C_i}^t) * \prod_{j \neq i}(1 - Prob_{C_iC_j}^t). \qquad (4)$$

In order to slow the within-herd spread, a time-dependent scaling function was introduced:

$$f(\Delta t) = 1 + exp(-k * (\Delta t - x)), \qquad (5)$$

where Δt is the simulation time since the introduction of LA-MRSA in the herd, and k and x are read-in parameters defining the steepness and the midpoint of the scaling function. The within-compartment transmission rates $\beta_{C_i}^t$ were divided by the scaling function. The time-shifted transmission rates led to a similar but delayed level of within-herd prevalence (Figures S1-S5).

Mimicking the within-herd dynamics in 100 large production herds for 365 days using the transmission rates adapted by Broens et al. (2012)[4] led to a median within-herd prevalence of 65% for herds using high-risk antibiotics and 59% for herds that did not use high-risk antibiotics (Figures S1-S4).

Spread via indirect contacts. The transmission between two herds H_1 and H_2 with the same owner was modelled using equation (2) to calculate the probability of infection $Prob_{H_iH_j}^t$ with $C_i = H_2$ and $C_j = H_1$. The number of LA-MRSA-positive pigs $N_{H_1}^t$ ($I_{H_1}^t$) was equivalent to the total number of LA-MRSA-positive sows, weaners and finishers in H_1. If H_1 was a large herd, the low-risk between-compartment transmission rate of H_1 was used, whereas if H_1 was small, the within-herd transmission rate of H_1 was used. If transmission was successful, new LA-MRSA-positive pigs were introduced to the sow compartment of herd H_2.
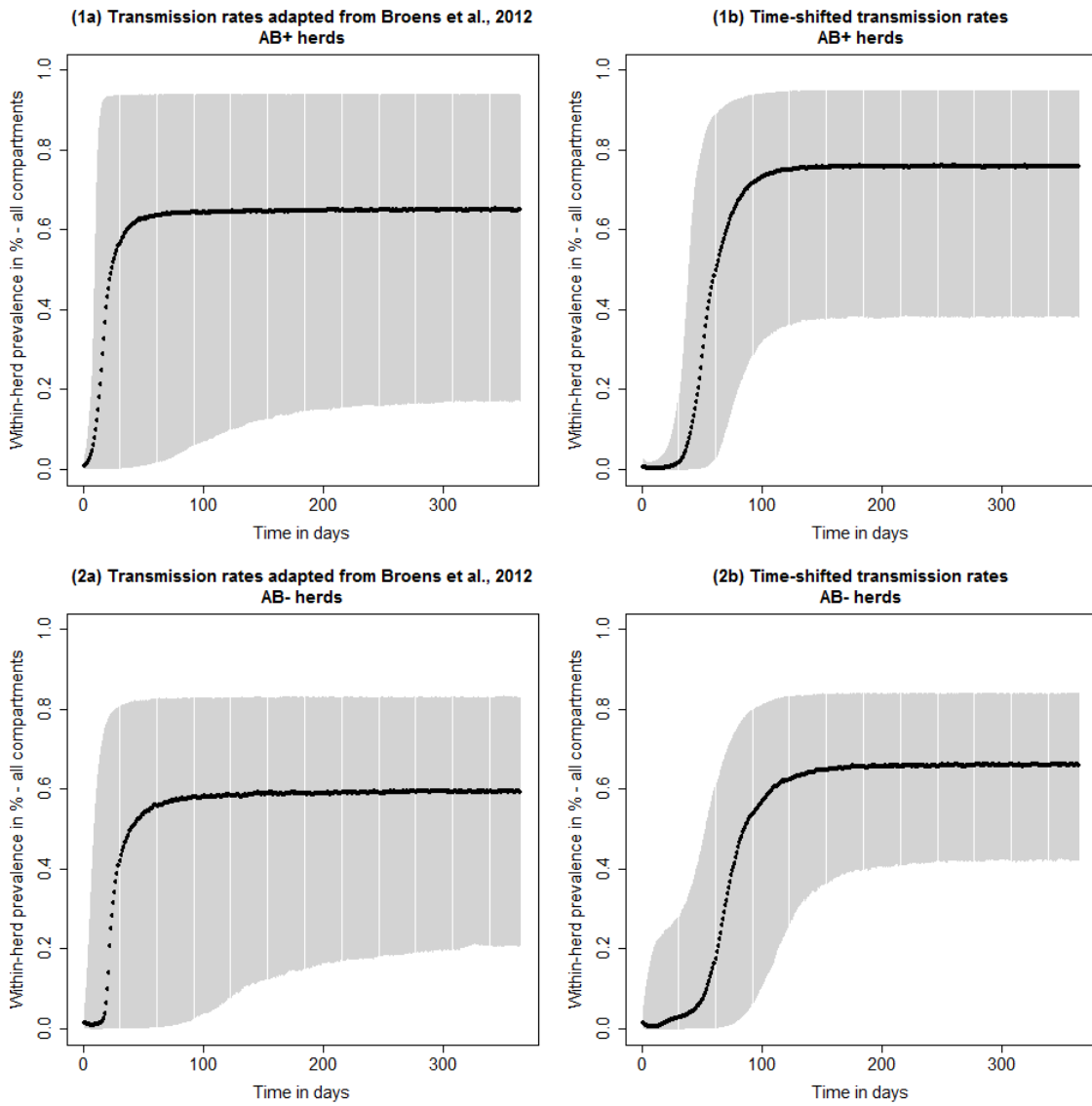
FIGURES

Figure S1. Development of the within-herd prevalence in large production herds in the first year after LA-MRSA initialisation in 100 production herds (1) using high-risk antibiotics, and (2) not using high-risk antibiotics for (a) transmission rates adapted from Broens et al.[4] (Table S5), and (b) time-shifted transmission rates. The black dotted line represents the median of 500 iterations and the grey area spans the 95% confidence interval.
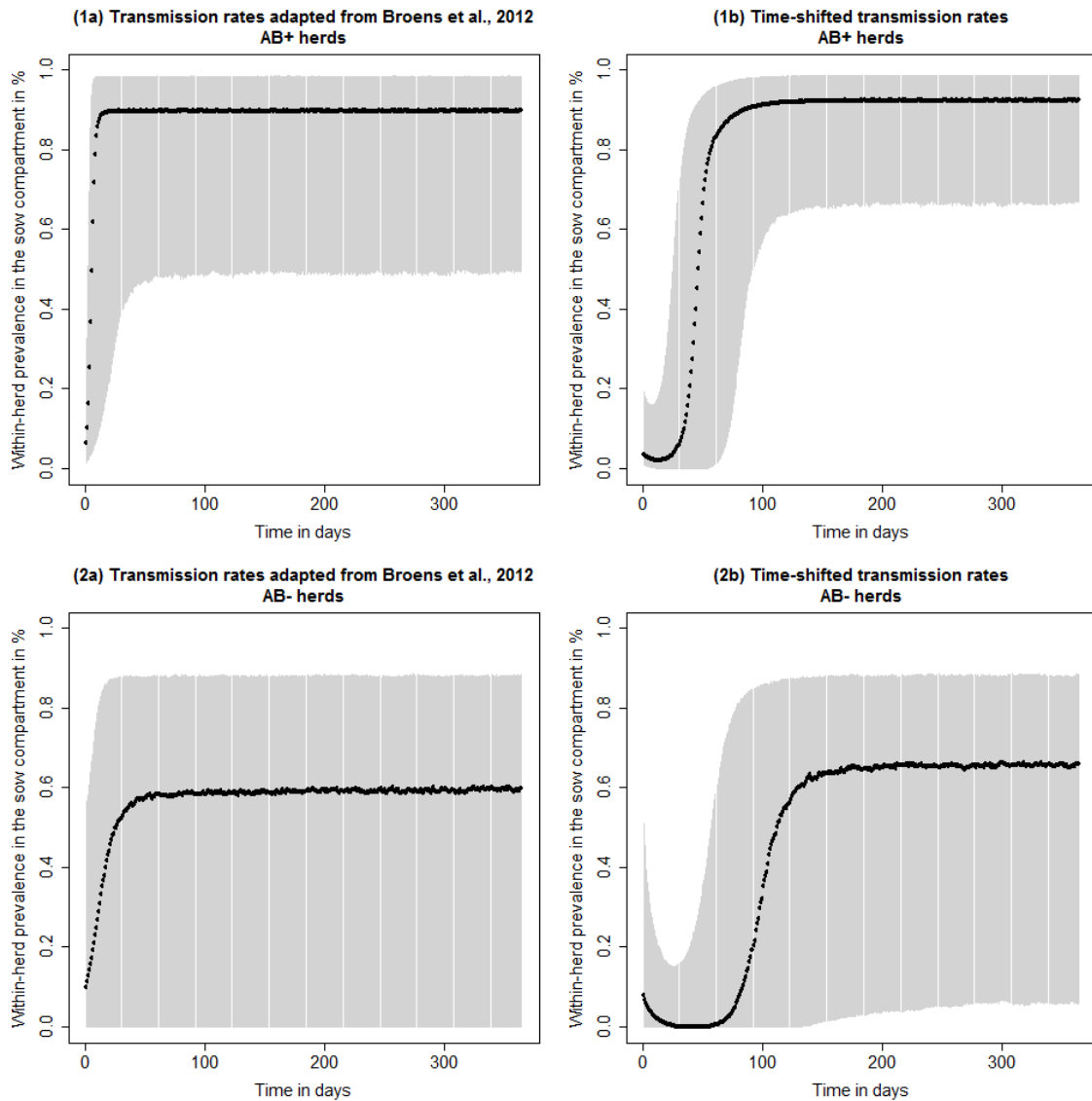
Figure S2. Development of the within-herd prevalence in the sow compartment in the first year after LA-MRSA initialisation in 100 production herds (1) using high-risk antibiotics, and (2) not using high-risk antibiotics for (a) transmission rates adapted from Broens et al.[4] (Table S5), and (b) time-shifted transmission rates. The black line represents the median of 500 iterations and the grey area spans the 95% confidence interval.

Figure S3. Development of the within-herd prevalence in the weaner compartment in the first year after LA-MRSA initialisation in 100 production herds (1) using high-risk antibiotics, and (2) not using high-risk antibiotics for (a) transmission rates adapted from Broens et al.[4] (Table S5), (b) time-shifted transmission rates, and (3) time-shifted and scaled transmission rates. The black line represents the median of 500 iterations and the grey area spans the 95% confidence interval.

Figure S4. Development of the within-herd prevalence in the finisher compartment in the first year after LA-MRSA initialisation in 100 production herds (1) using high-risk antibiotics, and (2) not using high-risk antibiotics for (a) transmission rates adapted from Broens et al.[4] (Table S5), and (b) time-shifted transmission rates. The black line represents the median of 500 iterations and the grey area spans the 95% confidence interval.
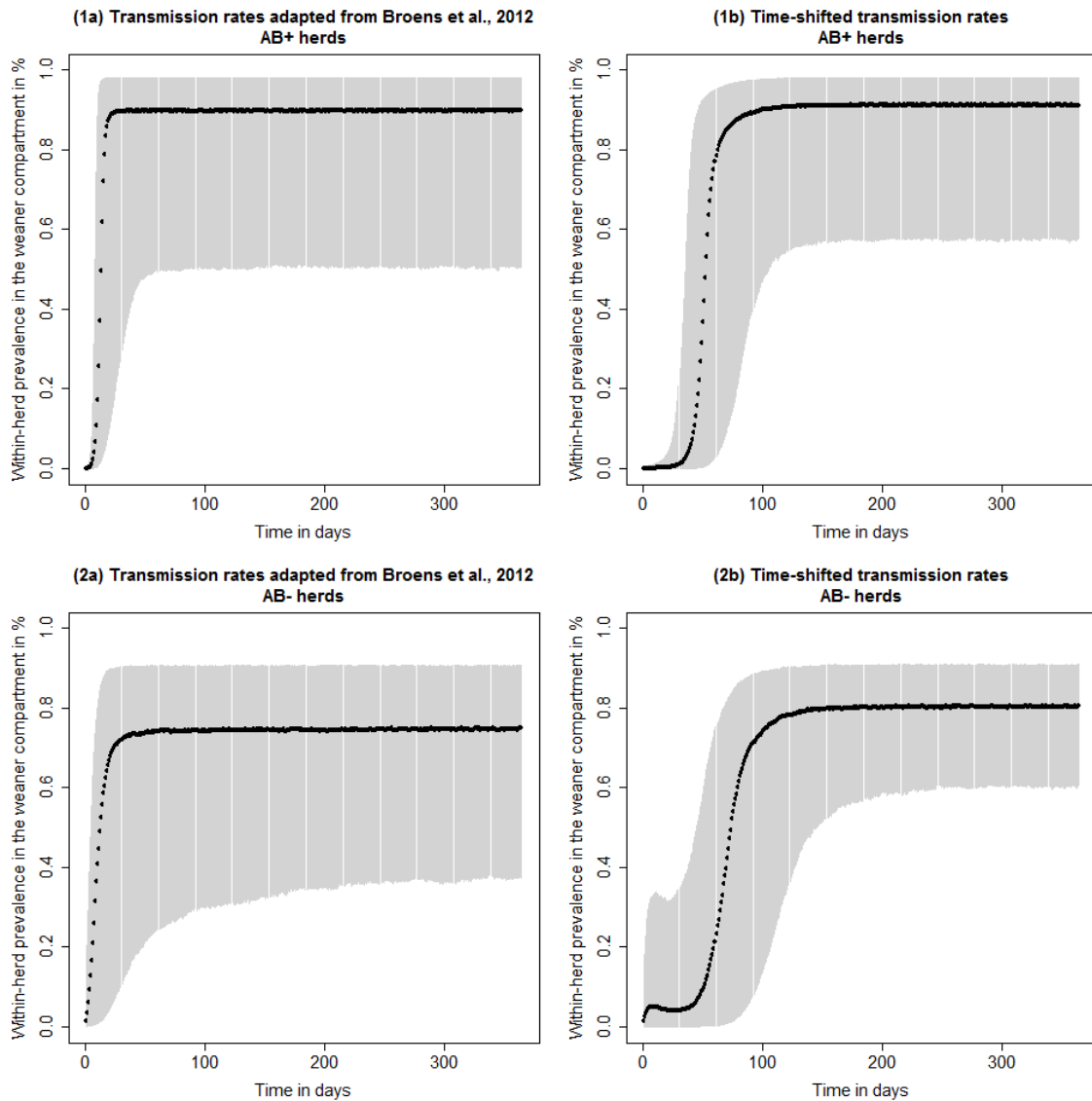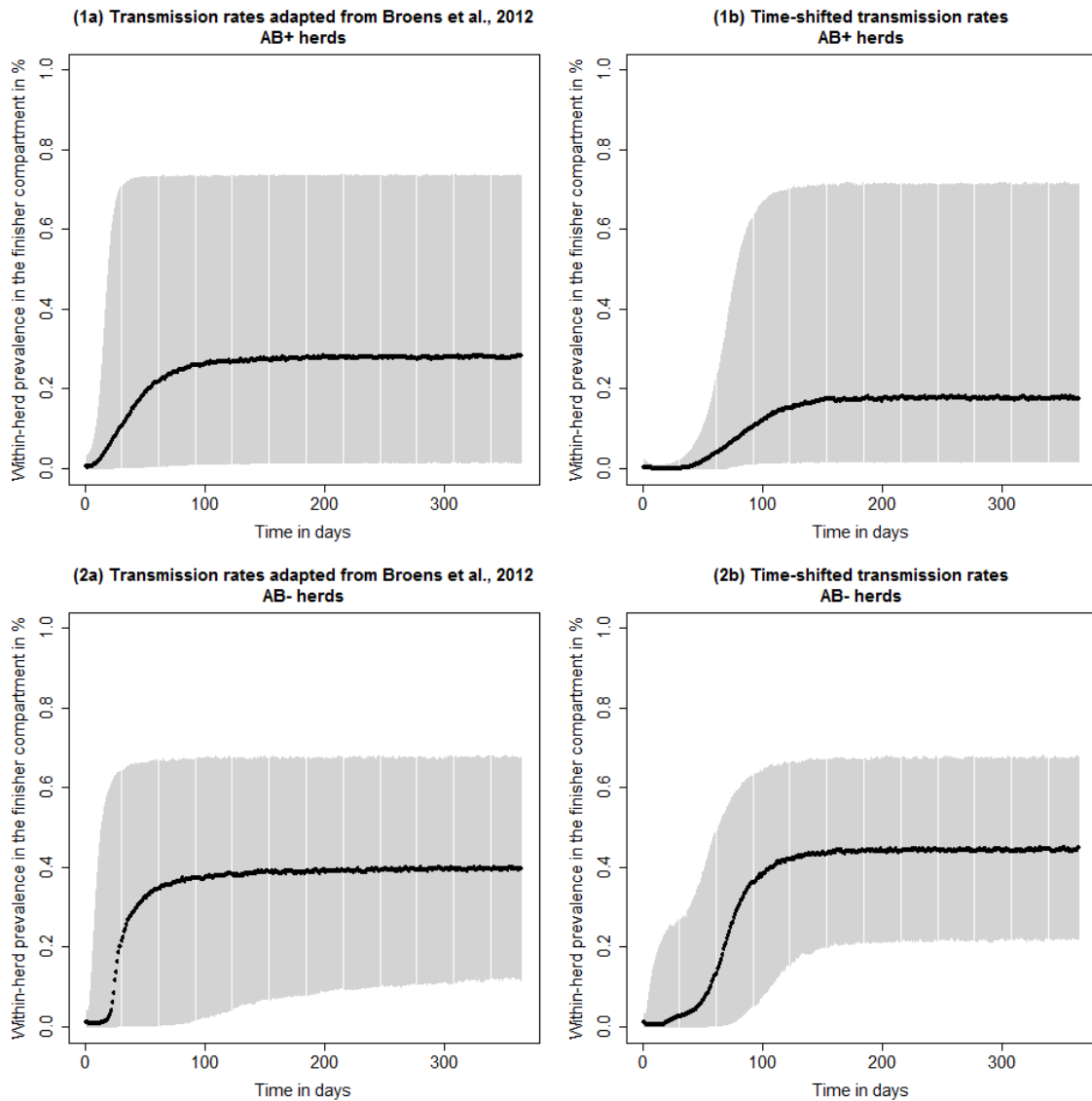
Figure S5. Development of the within-herd prevalence in small herds in the first year after LA-MRSA initialisation in 100 production herds (1) using high-risk antibiotics, and (2) not using high-risk antibiotics for (a) transmission rates adapted from Broens et al.[4] (Table S5), and (b) time-shifted transmission rates. The black line represents the median of 500 iterations and the grey area spans the 95% confidence interval.
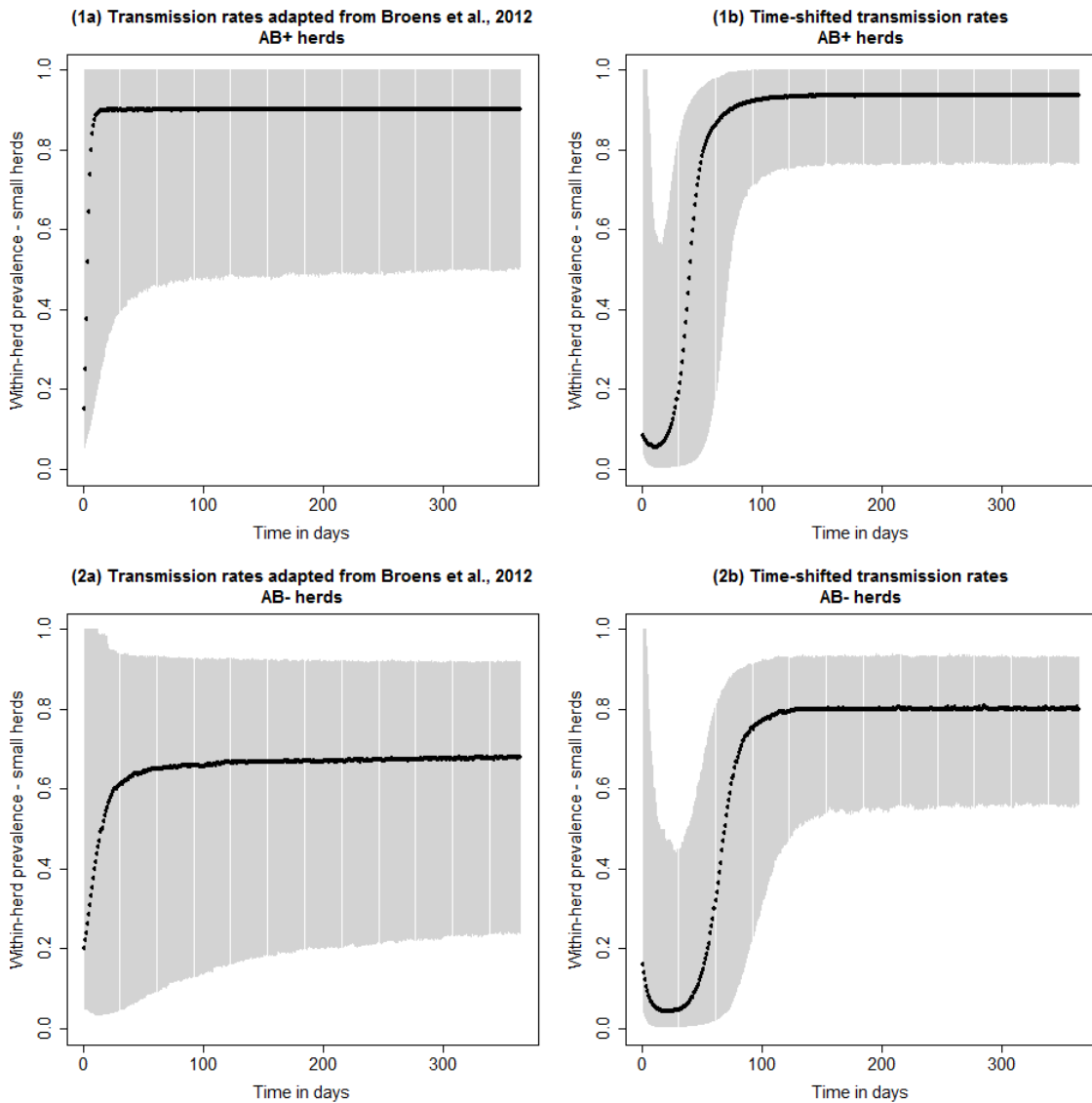
Figure S6. Violin plots summarising the herd prevalence in all herds in 2010 and 2011 based on 500 iterations of 17 LA-MRSA initialisation scenarios using time-shifted transmission rates adapted from Broens et al.[4], and modelling transmission only via animal movements.
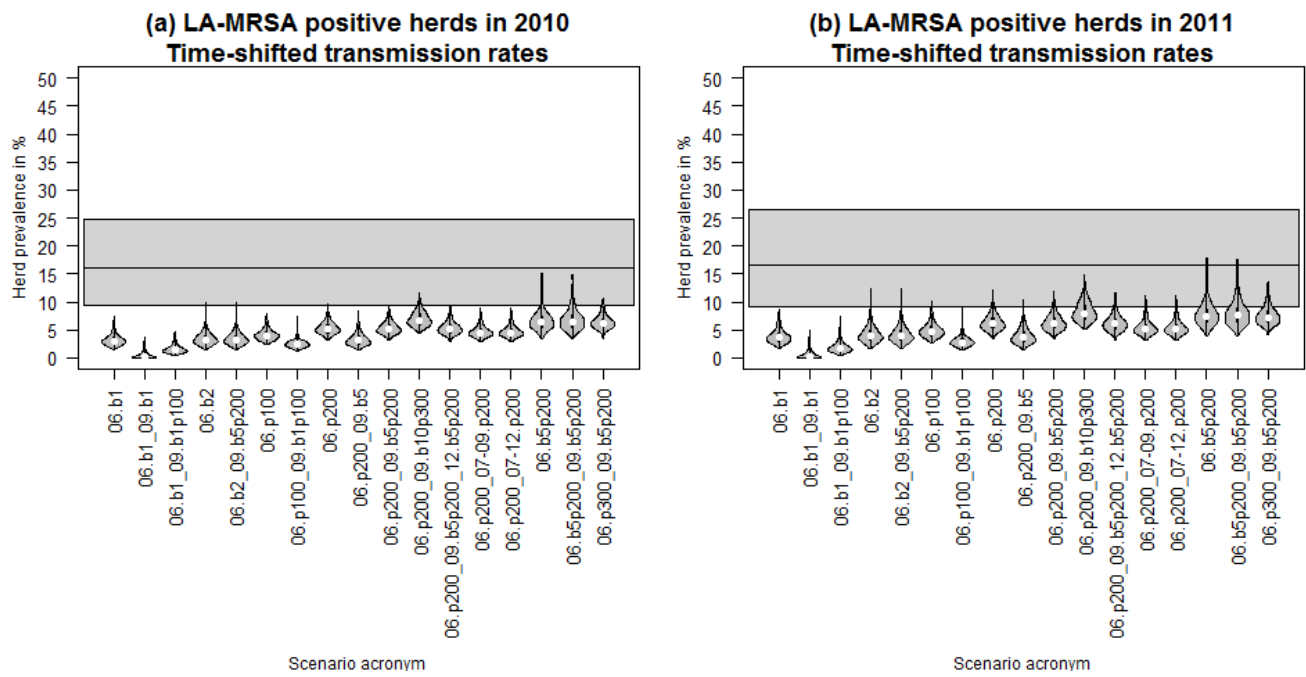
Figure S7. Violin plots summarising the herd prevalence in all herds in 2010 and 2011 based on 500 iterations of 17 LA-MRSA initialisation scenarios using time-shifted transmission rates adapted from Broens et al.[4], and modelling transmission via animal movements and via indirect contacts between herds.
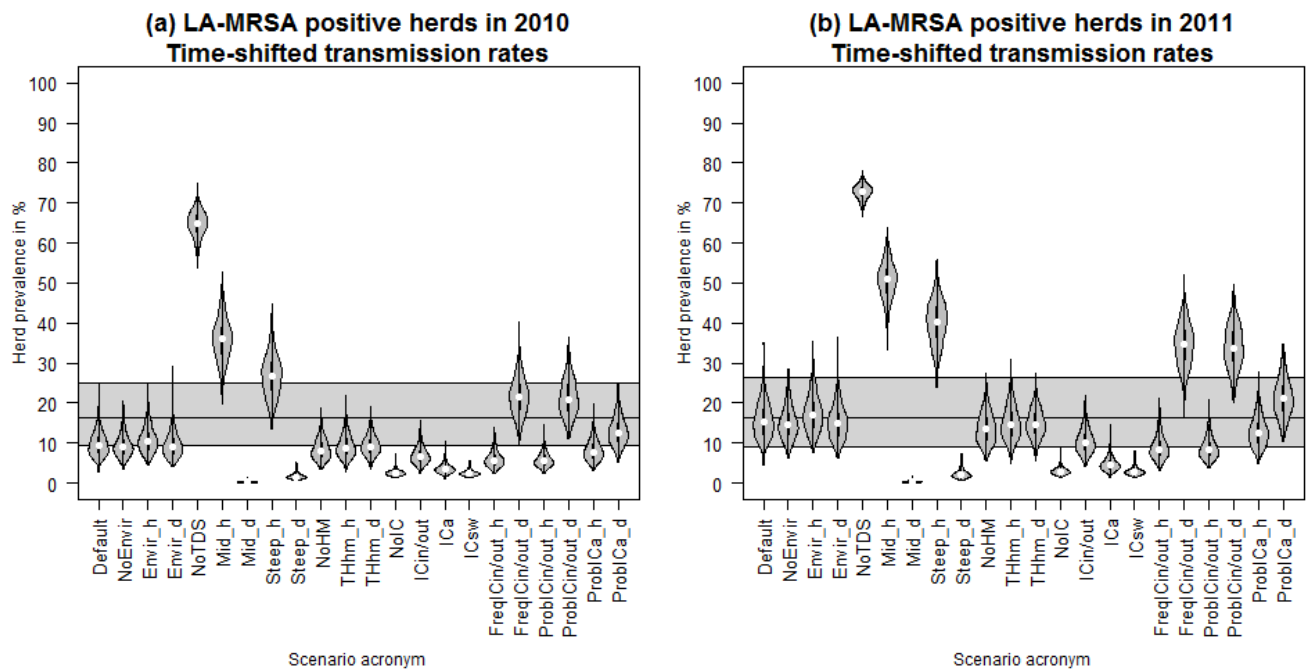
Figure S8. Violin plots summarising the herd prevalence in all herds in 2010 and 2011 based on 500 iterations of 21 LA-MRSA sensitivity analysis scenarios using time-shifted transmission rates adapted from Broen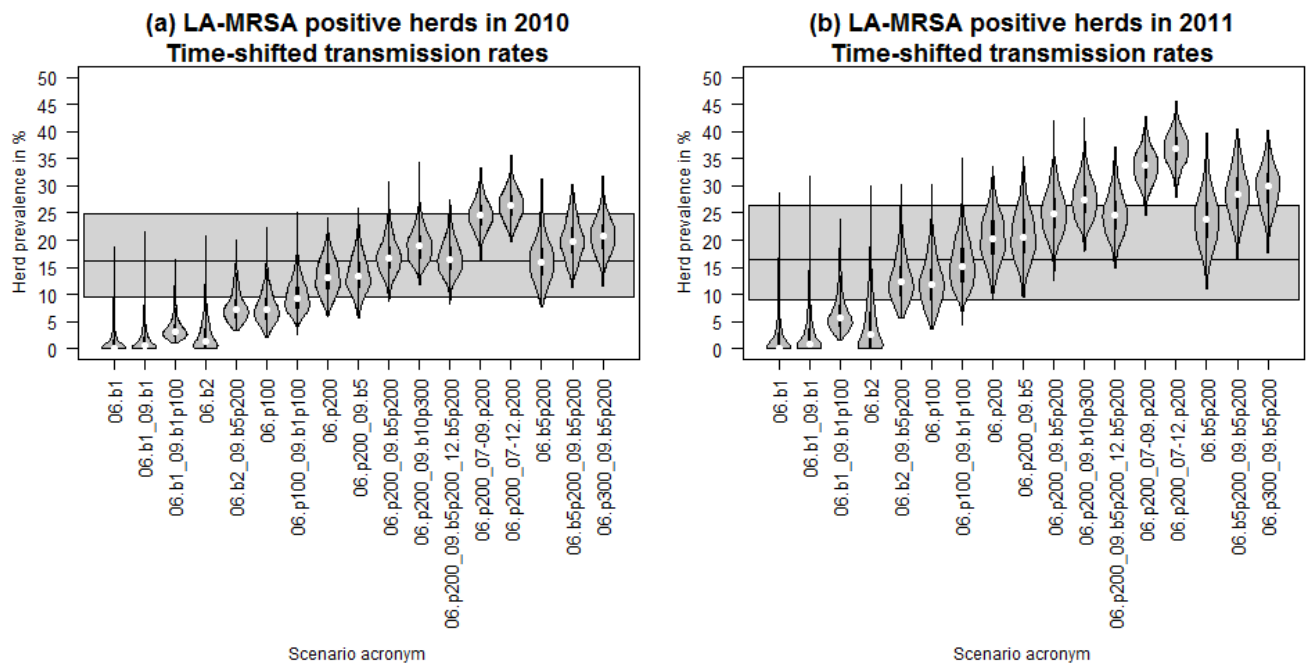s et al.[4], and modelling transmission via animal movements and via indirect contact among herds. The first violin represents the results of the default initialisation scenario 06.b1_09.b1p100.
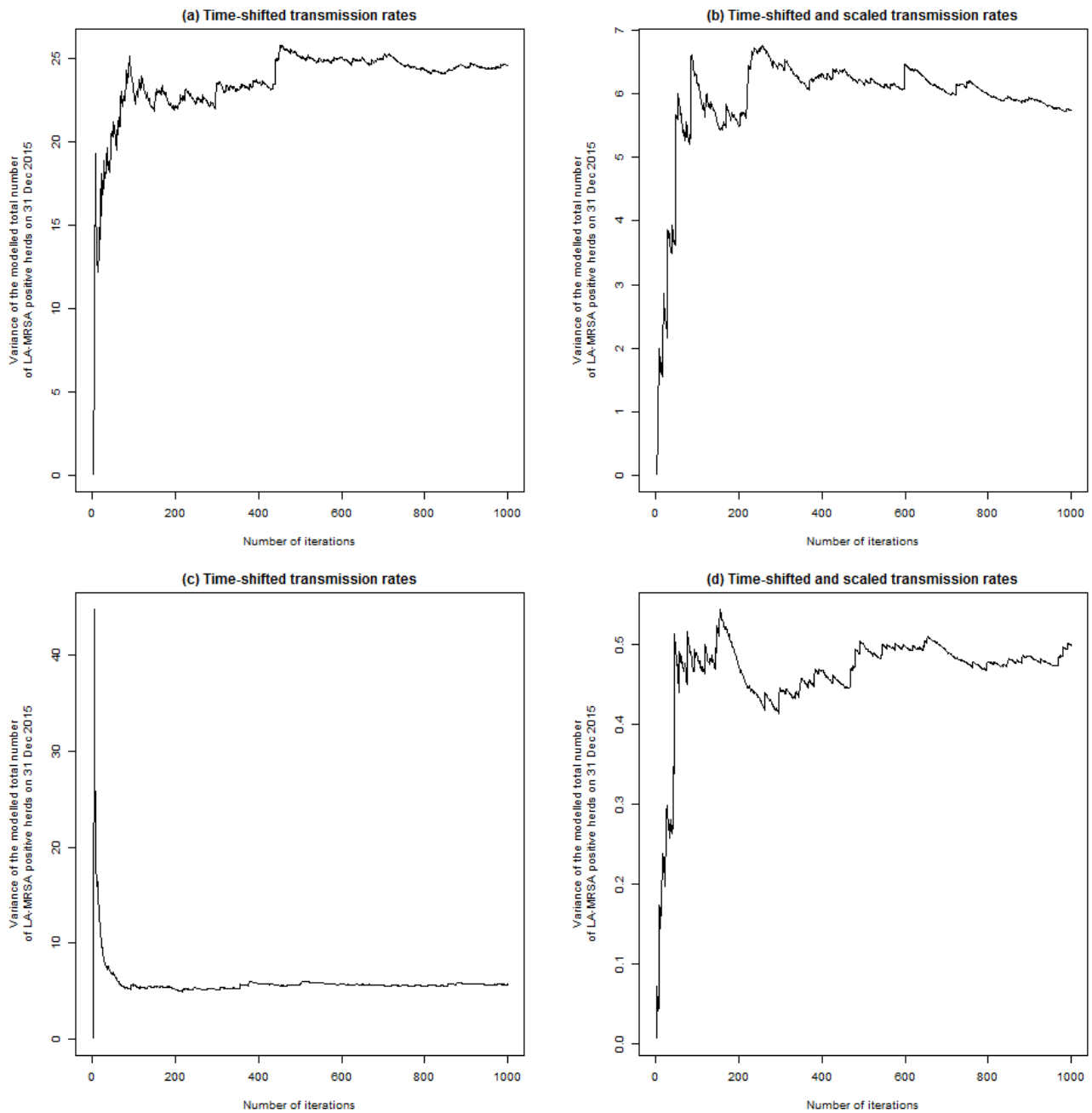
Figure S9. Variance of the total number of LA-MRSA-positive herds on 31st December 2015 against the number of simulation repetitions. Convergence is assumed when the variance stabilises. All convergence plots refer to the scenario with LA-MRSA initialisation in 100 production herds in 2006 and re-introduction for one breeding and multiplier herd and 100 production herds in 2009. (a) and (b) represent scenarios including indirect transmission routes, while (c) and (d) represent the results for transmission via pig movements only.

TABLES

Table S1. Herd categories related to the combination of sows, weaners, and finishers registered in the CHR, used to estimate the number of sows, weaners and finishers in herds that did not register any pigs.

Category	Sows registered	Weaners registered	Finishers registered
1	yes	yes	yes
2	yes	yes	no
3	yes	no	yes
4	no	yes	yes
5	yes	no	no
6	no	yes	no
7	no	no	yes

Table S2. Herd categories related to the type of production based on the registered number of sows and finishers.

Category	Type of production	Definition
A	Finisher herd	> 7.5 finishers per sow
B	Sow herd	< 5 finishers per sow
C	Integrated herd	$5 – 7.5$ finishers per sow

Table S3. Assumed age group (s = sows, w = weaners, f = finishers) of pigs moved **out** of the sending herd / **in** to the receiving herd. The letter x is used when the movement type is dependent on a defined threshold (Table S4). Below or equal to this threshold, finishers are assumed to be moved out of the sending herd and sows are assumed to be moved in to the receiving herd. Above this threshold, it is assumed that weaners/finishers were moved in to / out of the sending / receiving herd.

Herd category of sending herd	Herd category of receiving herd										
	1A	1B	1C	2A	2B	2C	3B	4A	5B	6A	7C
1A	w/f	f/s	f/s	w/f	f/s	f/s	f/s	w/f	f/s	w/f	w/w
1B	f/s	f/s	f/s	f/s	f/s	f/s	f/s	w/f	f/s	w/f	w/w
1C	x	x	x	x	x	x	f/s	w/f	f/s	w/f	w/w
2A	w/f	f/s	f/s	w/f	f/s	f/s	f/s	w/f	f/s	w/f	w/w
2B	f/s	f/s	f/s	f/s	f/s	f/s	f/s	w/f	f/s	w/f	w/w
2C	x	x	x	x	x	x	f/s	w/f	f/s	w/f	w/w
3B	w/f	w/f	w/f	w/f	w/f	w/f	w/s	w/f	w/s	w/f	w/w
4A	w/f	w/f	w/f	w/f	w/f	w/f	w/s	w/f	w/s	w/f	w/w
5B	w/f	w/f	w/f	w/f	w/f	w/f	w/s	w/f	w/s	w/f	w/w
6A	f/f	f/f	f/f	f/f	f/f	f/f	f/s	f/f	f/s	f/f	f/w
7C	w/f	w/f	w/f	w/f	w/f	w/f	w/s	w/f	w/s	w/f	w/w

Table S4. Assumed thresholds for setting the age group of movements if the movement type is given as x in Table S3. The thresholds are dependent on the registered herd type and for production, organic and hobby herds on the size of the herd. In small herds, homogeneous mixing of pigs is assumed, whereas separate compartments for the three age groups (sows, weaners, and finishers) were modelled for large herds. The number of pigs assumed to constitute a small herd was set to 200 animals.

Threshold for movement types	Production (small)	Organic (small)	Breeding and multiplier	Weaner	Hobby (small)	Production (large)	Organic (large)	Hobby (large)
Breeding sites								
Breeding and multiplier herds	3	3	50	20	3	50	50	50
Production sites								
Production (small)	3	3	3	3	3	3	3	3
Production (large)	3	3	20	20	3	20	20	20
Organic (small)	3	3	3	3	3	3	3	3
Organic (large)	3	3	20	20	3	20	20	20
Weaner herds	3	3	3	3	3	3	3	3
Hobby sites								
Hobby herds (small)	3	3	3	3	3	3	3	3
Hobby herds (large)	3	3	20	20	3	20	20	20

Table S5. Assumed values for a PERT distribution to define herd-specific cure rates and transmission rates based on the use of high-risk antibiotics, adapted by Broens et al.[4] The most likely (mode) and assumed minimum and maximum values for the PERT distributions were calculated based on values for R_0 (and their 95% CI) resulting from multivariable analysis of Dutch data, with 10.3 days taken to be the duration of the infectious period[5]. PERT distributions were defined as transformation of the Beta distribution with minimum (min), maximum (max) and most likely value (mode) and a mean $\mu = \frac{min+4\cdot mode+max}{6}$.

Use of high-risk antibiotics	Cure rate (all herds)	Within-compartment transmission rate	Low-risk between-compartment transmission rate	High-risk between-compartment transmission rate	Transmission rate in small herds
no	min = 0.056, max = 0.385, mode = 0.097	min = 0.111 max = 0.856 mode = 0.307	min = 0.00175 max = 0.00301 mode = 0.00233	min = 0.07184 max = 0.48155 mode = 0.18301	min = 0.111 max = 0.856 mode = 0.307
yes		min = 0.211 max = 2.924 mode = 0.784	min = 0.00330 max = 0.01029 mode = 0.00583	min = 0.13689 max = 1.64515 mode = 0.46796	min = 0.211 max = 2.924 mode = 0.784

Table S6. Distance probabilities of indirect contact among herds for the different types of contact and distance categories.

Distance category (up to … km)	Contact from indoor herd	Contact from outdoor herd	Contact related to abattoir movements
1	0.12	0.12	0.0054
3	0.24	0.24	0.0224
10	0.30	0.29	0.1898
15	0.083	0.089	0.1503
20	0.083	0.089	0.1252
30	0.054	0.050	0.1747
40	0.01714	0.01714	0.1347
50	0.01714	0.01714	0.0823
60	0.01714	0.01714	0.0454
70	0.01714	0.01714	0.0274
80	0.01714	0.01714	0.0141
90	0.01714	0.01714	0.0099
100	0.01714	0.01714	0.0108
110	0	0	0.0041
120	0	0	0.0025
130	0	0	0.00018
140	0	0	0.00006
150	0	0	0.00006
160	0	0	0.00006
170	0	0	0.00006
180	0	0	0.00006
190	0	0	0.00006
200	0	0	0.00006
210	0	0	0.00006
220	0	0	0.00006
230	0	0	0.00006
240	0	0	0.00006
250	0	0	0.00006
350	0	0	0.00006
1,000	0	0	0.00006

Table S7. LA-MRSA initialisation scenarios tested using the developed simulation model.

Acronym	First introduction of LA-MRSA in the simulation model	Initialisation of LA-MRSA-positive herds at later points in time
06.b1		none
06.b1_09.b1	**2006:** - 1 breeding and multiplier herd	**2009:** - 1 breeding and multiplier herd
06.b1_09.b1p100		**2009:** - 1 breeding and multiplier herd - 100 production herds
06.b2		none
06.b2_09.b5p200	**2006:** - 2 breeding and multiplier herds	**2009:** - 5 breeding and multiplier herds - 200 production herds
06.p100		none
06.p100_09.b1p100	**2006:** - 1% of production herds (100 herds)	**2009:** - 1 breeding and multiplier herd - 100 production herds
06.p200		none
06.p200_09.b5		**2009:** - 5 breeding and multiplier herds
06.p200_09.b5p200		**2009:** - 5 breeding and multiplier herds - 200 production herds
06.p200_09.b10p300	**2006:** - 2% of production herds (200 herds)	**2009:** - 10 breeding and multiplier herds - 300 of production herds
06.p200_09.b5p200_ 12.b5p200		**2009:** - 5 breeding and multiplier herds - 200 production herds **2012:** - 5 breeding and multiplier herds - 200 production herds
06.p200_07-09.p200		**2007-2009:** - 200 production herds each year
06.p200_07-12.p200		**2007-2012:** - 200 production herds each year
06.b5p200	**2006:** - 2% of production herds (200 herds)	none
06.b5p200/09.b5p200	- 2% of breeding and multiplier herds (5 herds)	**2009:** - 5 breeding and multiplier herds - 200 production herds
06.p300/09.b5p200	**2006:** - 3% of production herds (300 herds)	**2009:** - 5 breeding and multiplier herds - 200 production herds

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