Sensitivity analysis to identify key parameters influencing infection dynamics in a pig batch

Amandine Lurette, Suzanne Touzeau, Matieyendou Lamboni, Hervé Monod

► To cite this version:

Amandine Lurette, Suzanne Touzeau, Matieyendou Lamboni, Hervé Monod. Sensitivity analysis to identify key parameters influencing infection dynamics in a pig batch. *Journal of Theoretical Biology*, 2009, 258 (1), pp.43-52. 10.1016/j.jtbi.2009.01.026 . hal-00554569

HAL Id: hal-00554569

<https://hal.science/hal-00554569>

Submitted on 11 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Author's Accepted Manuscript

Sensitivity analysis to identify key parameters influencing *Salmonella* infection dynamics in a pig batch

Amandine Lurette, Suzanne Touzeau, Matieyendou Lamboni, Hervé Monod

PII: S0022-5193(09)00030-7
DOI: doi:10.1016/j.jtbi.2009.01.026
Reference: YJTBI5441

www.elsevier.com/locate/jtbi

To appear in: *Journal of Theoretical Biology*

Received date: 28 May 2008
Revised date: 21 January 2009
Accepted date: 21 January 2009

Cite this article as: Amandine Lurette, Suzanne Touzeau, Matieyendou Lamboni and Hervé Monod, Sensitivity analysis to identify key parameters influencing *Salmonella* infection dynamics in a pig batch, *Journal of Theoretical Biology* (2009), doi:10.1016/j.jtbi.2009.01.026

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Sensitivity analysis to identify key parameters influencing *Salmonella* infection dynamics in a pig batch

Amandine Lurette^{a,b,*} Suzanne Touzeau^c

Matieyendou Lamboni^c Hervé Monod^c

^aINRA, UMR1300 Bio-agression, Épidémiologie et Analyse de Risque, F-44300

Nantes, France

^bENVN, UMR1300 Bio-agression, Épidémiologie et Analyse de Risque, F-44300

Nantes, France

^cINRA, UR341 Mathématiques et Informatique Appliquées, F-78350

Jouy-en-Josas, France

Abstract

In the context of managed herds, epidemiological models usually take into account relatively complex interactions involving a high number of parameters. Some parameters may be uncertain and/or highly variable, especially epidemiological parameters. Their impact on the model outputs then must then be assessed by a sensitivity analysis, allowing to identify key parameters. The prevalence over time is an output of particular interest in epidemiological models, so sensitivity analysis methods adapted to such dynamic output are needed.

In this paper, such a sensitivity analysis method, based on a principal component analysis and on analysis of variance, is presented. It allows to compute a

generalised sensitivity index for each parameter of a model representing *Salmonella* spread within a pig batch. The model is a stochastic discrete-time model describing the batch dynamics and movements between rearing rooms, from birth to slaughterhouse delivery. Four health states were introduced: *Salmonella*-free, seronegative shedder, seropositive shedder and seropositive carrier. The indirect transmission was modelled via an infection probability function depending on the quantity of *Salmonella* in the rearing room.

Simulations were run according to a fractional factorial design enabling the estimation of main effects and two-factor interactions. For each of the 18 epidemiological parameters, four values were chosen, leading to 4096 scenarios. For each scenario, 15 replications were performed, leading to 61 440 simulations. The sensitivity analysis was then conducted on the seroprevalence output.

The parameters governing the infection probability function and residual room contaminations were identified as key parameters. To control the *Salmonella* seroprevalence, efficient measures should therefore aim at these parameters. Moreover, the shedding rate and maternal protective factor also had a major impact. Therefore, further investigation on the protective effect of maternal or post-infection antibodies would be needed.

Key words: epidemiological model, parameter uncertainty and variability, dynamic output, seroprevalence, analysis of variance

* Corresponding author. Tel.: +33(0)240687821; fax: +33(0)240687768.

Email addresses: Amandine.Lurette@vet-nantes.fr (Amandine Lurette),
Suzanne.Touzeau@jouy.inra.fr (Suzanne Touzeau),
Matieyendou.Lamboni@jouy.inra.fr (Matieyendou Lamboni),
Herve.Monod@jouy.inra.fr (Hervé Monod).

1 **1 Introduction**

2 Epidemiological models are useful tools for representing infection processes.
 3 They are often used to predict the spread of a pathogen in a population or to
 4 assess the efficacy of control measures on that spread (Diekmann and Heester-
 5 beek, 2000). In managed systems such as pig herds, they usually couple the
 6 population dynamics and the pathogen transmission, to take into account the
 7 relatively complex interactions between demography, management and infec-
 8 tion. In general, parameters governing the herd population dynamics are well
 9 known, even though they may exhibit some stochasticity due the variabil-
 10 ity among individuals in the batch. Their values and range of variation can
 11 be assessed from various data sources (ITP, 2000, 2006). In contrast, host–
 12 pathogen interactions are not so well known. This lack of knowledge induces
 13 uncertainty on the parameters involved in the herd infection processes. The
 14 impact of these uncertain and variable parameters on the pathogen spread can
 15 generally be best assessed by a sensitivity analysis, as analytical tractability in
 16 such complex models is not ensured. A sensitivity analysis describes the effect
 17 of parameter variations on model outputs. It identifies key parameters, i.e.
 18 parameters that influence the outputs most, which is useful for modelling and
 19 control purposes: on the one hand, improving knowledge on these parameters
 20 increases the model accuracy; on the other hand, control measures acting on
 21 these parameters will have a greater impact on the outputs.

22 The prevalence of seropositive animals over time (seroprevalence trajectory) is
 23 an output of particular interest in epidemiological models, as control measures
 24 often aim at reducing the prevalence and may not be applied uniformly over
 25 time. Most sensitivity analysis methods are adapted to scalar outputs (Saltelli

et al., 2000) and cannot be applied to such dynamic outputs. However, some methods have been developed to analyse time series outputs (Campbell et al., 2006). They use classical statistical tools on variables that summarise the trajectory variability. The method developed by Lamboni et al. (2008) is based on a principal component analysis applied to the trajectories. It maximises the information that is retained from the output variability. It has already been used to analyse various agronomic models and can easily be applied to an epidemiological model.

The control of *Salmonella* prevalence in pig herds is a major step to reduce the pork food chain contamination. Infected pigs are asymptomatic carriers that cannot be directly detected by observation. Serological and bacteriological detection methods do exist, but they cannot be systematically applied to all pigs sent to the slaughterhouse, for practical and economical reasons. Moreover, *Salmonella* are ubiquitous bacteria that survive well in the environment (Murray, 2002). Hence, eliminating the bacteria in a contaminated herd is not a very realistic goal. Control measures should rather aim at reducing the prevalence level. To achieve this goal, the parameters that influence the *Salmonella* spread and prevalence most need to be identified. A modelling approach coupled with a sensitivity analysis can be applied to identify these key parameters.

A simulation model representing the *Salmonella* spread within a farrow-to-finish pig herd implementing batch-farrowing management was developed by Lurette et al. (2008a). This model details both the sow and pig dynamics (Lurette et al., 2008b) and the *Salmonella* infection characteristics. In such a herd, sows are distributed in groups of equal size called batches and their reproductive cycles are synchronised. At regular intervals (usually three weeks),

52 a batch of sows is inseminated and their weaned pigs are managed together
 53 as a batch until their slaughterhouse delivery. Each batch of pigs is usually
 54 housed in a separate room, which is decontaminated between two batches.
 55 Batches of pigs may interact, mainly through batch mixing at the end of the
 56 finishing period. However, even if it occurs under normal pig growth conditions
 57 (i.e. adequate feed and no diseases affecting pig growth), it only concerns a
 58 low number of pigs (Lurette et al., 2008b). *Salmonella* transmission is mostly
 59 due to indirect contacts among animals via their rearing room. Infected pigs
 60 shed the bacteria intermittently (Kranker et al., 2003); it is then transmitted
 61 to susceptible pigs by the oro-fecal route. Due to the limited contacts be-
 62 tween batches, *Salmonella* transmission is stronger at the within-batch level.
 63 So we chose to focus in this study on a single batch of pigs, from birth to
 64 slaughterhouse delivery.

65 The aim of this paper is therefore to identify the parameters that contribute
 66 most to the variability of the *Salmonella* seroprevalence in a batch of pigs,
 67 using a sensitivity analysis based on a principal components analysis. We will
 68 first describe the pig batch epidemiological model, followed by the sensitiv-
 69 ity analysis. Then we will present and discuss the results obtained with this
 70 method.

71 **2 Model description**

72 We developed a stochastic model to represent the *Salmonella* transmission
 73 within a batch of pigs, from their birth to their slaughterhouse delivery. The
 74 model has a discrete one-week time step, which is suited both to the repre-
 75 sentation of the farmer task planning and to the epidemiological time scale.

As the carriage of *Salmonella* in pigs is generally subclinic, the infection does not affect the pig demography. Hence, the pig batch model and the epidemiological model are first presented separately. They are then coupled by distributing the animals of the batch into the infection states. Finally, the parameters and initial conditions are described.

2.1 Pig batch model

Pigs in a batch are born simultaneously from a batch of sows at time $t = 0$. The litter size L is fixed. Pigs pass through three growing stages during their lifetime, denoted by X , corresponding to the occupancy of three rooms: (i) the suckling stage, a 4-week period from birth to weaning ($X = S, D_S = 4$), takes place with the sows in the farrowing room; (ii) the 8-week post-weaning period ($X = PW, D_{PW} = 8$) takes place in the post-weaning room; (iii) the finishing stage takes place in the finishing room and lasts up to 14 weeks ($X = F, D_F = 14$). The number of pigs in the batch at time $t \in \{0, 1, \dots, 25\}$ is given by $P(t)$. At each time step, the number of pigs decreases because of mortality and, at the end of the finishing stage, because of slaughterhouse delivery.

The mortality rate μ_X is assumed to be constant in each growing stage X and differs between stages.

At each delivery time (usually every two weeks), producers send groups of finishers with a given slaughtering weight. As out-of-range pigs are sold at a lower price, they are kept in the herd until they reach the slaughtering weight or until their room needs to be emptied. Because of pig growth variability,

99 a batch leaves the herd at different times. To represent the proportion of
 100 the batch that has reached the slaughtering weight over time, a lognormal
 101 distribution is used (with parameters a_α , mean age at slaughtering weight
 102 and a_σ , its standard deviation). This distribution represents the variability
 103 among individual animals reported by technical data (ITP, 2006). Let φ be
 104 the associated probability density function and Δt the time interval between
 105 two deliveries (usually $\Delta t = 2$ weeks), assuming they start at $t = 1$. At each
 106 delivery time $t = k\Delta t (k \in \mathbb{N})$, the proportion of pigs sent to the slaughterhouse
 107 to the initial number of pigs $P(0) = L$, corresponding to pigs that have reached
 108 the required weight since the last delivery, is given by: $\int_{t-\Delta t}^t \varphi(s)ds$. Moreover,
 109 delivery of finishing pigs only occurs between 22 and 25 weeks of age.

All remaining pigs are delivered at the last delivery time (25 weeks of age)
 $t_m = \max_{k \in \mathbb{N}} \{k\Delta t : k\Delta t \leq 25\}$ because the room needs to be emptied. The
 proportion of pigs delivered to the slaughterhouse at time t , calculated from
 the pig population $P(t-1)$, is given by:

$$d(t) = \begin{cases} 0 & \text{if } t < 22 \text{ or if } t \neq k\Delta t, k \in \mathbb{N} \text{ (not a delivery time),} \\ \frac{\int_{t-\Delta t}^t \varphi(s)ds}{1 - \int_0^{t-\Delta t} \varphi(s)ds} & \text{if } 22 \leq t = k\Delta t < t_m, k \in \mathbb{N} \text{ (delivery time),} \\ 1 & \text{if } t = t_m \text{ (room is emptied).} \end{cases}$$

The number of pigs at time t is hence obtained from the following equations:

$$P(t) = \begin{cases} L & \text{if } t = 0 \text{ (birth),} \\ (1 - \mu_S)P(t-1) & \text{if } 0 < t \leq 4 \text{ (suckling period),} \\ (1 - \mu_{PW})P(t-1) & \text{if } 4 < t \leq 12 \text{ (post-weaning period),} \\ (1 - \mu_F)(1 - d(t))P(t-1) & \text{if } 12 < t \leq 25, \text{ (finishing period).} \end{cases}$$

At each time step, mortality is assumed to take place first, so slaughterhouse deliveries are given by: $D(t) = (1 - \mu_F)d(t)P(t - 1)$.

2.2 *Salmonella* epidemiological model

The epidemiological model was developed by Lurette et al. (2008a). Infected animals shed *Salmonella* in their feces and, hence, contaminate their local environment, i.e. their rearing room. The model represents the indirect fecal-oral transmission via encounters with the free-living *Salmonella* in contaminated feces on the room floor, the pen separations and the pig bodies. The free-living *Salmonella* in the room are modelled as a quantity of *Salmonella* infectious units denoted $Q(t)$ at time t .

Four mutually exclusive health states (Y) were identified and selected from the literature and from expert opinion. A susceptible pig free of *Salmonella* ($Y = F$) becomes a shedding pig ($Y = Sh$) after ingesting the bacteria. After a seroconversion delay, it is called a seropositive shedding pig ($Y = Shs$). The shedding is intermittent. When it stops, the pig becomes a seropositive carrier pig ($Y = Cs$). The shedding can be reactivated, especially under stressful conditions. The number of pigs in each state Y at time t is given by $P(t, Y)$, where $P(t) = \sum_Y P(t, Y)$ represents the total population size. All transitions are stochastic: the number of pigs which undergo a transition between two states is drawn in a binomial law; the first parameter is the number of pigs in the initial state, the second is the individual transition probability.

Assuming homogeneous mixing, each pig is exposed to $Q(t)/P(t)$ *Salmonella* infectious units. Ingestion is considered to have a logarithmic effect, so the

effective quantity of *Salmonella* infectious units for each susceptible pig is: $q(t) = \log(1 + Q(t)/P(t))$. The probability of infection for a susceptible pig is an increasing function of q with two thresholds:

$$f(q) = \begin{cases} 0 & \text{if } q = 0, \\ b_1 & \text{if } 0 < q \leq q_1, \\ b_1 + \frac{b_2 - b_1}{q_2 - q_1}(q - q_1) & \text{if } q_1 < q \leq q_2, \\ b_2 & \text{if } q > q_2. \end{cases}$$

131 This semi-log sigmoid-like function is very similar to the classical dose-response
132 relationships, very commonly used in pharmacokinetics. The number of sus-
133 ceptible pigs that become infected is calculated at each time step from the
134 following binomial law: $\text{Bin}(P(t, F), f(q(t)))$.

135 The probability that a shedder pig becomes seropositive derives from the sero-
136 conversion delay λ_1 and is equal to: $1 - \exp(-1/\lambda_1)$. Similarly, the probability
137 that a seropositive shedding pig stops shedding *Salmonella* depends on the
138 shedding period duration $\lambda_2(t)$. The shedding duration follows a lognormal
139 distribution (with parameters $\lambda_{2\alpha}$ and $\lambda_{2\sigma}$, mean and standard deviation) and
140 is recalculated at each time step t to account for environmental variability.
141 The probability that a seropositive carrier pig starts shedding again is β . As
142 previously, the pigs which undergo a state change at each time step are drawn
143 from binomial laws using these three individual transition probabilities.

Hence, we obtain the following system of equations, that describes the popu-

lation evolution in the four health states:

$$\left\{ \begin{array}{l} P(t, F) = P(t-1, F) - \text{Bin}(P(t-1, F), f(q(t-1))), \\ P(t, Sh) = P(t-1, Sh) + \text{Bin}(P(t-1, F), f(q(t-1))) \\ \quad - \text{Bin}\left(P(t-1, Sh), 1 - \exp\left(\frac{-1}{\lambda_1}\right)\right), \\ P(t, Shs) = P(t-1, Shs) + \text{Bin}\left(P(t-1, Sh), 1 - \exp\left(\frac{-1}{\lambda_1}\right)\right) \\ \quad - \text{Bin}\left(P(t-1, Shs), 1 - \exp\left(\frac{-1}{\lambda_2(t-1)}\right)\right) + \\ \quad - \text{Bin}(P(t-1, Cs), \beta), \\ P(t, Cs) = P(t-1, Cs) + \text{Bin}\left(P(t-1, Shs), 1 - \exp\left(\frac{-1}{\lambda_2(t-1)}\right)\right) \\ \quad - \text{Bin}(P(t-1, Cs), \beta). \end{array} \right.$$

Finally, the *Salmonella* infectious units are subject to a degradation process at each time step with a fixed rate ν . They are incremented by the infectious units shed by seropositive and seronegative shedder pigs. The resulting dynamics of the *Salmonella* infectious units is the following:

$$Q(t) = (1 - \nu)Q(t-1) + q_e P(t, Sh) + q_e \pi_+ P(t, Shs).$$

144 where q_e is the shedding rate, i.e. the quantity of infectious units shed by a
145 seronegative shedder pig, and π_+ is the shedding ratio between a seropositive
146 and a seronegative shedder pig.

147 2.3 Coupling the models

148 The pig batch model and the epidemiological models are coupled as follows.
149 At each time step, mortality and slaughterhouse delivery are first applied
150 uniformly over the four epidemiological states in the batch. The number of

151 pigs in epidemiological state Y delivered to the slaughterhouse at time t is
 152 therefore : $D(t, Y) = (1 - \mu_F)d(t)P(t - 1, Y)$; $D(t) = \sum_Y D(t, Y)$ is the total
 153 number of pigs delivered. Then the epidemiological transitions are drawn and
 154 finally the number of *Salmonella* infectious units is updated.

155 Some epidemiological transitions and parameters depend on the pig growing
 156 stage. The susceptibility of piglets to *Salmonella* infection is considered lower
 157 during the suckling period than during the other growing stages, due to a ma-
 158 ternal protective immunity. So, during the suckling period S , the probability
 159 of infection $f^S(q) = \varepsilon f(q)$, ε being a maternal protective factor ($\varepsilon < 1$); during
 160 all other stages $X \in \{PW, F\}$, $f^X(q) = f(q)$. The shedding rate also depends
 161 on the growing stage. Let q_e be the shedding rate of a finisher pig and π_X be
 162 the shedding ratio between a pig in stage $X = S, PW$ and a finishing pig; the
 163 shedding rate in stage X is $q_e \pi_X$. Finally, piglets undergo a supplementary
 164 stress at weaning, which increases the probability β that a carrier pig starts
 165 shedding again. Denoting by γ the value of this probability at weaning time
 166 $t = 5$, at any other time, it is given by $\beta = \pi_\beta \gamma$, with $\pi_\beta < 1$.

Between two batches, rooms are cleaned and disinfected, but residual *Salmonella*
 may remain in the room. When piglets are born, the room can also have been
 contaminated by the sows. So when the pig batch enters each rearing room,
 the number of *Salmonella* infectious units is set to a residual value denoted
 Q_X , X being the corresponding stage. The number of *Salmonella* infectious

units is then given by the following equations:

$$Q(t) = \begin{cases} Q_S & \text{if } t = 0 \\ & \text{(birth),} \\ (1 - \nu)Q(t - 1) + q_e\pi_S P(t, Sh) + q_e\pi_+\pi_S P(t, Shs) & \text{if } 0 < t \leq 4 \\ & \text{(suckling),} \\ Q_{PW} & \text{if } t = 5 \\ & \text{(weaning),} \\ (1 - \nu)Q(t - 1) + q_e\pi_{PW} P(t, Sh) + q_e\pi_+\pi_{PW} P(t, Shs) & \text{if } 5 < t \leq 12 \\ & \text{(post-weaning),} \\ Q_F & \text{if } t = 13 \\ & \text{(finishing),} \\ (1 - \nu)Q(t - 1) + q_e P(t, Sh) + q_e\pi_+ P(t, Sh) & \text{if } 13 < t \leq 25 \\ & \text{(finishing).} \end{cases}$$

167 2.4 Model parameters and initial condition

168 The demographic parameters used for the pig herd model are known from the
169 published performance data (ITP, 2000, 2006) and are detailed in Table 1.

170 The epidemiological parameters, however, are not so well known. The infor-
171 mation available is presented in Table 2.

172 At the beginning of the simulation, we assume that piglets are born *Salmonella*-
173 free. So $P(0, F) = L$ and $P(0, Y) = 0$ for $Y \neq F$. Contamination of the batch
174 is initiated by the residual *Salmonella* infectious units in the rooms Q_Y . Their

Table 1

Demographic parameters used in the batch model.

Name	Description	Value
D_S	Duration of the suckling period	4 weeks*
D_{PW}	Duration of the post-weaning period	8 weeks*
D_F	Duration of the finishing period	14 weeks*
μ_S	Mortality rate for suckling pigs	0.01 week ^{-1†}
μ_{PW}	Mortality rate for post-weaning pigs	0.005 week ^{-1†}
μ_F	Mortality rate for finishing pigs	0.002 week ^{-1†}
a_α	Mean age at slaughtering weight	25.5 weeks*
a_σ	Standard deviation —	1.5 weeks*

* from (ITP, 2000). † from (ITP, 2006).

values are given in Table 2. Slaughterhouse deliveries from the herd may occur every $\Delta t = 2$ weeks, starting at $t = 0$; so the room is emptied at $t_m = 25$.

All simulations were performed using Scilab 4.0.¹

3 Sensitivity analysis

The aim of a sensitivity analysis is to define which parameters have the greatest impact on given model outputs. We chose two outputs. The first one is the *Salmonella* seroprevalence in the batch over time, from the piglet birth until

¹ Scilab, a free scientific software for numerical computations: <http://www.scilab.org/>

Table 2

Epidemiological parameters used in the batch model.

Name	Description	Values tested
q_1	Lower infection probability threshold	1, 2, 3, 4 log(S.i.u.)
q_2	Saturation infection probability threshold	4, 4.7, 5, 6 log(S.i.u.)
b_1	Lower infection probability	10^{-7} , 10^{-6} , 10^{-4} , 10^{-2}
b_2	Saturation infection probability	0.05, 0.1, 0.3, 0.5
λ_1	Seroconversion delay	1, 2, 3, 4 weeks*
$\lambda_{2\alpha}$	Shedding period duration: mean	1, 3, 6, 10 weeks [†]
$\lambda_{2\sigma}$	Shedding period duration: standard deviation	1, 2, 3, 4 weeks
γ	Probability of shedding reactivation due to stress	0.1, 0.2, 0.4, 0.6
π_β	Ratio: shedding reactivation / γ	0.1, 0.4, 0.7, 1
ε	Maternal protective factor	0, 0.1, 0.3, 1
ν	<i>Salmonella</i> degradation rate	0, 0.3, 0.5, 0.8 week ^{-1‡}
q_e	Shedding rate for seronegative finishing pigs	10^2 , 5.10^3 , 10^5 , 5.10^6 S.i.u.(week) ⁻¹
π_S	Ratio: shedding rate for suckling pigs / q_e	0.1, 0.2, 0.4, 0.6
π_{PW}	Ratio: shedding rate for post-weaning pigs / q_e	0.1, 0.2, 0.4, 0.6
π_+	Ratio: shedding rate for seropositive pigs / q_e	0.1, 0.4, 0.7, 1
Q_S	Residual contamination: farrowing room	0, 10^2 , 10^4 , 10^6 S.i.u.
Q_{PW}	Residual contamination: post-weaning room	0, 10^2 , 10^4 , 10^6 S.i.u.
Q_F	Residual contamination: finishing room	0, 10^2 , 10^4 , 10^6 S.i.u.

S.i.u.: *Salmonella* infectious units.

* from (van Winsen et al., 2001; Fravallo et al., 2003).

[†] (Davies et al., 1998; Nielsen et al., 1995; van Winsen et al., 2001; Kranker et al., 2003; Wong et al., 2002).

[‡] (Plachá et al., 2001; Boes et al., 2005; Nicholson et al., 2005).

their slaughterhouse delivery. The seroprevalence corresponds to the proportion of seropositive shedding and carrying pigs in the batch. It is calculated at each time step by:

$$\psi(t) = \frac{\sum_{Y \in Shs, Cs} P(t, Y)}{P(t)}.$$

The second output is the mean seroprevalence at slaughterhouse delivery, calculated as follows:

$$\Omega = \frac{\sum_{t=22}^{25} \sum_{Y \in Shs, Cs} D(t, Y)}{\sum_{t=22}^{25} D(t)}$$

179 As the demographic parameters are well known, we chose to perform the
180 analysis on the epidemiological parameters given in Table 2, whose values are
181 uncertain. We used a design of experiments to define which simulations to run.
182 Then the resulting outputs were analysed.

183 3.1 Design of experiments

184 The simulation model described in the previous section has 18 epidemiological
185 parameters, also called “factors”. To study the sensitivity of the outputs to
186 these parameters, we used a factorial experimental design, with four parameter
187 values, called “levels”, per factor. As the model is stochastic, each combination
188 of levels of factors, i.e. each parameter set or “scenario”, was replicated 15
189 times. This number of replications was found to be largely sufficient to get
190 robust results. It also allowed to obtain quite precise estimates of the variances
191 between replications for each scenario.

192 A complete factorial design corresponds to 4^{18} scenarios, that is 15×4^{18} sim-
193 ulations, which is not feasible. Therefore, we used a fractional factorial design
194 (Kobilinsky, 1997; Box et al., 1978). A resolution V design is orthogonal and

it enables the estimation of main effects and two-factor interactions, assuming that the higher order interactions are negligible. A resolution V design for 18 factors can be obtained with 4096 scenarios, which corresponds to 61 440 simulations with 15 replications. The fractional factorial design we used was produced by the FACTEX procedure of the SAS 8.0/QC module.² Alternative designs could have been used, in particular response surface designs (Myers and Montgomery, 2002) or space-filling designs (Fang et al., 2006). In the present study, we gave priority to orthogonal and balanced designs.

3.2 Sensitivity analysis on the seroprevalence over time

To analyse the seroprevalences over time $\psi(t)$ obtained with the fractional factorial design described above, we used a method developed by Lamboni et al. (2008). We only give here a short description of this method. The seroprevalence outputs can be represented in a $N \times p$ table denoted T , with $N = 61\,440$ the number of simulations and $p = 23$ the number of seroprevalence output times ($t = 2, \dots, 24$). As the animals are born *Salmonella*-free at $t = 0$ and need a week for seroconversion when they become infected, $\psi(0) = \psi(1) = 0$ for each simulation; moreover, their room is emptied at $t = t_m = 25$, so $\psi(25) = 0$. Hence, these times are not included in the analysis.

A principal component analysis (PCA) with N individuals and p variables is performed on this table T . It consists in an eigenvalue decomposition of the matrix of correlations between the columns of T , $\tilde{T}'\tilde{T}$, where $\tilde{T}$ is obtained by centring and normalising each column of T . Let u_1 denote the first eigenvector

² SAS/QC 8 User's Guide, Introduction to the FACTEX procedure: <http://v8doc.sas.com/sashtml/qc/chap14/index.htm>

217 associated with the largest eigenvalue. The first component u_1 thus obtained
 218 is the linear combination of the variables that explains the maximum of vari-
 219 ability – or inertia – among the simulations. The second component is the
 220 second best combination to explain the variability, conditionally on being or-
 221 thogonal to the first component, etc. Usually, four components are enough to
 222 explain most of the variability among the simulations. In this study, only three
 223 components were needed.

224 As a result of the PCA, each simulation corresponding to a line in table T is
 225 given a “score” on each component. For the first component, it corresponds
 226 to the scalar product of u_1 and the corresponding line of the T matrix. The
 227 scores are similarly obtained for each subsequent component. Each simulation
 228 is hence described by a scalar value called score for each component.

229 An ANOVA was then performed on the simulation scores for each of the first
 230 three principal components, to compare the influence of the 18 epidemiological
 231 factors on the seroprevalence. The model included all main effects and all two-
 232 factor interactions. Sensitivity indices and total sensitivities were calculated for
 233 each component $i \in \{1, 2, 3\}$. The sensitivity index SI_w^i associated with each
 234 factorial term w (main effect or interaction) is defined as the ratio between the
 235 sum of squares associated with that term and the total sum of squares. The
 236 total sensitivity TS_f^i is given for each factor f by the sum of the sensitivity
 237 indices corresponding to that factor; it gives the contribution of the factor and
 238 its two-factor interactions (Saltelli et al., 2000).

239 These indices describe the impact of the epidemiological parameters on the
 240 seroprevalence output. To assess the impact of the model stochasticity, which
 241 represents the variability among individuals in the batch, an extra sensitivity

242 index RS^i was calculated for each component i as the ratio of the sum of
 243 squares within scenario summed over all scenarios to the total sum of squares.

244 This analysis was performed with the R software.³

245 3.3 Sensitivity analysis on the mean seroprevalence at slaughterhouse deliv- 246 ery

247 An ANOVA was also performed to compare the influence of the 18 epidemi-
 248 ological parameters on the mean seroprevalence of delivered pigs Ω . It was
 249 calculated for each scenario defined by the fractional factorial design described
 250 above.

251 4 Results

252 We tested several sets of simulations with 10 replications per scenario. The
 253 sensitivity analysis was conducted on each set. Results were stable in terms
 254 of sensitivity index values and parameter order. Therefore, the 15 replications
 255 per scenario performed for this study ensure that the results are robust.

256 4.1 Influence of factors on the seroprevalence over time

257 At each time step from birth to slaughterhouse delivery and for each sce-
 258 nario, the average seroprevalence was calculated over the 15 replications per-
 259 formed for the sensitivity analysis. The percentiles of the average seropreva-

³ The R Project for Statistical Computing: <http://www.r-project.org/>

lences across the 4096 scenarios are represented at each time step in Fig. 1. They show a global increase in seroprevalence over time, but they also exhibit a high variability. In 10% of the scenarios, no infection is found. In 10% of the scenarios, the batch is almost entirely infected at the slaughterhouse delivery. Box-plots at each time step and for each percentile are also drawn in Fig. 1. They show the seroprevalence variability between replicates due to model stochasticity. Each box-plot is based on the 3×15 seroprevalences associated with the 3 scenarios closest to a given percentile at a given time step. As stated previously, no infection is found for the 10th percentile. For the other percentiles, the variability due to model stochasticity appears to be quite lower than the variability due to the epidemiological factors, despite a few large outliers.

The inertia obtained for the first three principal components are 78.0%, 15.9% and 4.2%; the next component represented less than 1% of the total variability (Fig. 2). Results are described component by component, starting with the first component.

The sensitivity indices RS^i describing the impact of the model stochasticity for the first three components i are quite low:

$$RS^1 = 1.8\%, \quad RS^2 = 3.6\%, \quad RS^3 = 7.9\%.$$

The first principal component represents 78.0% of the total inertia. According to Fig. 3-A all time steps have comparable weights for this component, though somehow lower for the first time steps. So it corresponds more or less to an average seroprevalence effect. The most sensitive factors, which contributed to more than 20% of the variability for this component, are: q_1 , the saturation

Fig. 1. Percentiles of the average seroprevalence at each time step (lines) and seroprevalence variability between replicates (boxplots). At each time step, percentiles are calculated across the 4096 seroprevalences averaged over the 15 replications per scenario: mean (plain line), 10th percentile (dotted line, superposed with the abscissa axis), 50th percentile (dashed line), and 90th percentile (dash-dotted line). Each boxplot is calculated over all replications of the 3 scenarios that are most closely associated with a given percentile. In the boxplots: outliers for the 10th percentile (.,none), 50th percentile (*), and 90th percentile (o). Parameters are given in Tables 1 and 2.

281 infection probability threshold, b_2 , the saturation infection probability. The
 282 residual contamination in the farrowing room, Q_S and in the post-weaning
 283 room Q_{PW} explain more than 10% of the inertia; q_e , b_1 and ε , more than 5%
 284 each (Fig. 3-B). The cumulated sensitivity indices of the eight major main
 285 effects and two-factor interactions are higher than 70% (Fig. 3-C). For all
 286 epidemiological parameters, the contributions of their main effect and their

Fig. 2. Contribution to the total inertia of the seven first principal components: component contribution (black) and total inertia explained by the seven first components (grey). PC_X is the X^{th} component.

two-factor interactions are comparable. However, only one interaction appears in the eight most sensitive terms: $b_2:q_1$.

The second component only corresponds to 15.9% of the total inertia. On this component, the higher scores are attributed to simulations which exhibit higher contrasts between the beginning and the end of the simulation (Fig. 4-A). The parameters explaining more variability differ from the first component (Fig. 4-B). Two parameters contribute to ca. 40% of the inertia: ε , the maternal protective factor, and Q_S , the residual contamination of the farrowing room. Both are involved in the early infection of piglets. b_2 and q_1 , which govern the infection function, explain more than 10% of the inertia each. For all parameters, the contribution of the two-factor interactions is higher than the main effect contribution. The cumulated sensitivity indices of the eight major main factors and interactions is equal to 53 %; four interactions involving Q_S ,

Fig. 3. Sensitivity analysis on the seroprevalence over time: results of the ANOVA performed on the simulation scores of the first component (inertia: 78.0%). – **A** Loadings defining the component for each time variable (in abscissa). **B** Total sensitivities TS_f^1 for the 18 epidemiological parameters f ranked in descending order; sensitivities are split in main effect (black) and two-factor interactions (grey). **C** Sensitivity indices SI_w^1 of the eight main factorial terms w (main effects or interactions) in descending order; individual (black) and cumulated (grey) contributions.

ε , q_1 or b_2 are included (Fig. 4-C).

The third component contribution is very low: 4.2%. It highlights the trajectories in which the seroprevalence during the intermediate time steps was very different from the beginning and end of the simulation (Fig. 5-A). As for

Fig. 4. Sensitivity analysis on the seroprevalence over time: results of the ANOVA performed on the simulation scores of the second component (inertia: 15.9%). – **A** Loadings defining the component for each time variable (in abscissa). **B** Total sensitivities TS_f^2 for the 18 epidemiological parameters f ranked in descending order; sensitivities are split in main effect (black) and two-factor interactions (grey). **C** Sensitivity indices SI_w^2 of the eight main factorial terms w (main effects or interactions) in descending order; individual (black) and cumulated (grey) contributions.

the second component, interactions contribute more to the inertia than major effects; they are comparable for the most influential parameter Q_F . The Q_F total sensitivity is higher than 20% (Fig. 5-B). Parameters Q_F , Q_{PW} , q_1 and various two-factor interactions involving these three parameters as well as b_2 ,

Fig. 5. Sensitivity analysis on the seroprevalence over time: results of the ANOVA performed on the simulation scores of the third component (inertia: 4.2%). – **A** Loadings defining the component for each time variable (in abscissa). **B** Total sensitivities TS_f^3 for the 18 epidemiological parameters f ranked in descending order; sensitivities are split in main effect (black) and two-factor interactions (grey). **C** Sensitivity indices SI_w^3 of the eight main factorial terms w (main effects or interactions) in descending order; individual (black) and cumulated (grey) contributions.

308 q_1 and q_e explained more than 47% of the variability (Fig. 5-C).

309 4.2 Influence of factors on the seroprevalence at slaughterhouse delivery

310 The terms which had a higher than 5% effect on the seroprevalence at slaugh-
 311 terhouse delivery are, in descending order: q_1 (16.1%), b_2 (11.2%), b_1 (5.3%),
 312 three of the four parameters governing the infection probability function, and
 313 the residual room contaminations Q_S (5.3%) and Q_{PW} (5.2%). The statistical
 314 model explains only 62% of the variability of the output.

315 5 Discussion

316 The model developed in this study is a simplified version of a herd model, ob-
 317 tained by considering an independent pig batch that only interacts with the
 318 herd through residual room contaminations. It cannot take into account batch
 319 mixing. It corresponds to an all-in/all-out management system, which is the
 320 recommended and a frequent system under normal pig growth conditions, i.e.
 321 when pig growth duration is not affected by any disease or other external fac-
 322 tor. This batch model has allowed us to assess the *Salmonella* seroprevalence
 323 in a batch of pigs, from birth to slaughterhouse delivery and in the groups
 324 delivered to the slaughterhouse.

325 Sensitivity analyses were conducted to identify the parameters which had the
 326 greatest influence on the variability of these model outputs. The first anal-
 327 ysis, performed on the seroprevalence over time, was more informative than
 328 the analysis performed on the seroprevalence at slaughter age. Other sensitiv-
 329 ity analysis methods were used in previously published model describing the
 330 *Salmonella* spread within pig herds. Some graphically assessed the effect of
 331 infection probability variations on the seroprevalence of pigs at slaughter age

(Hill et al., 2008). Others, in a meta-modelling approach, used a generalised linear mixed model to estimate the influence of epidemiological parameters on scalar outputs: the percentage of contaminated carcasses at the end of the slaughter process and their serological status (van der Gaag et al., 2004). In this study, we analysed the seroprevalence trajectories, estimating that the time variable would provide valuable information.

Sensitivity analyses rank sources of uncertainty and variability, according to their influence on the model outputs. These sources need not be restricted to model parameters. Here, they also included the variability among individuals in a batch, because it induces notable variations on the batch seroprevalence. Results eventually showed that this individual variability had a negligible impact on the *Salmonella* seroprevalence variability compared to the epidemiological parameters. The range of values tested for these parameters was chosen especially broad to account for the uncertainty on these parameters and to emphasise their impact on the output variability. However, this result was not obvious. It highlights in the present case an urgent need for more accurate estimates of the epidemiological parameter values.

Several key epidemiological parameters were identified and can be grouped in three categories. The first category consists of q_1 , b_2 and b_1 , which govern the infection probability function. These parameters are the most influential ones, as together they explained more than 40% of the first component inertia (two-factor interaction not included), the first component representing more than 78% of the total inertia. In the second category, parameters related to the room contamination, Q_{PW} , Q_S , and Q_F are found. Their contribution to the seroprevalence variability appeared in the top eight of the first three components. The third and last category contains the *Salmonella* shedding

358 rate for a seronegative finishing pig q_e and the maternal protective factor ε .
 359 Their contribution was lower, but their impact cannot be neglected.

360 **Infection probability function** The infection probability function seems
 361 to have a major influence on the *Salmonella* infection dynamics. However, its
 362 four parameters do not have the same impact on the seroprevalence variability.
 363 Actually, q_1 and b_2 , corresponding respectively to the lower threshold and the
 364 saturation infection probability, are the most sensitive parameters. This is
 365 consistent with a rapid growth of the quantity of *Salmonella* infectious units
 366 in a room. As the batch size does not vary much with time, this quantity $Q(t)$
 367 increases with the effective quantity ingested by a pig $q(t)$. In low contaminated
 368 rooms ($q(t) \leq q_1$), the transmission remains low. Once the room contamination
 369 exceeds a given threshold ($q(t) > q_1$), the transmission increases rapidly and
 370 the infection probability reaches its saturation value ($f(q(t)) = b_2$). Further
 371 investigation would be needed to define this function more accurately. The
 372 major influence of the infection probability had already been shown by van der
 373 Gaag et al. (2004): in this study, the rate of infection within a group of pigs
 374 was the most influential factor on the percentage of contaminated carcasses
 375 at the end of the slaughter process. Control measures which would reduce the
 376 probability for a susceptible pig to become infected would be very efficient.
 377 They would involve: (i) a reduction of the contact rate between susceptible
 378 pigs and all sources of infection, by implementing a strict all-in/all-out housing
 379 system for instance; and/or (ii) a reduction of the probability of infection given
 380 such a contact, by acid feed (Farzan et al., 2006) or vaccination (Roesler et al.,
 381 2006).

382 **Residual room contaminations** The residual room contaminations were,
 383 as expected, quite important for the prevalence, especially as they were used to
 384 introduce the infection in the batch. Globally, the farrowing and post-weaning
 385 room contaminations had more impact on the seroprevalence over time. The
 386 batch was usually already infected when it entered the finishing room, so
 387 the contribution of shedding pigs to the room contamination overpowered
 388 the residual contamination. The second component brought out particularly
 389 strongly the residual farrowing room contamination. As this component em-
 390 phasised trajectories exhibiting strong differences in seroprevalence between
 391 the beginning and the end of the simulation, it is quite consistent. The in-
 392 fluence of the room contamination has been previously shown (Beloeil et al.,
 393 2003) and it highlights the need of cleaning and disinfecting the room between
 394 batches. This result is consistent with experimental results that showed that
 395 pigs removed at weaning or at 10 weeks of age from their herd and placed in
 396 *Salmonella*-free facilities became *Salmonella*-free delivered pigs (Dahl et al.,
 397 1997). Our study hence suggests that control measures should also concentrate
 398 on the residual room contamination, especially for the farrowing and the post-
 399 weaning rooms. This goal could be reached by: (i) a better cleaning-disinfection
 400 process, (ii) reducing the quantity of *Salmonella* shed by infected pigs, and (iii)
 401 reducing the survival of these bacteria in the environment (quicker removal of
 402 contaminated feces).

403 **Shedding** Control measures reducing the shedding duration were shown to
 404 be efficient by experimentation (e.g. with vaccination (Roesler et al., 2006),
 405 or with acid feed (Farzan et al., 2006; van Winsen et al., 2001)). However, in
 406 the range of variation tested here, the shedding duration did not have a great

407 impact on the seroprevalence variability. Therefore, further experiments should
 408 rather concentrate on the shedding quantity than on the shedding duration.

409 **Maternal protection** A partial maternal protection was represented by
 410 lowering the probability of infection for piglets during the first four weeks
 411 of life. The maternal protective factor had an intermediate influence in the
 412 first component and a major effect in the second component. We used a large
 413 range of variation for this factor, between 0 and 1, because not only is its value
 414 uncertain, its existence remains to be demonstrated. The transmission from
 415 sows to piglets seems to be a critical point for the initial contamination of pig
 416 batches (Lurette et al., 2008a). However, little evidence was found in the lit-
 417 erature to support the existence of a maternal protective factor due to passive
 418 immunity. Indeed, even if passive immunity has been found in piglets (Proux
 419 et al., 2000), no experiments have yet shown a potential protection induced
 420 by this immunity. Other authors modelling *Salmonella* spread within grower-
 421 finisher herds considered active immunity and represented either a complete
 422 immunity for a short period (10 days) following the infection (Hill et al., 2008),
 423 or a partial immunity for the seropositive animals (van der Gaag et al., 2004).
 424 We also attributed a partial immunity to the seropositive health states by
 425 reducing the shedding rate of seropositive animals (π_+). Additional data con-
 426 cerning the potential protective effect of maternal antibodies or post-infection
 427 antibodies are however needed to investigate these matters further.

428 Hill et al. (2008) and van der Gaag et al. (2004) highlighted the importance
 429 of the infection prevalence in weaner pigs and then the importance of the
 430 transmission between sows and their piglets on the slaughterhouse delivery
 431 seroprevalence. Our study has shown that early infection, occurring between

432 birth and weaning, seems to be the critical point of the *Salmonella* spread
 433 within a pig batch, and possibly within a herd. Literature reported that the
 434 prevalence of *Salmonella* at slaughter age resulted from the late infection of
 435 pigs in cases of multi-site herds (Davies et al., 1998; Nielsen et al., 1995).
 436 Actually, the serotype identified at the slaughterhouse differed from those
 437 found in the breeding and in the multiplying herds. In this study, the birth
 438 and the growth of pigs take place at the same place. Moreover, other observed
 439 data exhibit a correlation between the sow herd *Salmonella* status and the
 440 finishing pigs status (Nollet et al., 2005), which tends to support our findings.

441 6 Conclusion

442 This first work has allowed us to identify key parameters in *Salmonella* trans-
 443 mission from a model describing the *Salmonella* spread within a pig batch: first
 444 came parameters involved in the infection probability function, then paramete-
 445 ters related to the room contamination, and finally the *Salmonella* shedding
 446 rate and maternal protective factor. We deduced from these findings that effi-
 447 cient control measures should focus on reducing: (i) the probability of infection,
 448 like for instance acid feed, and vaccination; and (ii) the residual room contam-
 449 ination, especially for the farrowing room, with a better cleaning-disinfection
 450 process, or a quicker removal of contaminated feces. This study also high-
 451 lighted directions that should be further investigated to better understand the
 452 pathogen spread and control it better, such as the potential protective effect of
 453 maternal antibodies or post-infection antibodies. Given that the residual con-
 454 tamination of the rearing rooms and the early infection of piglets were shown
 455 to have quite an impact on the pathogen spread, it would be interesting to

study the influence of these parameters within a farrow-to-finish herd where
sows and pigs are housed together and where batch mixing can occur between
batches (Hébert, 2006).

References

- Beloeil, P. A., Chauvin, C., Proux, K., Rose, N., Queguiner, S., Eveno, E.,
Houdayer, C., Rose, V., Fravalo, P., Madec, F., 2003. Longitudinal sero-
logical responses to *Salmonella enterica* of growing pigs in a subclinically
infected herd. *Prev. Vet. Med.* 60 (3), 207–226.
- Boes, J., Alban, L., Bager, J., Mogelmose, V., Baggesen, D. L., Olsen, J. E.,
2005. Survival of *Escherichia coli* and *Salmonella* Typhimurium in slurry
applied to clay soil on a Danish swine farm. *Prev. Vet. Med.* 69 (3-4), 213–
228.
- Box, G. E. P., Hunter, W. G., Hunter, J. S., 1978. Statistics for experimenters:
an introduction to design, data analysis, and model building. Wiley series
in probability and mathematical analysis. John Wiley & Sons, New York.
- Campbell, K., McKay, M. D., Williams, B. J., 2006. Sensitivity analysis when
model output are functions. *Reliab. Eng. Syst. Saf.* 91 (10–11), 1468–1472.
- Dahl, J., Wingstrand, A., Nielsen, B., Baggesen, D. L., 1997. Elimination of
Salmonella Typhimurium infection by the strategic movement of pigs. *Vet.*
Rec. 140 (26), 679–681.
- Davies, P. R., Bovee, F. G., Funk, J. A., Morrow, W. E., Jones, F. T., Deen,
J. R., 1998. Isolation of *Salmonella* serotypes from feces of pigs raised in a
multiple-site production system. *J. Am. Vet. Med. Assoc.* 212 (12), 1925–
1929.
- Diekmann, O., Heesterbeek, J. A. P., 2000. Mathematical epidemiology of

- infectious diseases: model building, analysis and interpretation. Wiley Series
in Mathematical and Computational Biology. Wiley.
- Fang, K.-T., Li, R., Sudjianto, A., 2006. Design and modeling for computer
experiments. Computer Science and Data Analysis Series. Chapman &
Hall/CRC, Boca Raton, FL.
- Farzan, A., Friendship, R., Dewey, C. E., Warriner, K., Poppe, C., Klotins,
K., 2006. Prevalence of *Salmonella* spp. on Canadian pig farms using liquid
or dry-feeding. Prev. Vet. Med. 73 (4), 241–254.
- Fravalo, P., Cariolet, R., Proux, K., Salvat, G., 2003. Le portage asympto-
matique de *Salmonella enterica* par les porcs : résultats issus de la constitu-
tion d'un modèle en conditions expérimentales. In: 35èmes Journées de la
Recherche Porcine. ITP, INRA, Paris, France, pp. 393–400.
- Hébert, H., 27 octobre 2006. Modalités de conduite en bandes en élevage
porcin: effets sur les contacts entre animaux. Thèse vétérinaire, École Na-
tionale Vétérinaire de Nantes, France.
- Hill, A. A., Snary, E. L., Arnold, M. E., Alban, L., Cook, A. J. C., 2008.
Dynamics of *Salmonella* transmission on a British pig grower-finisher farm:
a stochastic model. Epidemiol. Infect. 136 (3), 320–333.
- ITP, 2000. Le mémento de l'éleveur de porcs. Institut Technique du Porc,
Paris, France.
- ITP, 2006. Le porc par les chiffres 2006. Institut Technique du Porc, Paris,
France.
- Kobilinsky, A., 1997. Les plans factoriels. In: Driesbeke, J.-J., Fine, J.,
Saporta, G. (Eds.), Plans d'expériences : applications à l'entreprise. Éditions
Technip, Paris, Ch. 3, pp. 69–209.
- Kranker, S., Alban, L., Boes, J., Dahl, J., 2003. Longitudinal study of
Salmonella enterica serotype typhimurium infection in three danish farrow-

- 508 to-finish swineherds. J. Clin. Microbiol. 41 (6), 2282–2288.
- 509 Lamboni, M., Makowski, D., Monod, H., Apr. 2008. Multivariate global
- 510 sensitivity analysis for discrete-time models, technical report available:
- 511 <http://www.inra.fr/miaj/public/nosdoc/rap2008-3.pdf>.
- 512 Lurette, A., Belloc, C., Touzeau, S., Hoch, T., Ezanno, P., Seegers, H., Fouri-
- 513 chon, C., Apr. 2008a. Modelling salmonella spread within a farrow-to-finish
- 514 pig herd, veterinary Research.
- 515 Lurette, A., Belloc, C., Touzeau, S., Hoch, T., Seegers, H., Fourichon, C.,
- 516 2008b. Modelling batch farrowing management within a farrow-to-finish pig
- 517 herd: influence of management on contact structure and pig delivery to the
- 518 slaughterhouse. Animal 2 (1), 105–116.
- 519 Murray, C., 2002. Mathematical epidemiology of infectious diseases: model
- 520 building, analysis and interpretation. Wiley Series in Mathematical and
- 521 Computational Biology. Wiley.
- 522 Myers, R. H., Montgomery, D. C., 2002. Response surface methodology : pro-
- 523 cess and product optimization using designed experiments, 2nd Edition.
- 524 Wiley Series in Probability and Statistics. Wiley-Interscience, New York.
- 525 Nicholson, F., Groves, S. J., Chambers, B. J., 2005. Pathogen survival during
- 526 livestock manure storage and following land application. Bioresour. Technol.
- 527 96 (2), 135–143.
- 528 Nielsen, B., Baggesen, D., Bager, F., Haugegaard, J., Lind, P., 1995. The
- 529 serological response to *Salmonella* serovars typhimurium and infantis in
- 530 experimentally infected pigs. The time course followed with an indirect anti-
- 531 LPS ELISA and bacteriological examinations. Vet. Microbiol. 47 (3-4), 205–
- 532 218.
- 533 Nollet, N., Houf, K., DeWulf, J., Duchateau, L., Zutter, L. D., Kruif, A. D.,
- 534 Maes, D., 2005. Distribution of *Salmonella* strains in farrow-to-finish pig

- 535 herds: A longitudinal study. J. Food Prot. 68 (10), 2012–2021.
- 536 Plachá, I., Venglovský, J., Sasáková, N., Svoboda, I. F., 2001. The effect of
 537 summer and winter seasons on the survival of *Salmonella* typhimurium and
 538 indicator micro-organisms during the storage of solid fraction of pig slurry.
 539 J. Appl. Microbiol. 91 (6), 1036–1043.
- 540 Proux, K., Houdayer, C., Humbert, F., Cariolet, R., Rose, V., Eveno, E.,
 541 Madec, F., 2000. Development of a complete ELISA using *Salmonella*
 542 lipopolysaccharides of various serogroups allowing to detect all infected pigs.
 543 Vet. Res. 31 (5), 481–490.
- 544 Roesler, U., Heller, P., Waldmann, K., Truyen, U., Hensel, A., 2006. Immuniza-
 545 tion of sows in an integrated pig-breeding herd using homologous inactivated
 546 *Salmonella* vaccine decreases the prevalence of *Salmonella* typhimurium in-
 547 fection in the offspring. J. Vet. Med. B. 53 (5), 224–228.
- 548 Saltelli, A., Chan, K., Scott, E. M. (Eds.), 2000. Sensitivity Analysis. Wiley
 549 series in Probability and Statistics. John Wiley & Sons.
- 550 van der Gaag, M. A., Vos, F., Saatkamp, H. W., van Boven, M., van Beek, P.,
 551 Huirne, R. B. M., 2004. A state-transition simulation model for the spread
 552 of *Salmonella* in the pork supply chain. Eur. J. Oper. Res. 156 (3), 782–798.
- 553 van Winsen, R. L., van Nes, A., Keuzenkamp, D., Urlings, H. A. P., Lip-
 554 man, L. J. A., Biesterveld, S., Snijders, J. M. A., Verheijden, J. H. M.,
 555 van Knapen, F., 2001. Monitoring of transmission of *Salmonella enterica*
 556 serovars in pigs using bacteriological and serological detection methods. Vet.
 557 Microbiol. 80 (3), 267–274.
- 558 Wong, D. M. A. L. F., Hald, T., van der Wolf, P., Swanenburg, M., 2002.
 559 Epidemiology and control measures for *Salmonella* in pigs and pork. Liv.
 560 Prod. Sci. 76 (3), 215–222.