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

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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

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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

26 et al., 2000) and cannot be applied to such dynamic outputs. However, some
27 methods have been developed to analyse time series outputs (Campbell et al.,
28 2006). They use classical statistical tools on variables that summarise the
29 trajectory variability. The method developed by Lamboni et al. (2008) is based
30 on a principal component analysis applied to the trajectories. It maximises the
31 information that is retained from the output variability. It has already been
32 used to analyse various agronomic models and can easily be applied to an
33 epidemiological model.

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

46 A simulation model representing the *Salmonella* spread within a farrow-to-
47 finish pig herd implementing batch-farrowing management was developed by
48 Lurette et al. (2008a). This model details both the sow and pig dynamics
49 (Lurette et al., 2008b) and the *Salmonella* infection characteristics. In such a
50 herd, sows are distributed in groups of equal size called batches and their re-
51 productive 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.

76 As the carriage of *Salmonella* in pigs is generally subclinic, the infection does
77 not affect the pig demography. Hence, the pig batch model and the epidemi-
78 ological model are first presented separately. They are then coupled by dis-
79 tributing the animals of the batch into the infection states. Finally, the pa-
80 rameters and initial conditions are described.

81 2.1 Pig batch model

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

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

95 At each delivery time (usually every two weeks), producers send groups of
96 finishers with a given slaughtering weight. As out-of-range pigs are sold at a
97 lower price, they are kept in the herd until they reach the slaughtering weight
98 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:

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

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

112 2.2 *Salmonella* epidemiological model

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

120 Four mutually exclusive health states (Y) were identified and selected from
 121 the literature and from expert opinion. A susceptible pig free of *Salmonella*
 122 ($Y = F$) becomes a shedding pig ($Y = Sh$) after ingesting the bacteria. After
 123 a seroconversion delay, it is called a seropositive shedding pig ($Y = Shs$). The
 124 shedding is intermittent. When it stops, the pig becomes a seropositive carrier
 125 pig ($Y = Cs$). The shedding can be reactivated, especially under stressful
 126 conditions. The number of pigs in each state Y at time t is given by $P(t, Y)$,
 127 where $P(t) = \sum_Y P(t, Y)$ represents the total population size. All transitions
 128 are stochastic: the number of pigs which undergo a transition between two
 129 states is drawn in a binomial law; the first parameter is the number of pigs in
 130 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).

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

177 All simulations were performed using Scilab 4.0.¹

178 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 , $5 \cdot 10^3$, 10^5 , $5 \cdot 10^6$ 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

195 it enables the estimation of main effects and two-factor interactions, assuming
 196 that the higher order interactions are negligible. A resolution V design for
 197 18 factors can be obtained with 4096 scenarios, which corresponds to 61 440
 198 simulations with 15 replications. The fractional factorial design we used was
 199 produced by the FACTEX procedure of the SAS 8.0/QC module.² Alter-
 200 native designs could have been used, in particular response surface designs
 201 (Myers and Montgomery, 2002) or space-filling designs (Fang et al., 2006). In
 202 the present study, we gave priority to orthogonal and balanced designs.

203 3.2 Sensitivity analysis on the seroprevalence over time

204 To analyse the seroprevalences over time $\psi(t)$ obtained with the fractional fac-
 205 torial design described above, we used a method developed by Lamboni et al.
 206 (2008). We only give here a short description of this method. The seropreva-
 207 lence outputs can be represented in a $N \times p$ table denoted T , with $N = 61\,440$
 208 the number of simulations and $p = 23$ the number of seroprevalence output
 209 times ($t = 2, \dots, 24$). As the animals are born *Salmonella*-free at $t = 0$ and
 210 need a week for seroconversion when they become infected, $\psi(0) = \psi(1) = 0$
 211 for each simulation; moreover, their room is emptied at $t = t_m = 25$, so
 212 $\psi(25) = 0$. Hence, these times are not included in the analysis.

213 A principal component analysis (PCA) with N individuals and p variables is
 214 performed on this table T . It consists in an eigenvalue decomposition of the
 215 matrix of correlations between the columns of T , $\tilde{T}'\tilde{T}$, where \tilde{T} is obtained by
 216 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/>

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

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

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

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

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

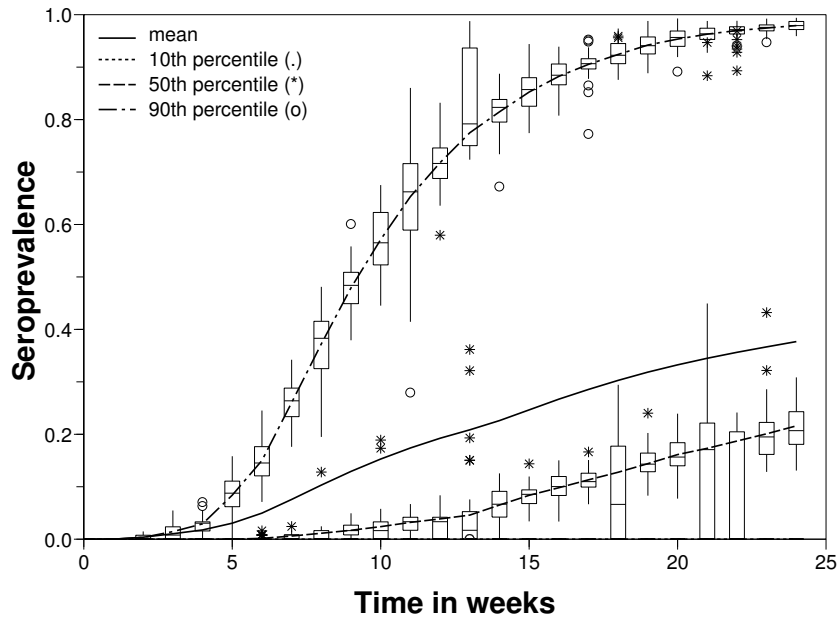


Fig. 1. Percentiles of the average seroprevalence at each time step (lines) and seroprevalence variability between replicates (boxplots). At each time step, percentiles are calculated across the 4096 seroprevalences averaged over the 15 replications per scenario: mean (plain line), 10th percentile (dotted 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

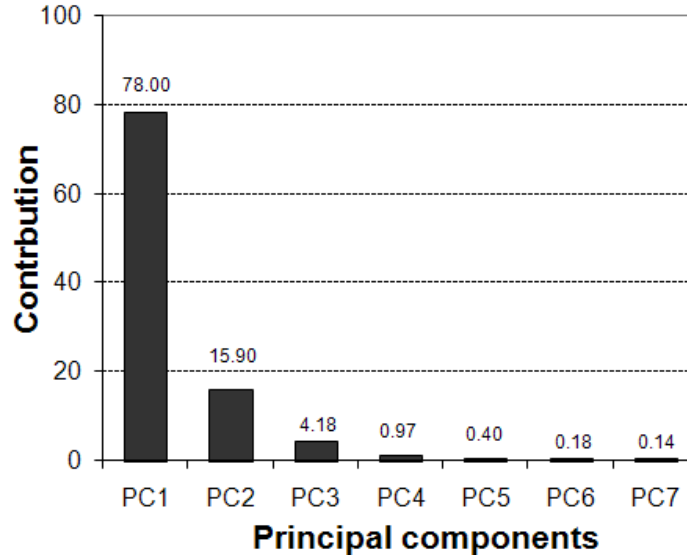


Fig. 2. Contribution to the total inertia of the seven first principal components: component contribution (black) and total inertia explained by the seven first components (grey). PC_X is the X^{th} component.

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

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

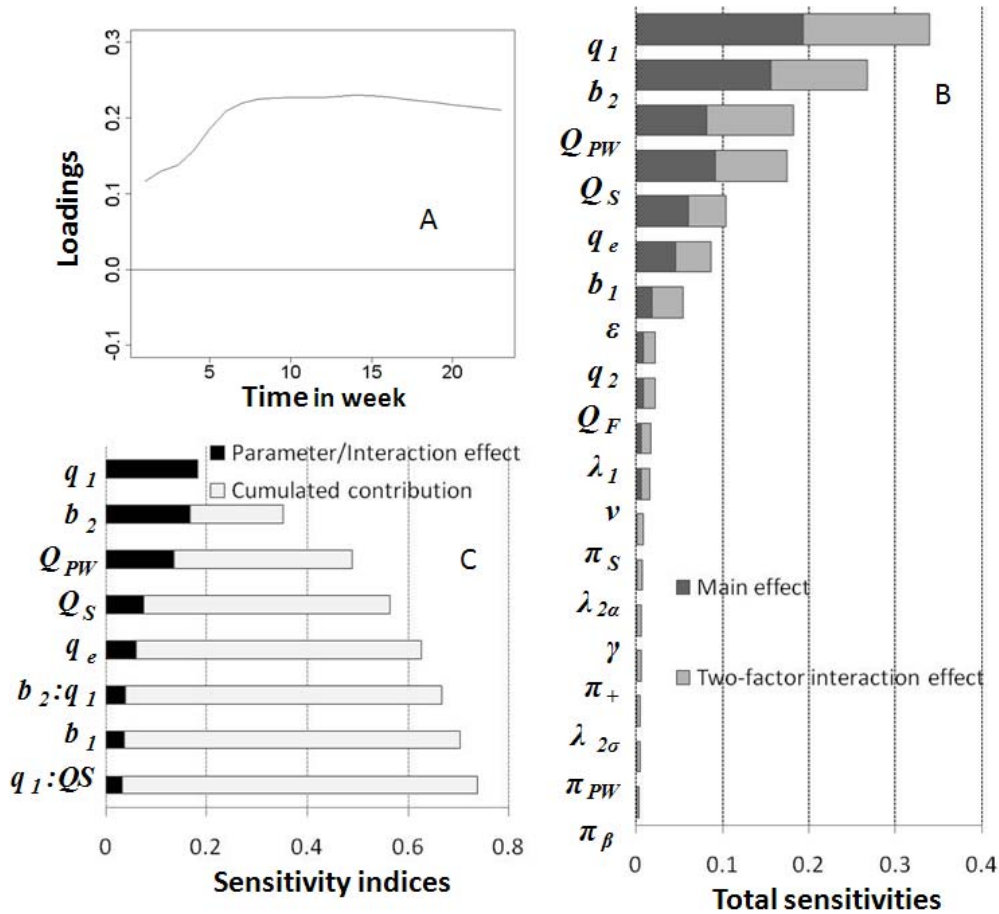


Fig. 3. Sensitivity analysis on the seroprevalence over time: results of the ANOVA performed on the simulation scores of the first component (inertia: 78.0%). – **A** Loadings defining the component for each time variable (in abscissa). **B** Total sensitivities TS_f^1 for the 18 epidemiological parameters 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.

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

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

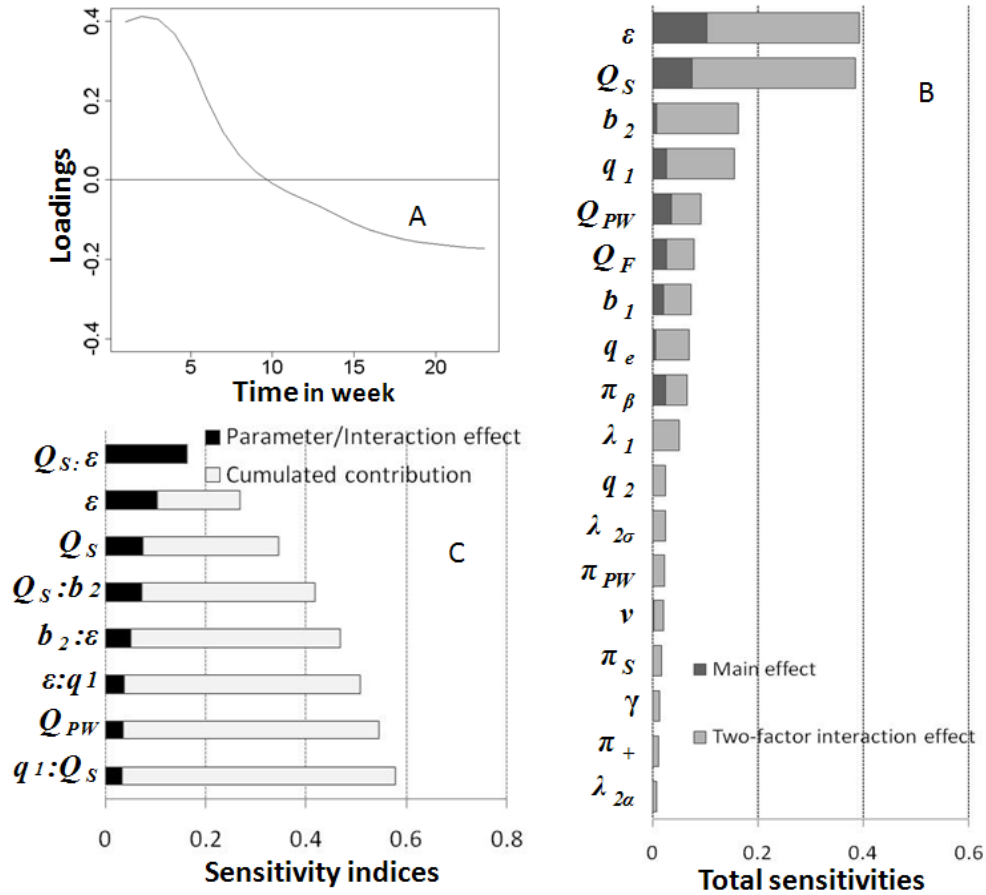


Fig. 4. Sensitivity analysis on the seroprevalence over time: results of the ANOVA performed on the simulation scores of the second component (inertia: 15.9%). – **A** Loadings defining the component for each time variable (in abscissa). **B** Total sensitivities TS_f^2 for the 18 epidemiological parameters 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.

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

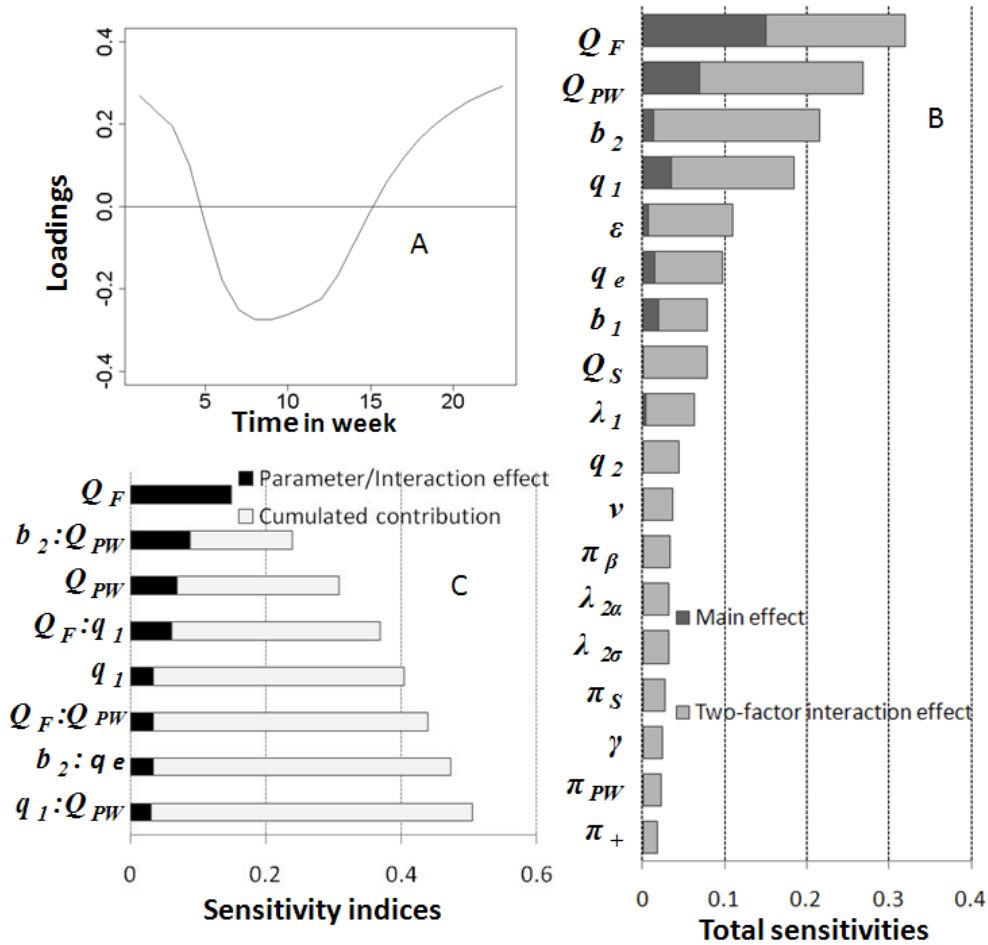


Fig. 5. Sensitivity analysis on the seroprevalence over time: results of the ANOVA performed on the simulation scores of the third component (inertia: 4.2%). – **A** Loadings defining the component for each time variable (in abscissa). **B** Total sensitivities TS_f^3 for the 18 epidemiological parameters 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

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

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

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

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

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