Risk Analysis, Vol. 27, No. 5, 2007 DOI: 10.1111/j.1539-6924.2007.00951.x

Special Issue: The Future of BSE Assessments

Influence of Routine Slaughtering on the Evolution of BSE: Example of British and French Slaughterings

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The aim of this article is to build a methodology allowing the study and the comparison of the potential spread of BSE at the scale of countries under different routine slaughtering conditions in order to evaluate the risk of nonextinction due to this slaughtering. We first model the evolution in discrete time of the proportion of animals in the latent period and that of infectives, assuming a very large branching population not necessarily constant in size, two age classes, less than 1-year-old animals, and adult animals. We analytically derive a bifurcation parameter ρ_0 allowing us to predict either endemicity or extinction of the disease, which has the meaning of an epidemiological reproductive rate. We show that the classical reproductive number R_0 cannot be used for prediction if the size of the population, when healthy, does not remain stable throughout time. We illustrate the qualitative results by means of simulations with either the British routine slaughtering probabilities or the French ones, the other conditions being assumed identical in both countries. We show that the French probabilities lead to a higher risk of spread of the disease than the British ones, this result being mainly due to a smaller value of the routine slaughtering probability of the adult animals in France than in Great Britain.

KEY WORDS: Basic reproductive number; BSE; endemicity; extinction; incubation; reproductive rate; risk; slaughtering.

1. INTRODUCTION

It is well recognized that measures that aim to decrease the exposure level, or to remove the animals at risk, may have an important influence on the spread of BSE. Since the beginning of the BSE epidemic first diagnosed in England in November 1986, though it has been retrospectively recognized that a clinically affected animal examined in 1985 was suffering from BSE, successive measures were taken first in Great Britain and then in every country where occurrence of BSE seemed possible. But the importance of the influence of the routine culling itself on the spread of the disease is unknown and the crucial question is: Are there any routine slaughterings more risky than others? Our main goal in this article is to build a methodology for being able to study this influence according to different survival functions, assuming identical infection parameters in the compared countries. The method is illustrated by comparing this influence under the British routine slaughtering and the French one, the difference between the two countries' conditions consisting in culling the calves at a much larger probability in France than in Great Britain and culling the older animals at a smaller probability in France than in Great Britain.

For this study, we assume that BSE is a *SEIR* disease.

In Section 2, we model the evolution of the proportion of animals in the state $h \in \{S, E, I\}$, when the population is very large, by a model in discrete time with two age classes, the calves (less than 1-year-old

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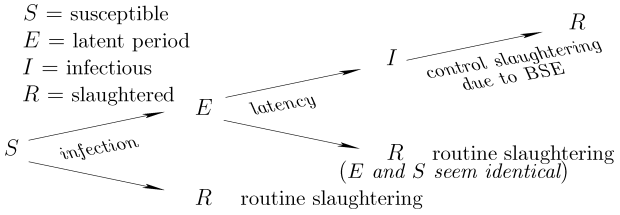

Fig. 1. Evolution of the health status of a healthy animal when it catches the disease.

animals) and the adult animals. The time unit chosen is 1 year for eliminating all seasonal effects due to calving or other breeding practices. The transmission routes are either horizontal or vertical (from the dam to its calf), and the transition probabilities are assumed identical for all animals of the same age class and, moreover, homogeneous in time, which means that one type of breeding is considered and successive control measures throughout the time are not taken into account. Two models are considered. The first model assumes that all individual transitions are Markovian, which means that the probability for an animal to undergo at the next time the transition $h \to k$ with $h \in \{S, E, I\}$ and $k \in \{S, E, I, R\}$, is independent of the time already past in h. According to this assumption, the time for an animal to achieve the transition follows a geometric probability distribution (corresponding to an exponential distribution in continuous time). Concerning the infection and the slaughtering, it is shown to be an acceptable assumption. But it seems *a priori* much less realistic concerning the incubation period law, which is generally considered as a unimodal law. Consequently, we also derive a model assuming that the incubation time follows a dirac distribution at T (all animals becoming infectious, achieve their latent period in exactly T years). This simple model is used for validating the qualitative prediction given in the Markovian setting by comparison to that given by this model.

Analytical results are given in Section 3. They are first given in the Markovian frame. This frame leads to some analytical results on the behavior of the model that could be more difficult or impossible to get in a more general semi-Markovian frame allowing any type of distribution for the transition times. We first derive a bifurcation parameter ρ_0 (thus allowing to predict the qualitative behavior of the disease), which is defined as an initial reproductive rate in the particular direction $i_1 = i_0$, where i_n is the proportion of infectives at time n. We compare it to the classical reproductive number R_0 (expected number of secondary cases produced by a primary case in a "virgin" population[12]) and show that R_0 is equivalent to ρ_0 and therefore may be used for prediction if and only if the population when healthy remains stable throughout time.

Moreover, since the models are nonlinear, the extinction predicted by ρ_0 (or equivalently by R_0 when the population when healthy remains stable throughout time) is local, that is, the disease dies out for $\rho_0 < 0$ only if the current (and unknown) proportion of infected animals is small enough, which is never guaranteed since the animals in the incubation stage are not observed and may be much more numerous than the clinical cases (see the simulations). Consequently, we also give conditions based on the current reproductive rate that lead to the extinction of the disease starting from any level of infectivity (global stability of the disease-free state).

We supplement these qualitative results by simulations (Section 4) in order to compare the influence of routine slaughtering in Great Britain with that in France, all other factors remaining identical in both countries. For simulating the model we must be able to estimate the unknown parameters of the model from data. Dynamical parameters are easily estimable from the observed survival curves but the probability $P_a^{E,I}$ of the transition $E \to I$ is not directly observable. Therefore, we first define the mean intrinsic latent time T_{R^c} of the censored Markovian transition $E \to I$ defined in such a way that $E \to R$ is forbidden. Indeed, T_{R^c} is, by construction, independent of the survival function, and therefore depends only on the disease at the opposite of the observed mean incubation period T in a given country, which depends strongly on the slaughtering ages in this country. We show that the probability to achieve the censored transition is equal to $T_{R^c}^{-1}$, implying that $P_a^{E,I}$ is function of T_{R^c}. But T_{R^c} is unobservable. So for calculating T_{R^c} from the observable mean incubation period T and in addition for validating the Markovian assumption with respect to the semi-Markovian one, we prove in Subsection 6.4 that, for any given value of T, there exists a unique value of T_{R^c} independent of the transmission probabilities and such that the qualitative asymptotic behavior (endemicity/extinction) of the disease in the Markovian setting is the same as in the semi-Markovian one when the incubation period distribution is a dirac law at T. Moreover, T_{R^c} is a function of T and of the routine dynamical parameters, which are all easily estimable. The simulations are done under either the French survival curve based on routine slaughtering or under the British one. To avoid confounding effects due to other factors, we assume that the other factors (T_{R^c}, infection parameters, stability of the population size) are identical in both countries, and we assume that the

control measures do not change with time. The value of T_{R^c} is calculated from T, which itself is roughly estimated from the British epidemic used as a reference data set since it is the most informative. Simulations are done with the probability 0.1 for a calf to be infected by the vertical route, the mean incubation time $T = 5$, and under different levels of the horizontal transmission in order to get different types of behavior.

We also study the influence of the slaughtering of each calf whose mother is infectious and show that this control slaughtering has a negligible influence on the disease, leading to the extinction of the disease only when the value of ρ_0, under the routine slaughtering, is already closed to the bifurcation threshold 0.

Some details of the model elaboration and of the analytical results are given in the Appendix and all the proofs may be found in References 1 and 2.

2. MATERIALS AND METHODS

2.1. Hypotheses

The following hypotheses are assumed for elaborating the models.

- H1: We assume two age classes for the slaughtering probabilities, the infection probabilities, and the transition probability from E to I. This leads to two subpopulations, the calves at most 1 year old, and the other animals, called "adults." Concerning slaughtering, this assumption is consistent with the survival function $\{S_a\}$ when it may be assumed exponential for $a \geq 1$ since in this case the probability for an animal to survive from age a to age $a + 1$, defined by $1 - P_a^{S,R} = S_{a+1}\, S_a^{-1}$, is constant for all $a \geq 1$. The approximation of the survival function from $a = 1$ by an exponential function is a reasonable assumption considering the observed survival curves in Great Britain and in France (Fig. 2). Concerning the infection, the two age classes assumption is consistent with previous studies on ages at risk. In Reference 3, British dairy cattle were estimated at risk in the first 6 months of life, adult cattle were at relatively low risk of infection, and between 6 and 24 months of age, risk profiles reflected feeding patterns of proprietary concentrates in each of the autumn- and spring-born cohorts. In France, the peak risk of bovine infection was estimated between 6 and 12 months of age.[4] Now concerning the probability $P_a^{E,I}$ of the transition $E \to I$ for an animal infected at age a, it is easy to show that the probability $P_a^{E,I}(1 - P_a^{E,R})^{-1}$ of the censored transition $E \to I$, which, assumes that slaughtering an animal in the state E is forbidden, is equal to

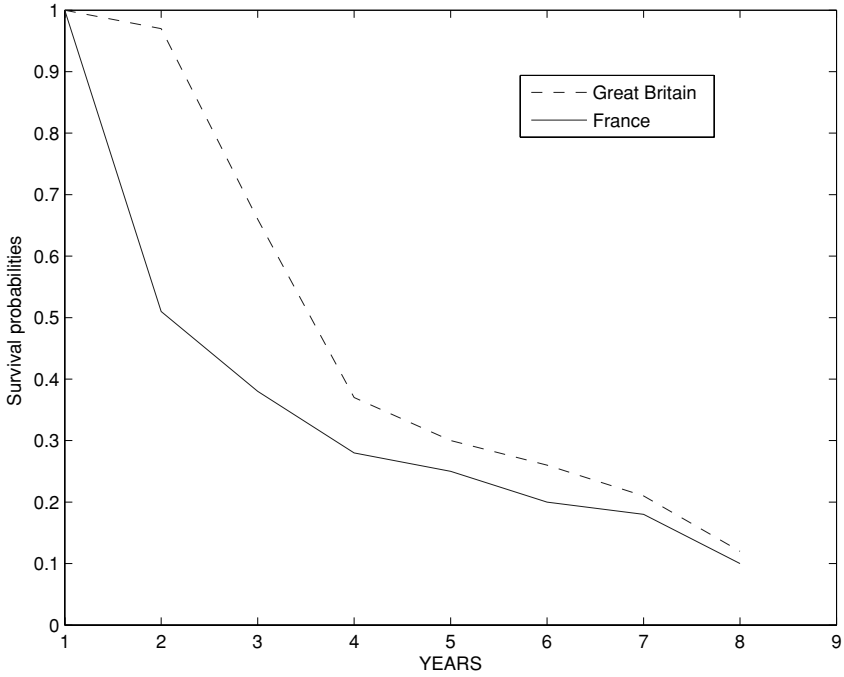

Fig. 2. Survival probabilities of cattle in Great Britain and in France.

$T_{R^c}^{-1}$, where T_{R^c} is the mean time of this censored transition (see Section A.4). Therefore, T_{R^c} is the mean intrinsic incubation time independent of the slaughtering. Moreover, we assume that T_{R^c} is independent of the age $a \geq 1$ of infection leading to $P_a^{E,I}$ constant for all $a \geq 1$. We denote b the calves class and a the adult class.

- H2: Two general routes of transmission are considered: a vertical (maternal) route with probability $\bar{q}$ from an infectious dam to its calf, the source of which, *in utero* or at birth or both, does not need to be known, since these two types of vertical transmission are not separately identifiable in the model,(1) and a horizontal transmission route that cumulates all the possible sources of such route. Direct ingestion of the infectious BSE agent via meat and bone meal (MBM) is commonly regarded as the main route of infection for cattle. Until 1988 in Great Britain and 1990 in France, MBM was incorporated to the ruminant food. Afterward, until 1996, cross-contamination of this food by contaminated food for other farm animals was possible. Infection due to the ingestion of disseminated pathogenic agents in the environment has also been envisaged. In Reference 5, another plausible route of infection is proposed, namely, the ingestion of MBM by mother animals who subsequently pass on the infectious agent in their colostrum and thus infect their offspring. According to the author, this theory could explain why, although infection is thought to occur at very early stages in life, many BSE animals had not received feeds containing MBM when calves. This route is considered here as a horizontal one if the dam is not yet infectious when infecting its calf, and otherwise as a vertical route. We assume that the probability for a susceptible adult to be infected during the year $n + 1$, when it survives during this year, is the same for all animals, depends on the past infection only through the proportion i_n of infectives at time n, and depends on the time only through the value taken by i_n. We denote it $\bar{a}(i_n)$. These hypotheses mean that the exposure of a susceptible animal to contaminated material that dates of more than one year is negligible, and only one type of breeding (classically the dairy ones) is considered (in Reference 6, the odds of a dead cow being a BSE case among all dead cattle was found 3.2 times higher for dairy breeds compared to beef suckler breeds, which confirmed British findings). The different sources of the horizontal transmission route do not need to be specified. The function $\bar{a}(\cdot)$ is assumed to be continuous with at least a first derivative in a neighborhood of 0, and increasing with $\bar{a}(0) = 0$. The quantity $\bar{a}(1)$ represents the susceptibility/exposure parameter (probability for a S adult of being infected during a year) when the remaining population is assumed totally infectious at the previous year. The same hypotheses are assumed for the probability $\bar{b}\cdot$ for a calf to be infected via a horizontal route. A simple example of such functions is $\bar{a}(i) = 1 - a^i$, $\bar{b}(i) = 1 - b^i$, $a, b \in [0, 1]$. The exponential law can be obtained, for example, under the assumption of Reed-Frost type (Section A.1). The exponential function leads to the highest risks since infection may occur even for very small values, of i_n. But other forms could be chosen, especially for $\bar{a}(\cdot)$, such as sigmoid functions allowing threshold of infection since the theoretical results are valid for a very large class of functions.(1,2) An example of a simple increasing sigmoid function on $[0, 1]$ satisfying $\bar{a}(0) = 0$ is $\bar{a}(i) = (1 - a^i)^l, i \in [0, 1], a \in [0, 1], l \geq 2$.
- H3: Let $h \in \{S, E, I\}, k \in \{S, E, I, R\}$. Denote $P_a^{h,k}(i)$ the probability for an adult to undergo the transition $h \to k$ and $P_b^{h,k}(i)$ the probability for a calf with dam in state h to be k at the end of the first year of its life, when the proportion of infectives is i. All calves are assumed to be susceptible at birth since the transmission before birth by an infectious dam and that after birth are not separately identifiable in the model. Therefore, $P_b^{h,k}(i) = P_{b,mh}^{S,k}(i)$, where $P_{b,mh}^{S,k}(i)$ is the probability for a S calf the mother of which is h to undergo the transition $S \to k$ during its first year of life. The adult animals, whether they are susceptible or in incubation, are assumed to have the same strictly positive probability $P_a^{S,R} = P_a^{E,R}$ independent of i to be slaughtered, and in the same way, the calves the dam of which are either susceptible or in incubation are assumed to have the same probability $P_{b,mS}^{S,R} = P_{b,mE}^{S,R}$ independent of i to be slaughtered during the first year. We assume, moreover, that the control slaughtering probability is higher than the routine slaughtering: $P_a^{I,R} \geq P_a^{S,R} > 0$, $P_{b,mI}^{S,R} \geq P_{b,mS}^{S,R} \geq 0$.

- H4: Importations of animals are not taken into account; the influence of other cattle diseases are not considered either.

2.2. Models (See Section A.2)

First assume Markovian individual transitions. Their probability to be achieved during the year $n+1$ given the proportion i_n of infectives at the previous year are the following:

- For the adults:

$$S \xrightarrow{P_a^{S,E}(i_n) = \bar{a}(i_n)\left(1 - P_a^{S,R}\right)} E \xrightarrow{P_a^{E,I} = T_{R^c}^{-1}\left(1 - P_a^{E,R}\right)} I \xrightarrow{P_a^{I,R}} R$$

$$E \xrightarrow{P_a^{E,R}} R$$

$$S \xrightarrow{P_a^{S,R}} R$$

- For the calves with dam in the state $h \in \{S, E\}$:

$$S \xrightarrow{P_b^{h,E}(i_n) = P_{b,mh}^{S,E}(i_n) = \bar{b}(i_n)\left(1 - P_{b,mh}^{S,R}\right)} E$$

$$\xrightarrow{P_b^{h,R} = P_{b,mh}^{S,R}} R$$

- For the calves with dam in the state I:

$$S \xrightarrow{P_b^{I,E}(i_n) = P_{b,mI}^{S,E}(i_n) = (1 - qb(i_n))(1 - P_{b,mI}^{S,R})} E,$$

$$\xrightarrow{P_b^{I,R} = P_{b,mI}^{S,R}} R$$

where $q = 1 - \bar{q}$, $b(\cdot) = 1 - \bar{b}(\cdot)$.

The elaboration of the model is explained in the Appendix (see also References 1, 2, 9). Denote e_n (resp. i_n) the probability for an animal in a very large branching population to be in the state E (resp. I) at time n. Assuming $(e_0, i_0) \neq (0, 1)$ with $e_0 + i_0 < 1$, the dynamical system on the probabilities sequence $\{e_n, i_n\}_n$ is:

$$(e_{n+1}, i_{n+1}) = F(e_n, i_n) = (F_1(e_n, i_n), F_2(e_n, i_n)),$$

where

$$\begin{aligned} e_{n+1} = F_1(e_n, i_n) &= \left[M(i_n)\right]^{-1}\left[(1 - (e_n + i_n))g(i_n)\right. \\ &\quad + e_n\left[1 - P_a^{E,R} - P_a^{E,I} + \tilde{m}\bar{b}(i_n)\left(1 - P_{b,mE}^{S,R}\right)\right] \\ &\quad \left. + i_n\left[\tilde{m}(1 - qb(i_n))\left(1 - P_{b,mI}^{S,R}\right)\right]\right] \\ i_{n+1} = F_2(e_n, i_n) &= \left[M(i_n)\right]^{-1}\left[e_n P_a^{E,I} + i_n\left(1 - P_a^{I,R}\right)\right] \end{aligned}$$

with the notations

$$g(i_n) = \bar{a}(i_n)\left(1 - P_a^{S,R}\right) + \tilde{m}\bar{b}(i_n)\left(1 - P_{b,mS}^{S,R}\right) \quad (1)$$

$$\begin{aligned} M(i_n) &= \lim_{N_0 \to \infty} \frac{N_{n+1}}{N_n} = 1 + \tilde{m} - \gamma_S - i_n(\gamma_I - \gamma_S) \\ \gamma_h &= P_a^{h,R} + \tilde{m} P_{b,mh}^{S,R}, \quad h \in \{S, I\}, \end{aligned} \quad (2)$$

where $\tilde{m}$ is the mean number of calves per year and per cow. In the particular case of $M(0) = 1$ (stable population size when healthy), we get:

$$\tilde{m} = \frac{P_a^{S,R}}{1 - P_{b,mS}^{S,R}}.$$

Now assume the following semi-Markovian setting: the time to achieve the latent period (transition $E \to I$) follows a dirac distribution δ_T, which means that an infected animal becoming infectious achieves its latent period in exactly T time units. The other transitions are assumed to have the same probabilities as previously. The model is, therefore, for $n \geq 0$ and $(\vec{e}_0, i_0) \neq (\vec{0}, 1)$ with $i_0 + \sum_j e_0^j < 1$,

$$\begin{aligned} (\vec{e}_{n+1}, i_{n+1}) &= G(\vec{e}_n, i_n) \\ &= (G_1(\vec{e}_n, i_n), \ldots, G_T(\vec{e}_n, i_n), G_{T+1}(\vec{e}_n, i_n)) \end{aligned}$$

with

$$\begin{aligned} e_{n+1}^1 = G_1(\vec{e}_n, i_n) &= \left[M(i_n)\right]^{-1}\left[(1 - (e_n + i_n))g(i_n)\right. \\ &\quad + e_n\left[1 - P_a^{E,R} - \tilde{P}_a^{E,I} + \tilde{m}\bar{b}(i_n)\left(1 - P_{b,mE}^{S,R}\right)\right] \\ &\quad \left. + i_n\left[\tilde{m}(1 - qb(i_n))\left(1 - P_{b,mI}^{S,R}\right)\right]\right] \\ e_{n+1}^j = G_j(\vec{e}_n, i_n) &= \left[M(i_n)\right]^{-1}\left[e_n^{j-1}\tilde{P}_a^{E,I}\right], \quad j = 2, T \\ i_{n+1} = G_{T+1}(\vec{e}_n, i_n) &= \left[M(i_n)\right]^{-1} \\ &\quad \times \left[e_n^T \tilde{P}_a^{E,I} + i_n\left(1 - P_a^{I,R}\right)\right], \end{aligned}$$

where $\tilde{P}_a^{E,I} = (1 - P_a^{E,R})$, $e_n = \sum_{j=1}^T e_n^j$.

3. ANALYTICAL RESULTS

3.1. Bifurcation Parameters and Reproductive Parameters (See Section A.3)

Assume first the Markovian model (all the times of transition, including $E \to I$, have geometric distributions).

In the theory of dynamical systems, the asymptotic behavior of the model (persistence vs. extinction) is given by the bifurcation parameter λ, defined

as the largest eigenvalue of the system linearized at 0. We get:

$$\lambda = [2M(0)]^{-1}\big[P_a^{E,E} + 1 - P_a^{I,R} + \sqrt{\big(P_a^{E,E} - \big(1 - P_a^{I,R}\big)\big)^2 + 4CCP_a^{E,I}}\big], \quad (3)$$

where

$$CC \overset{def.}{=} M(0)\frac{\partial F_1}{\partial i}(0,0) = g'(0) + \tilde{m}\bar{q}\big(1 - P_{b,mI}^{S,R}\big),$$

$$g'(0) = \bar{a}'(0)\big(1 - P_a^{S,R}\big) + \tilde{m}\bar{b}'(0)\big(1 - P_{b,mS}^{S,R}\big)$$

represents, for CC, the total infection capacity when the disease starts (mean number of newly infected animals produced by an infective per time unit), and for $g'(0)$ (first derivative of $g(\cdot)$ at 0), the infection capacity by the horizontal route when the disease starts. We see from Equation (3) that λ has no obvious epidemiological meaning. Then according to the classical theory of dynamical systems, when $\lambda > 1$, the disease-free equilibrium $(0, 0)$ is unstable which means the persistence of the disease, while when $\lambda < 1$, it is asymptotically locally stable, which means the extinction as the time tends to infinity, starting from a neighborhood of $(0, 0)$. Here, extinction and persistence concern the behavior of the proportions $\{e_n, i_n\}$ with respect to the total size of the population.

In the theory of epidemiological models, the usual quantity used for prediction is the basic reproductive ratio R_0, defined as the expected number of secondary cases produced by a primary case in a "virgin" population.[12] But this quantity is shown to behave as a bifurcation parameter only in some simple models expressed in terms of successive generations of infectives, and no proof exists in more general contexts, including overlapping generations of infectives, nonstable population sizes, or a nonnegligible incubation period. In particular, the link between λ and R_0 is generally not analyzed. Consequently, in order to get a quantity that is a bifurcation parameter with an epidemiological meaning, we analytically derived in References 1 and 2 the following reproductive rate ρ_0:

$$\rho_0 = \lim_{i_0 \to 0, i_1 = i_0} (e_1 - e_0) i_0^{-1}, \quad (4)$$

which allows the study of the fixed points $(e_1, i_1) = (e_0, i_0)$ of the Markovian dynamical system modeling the spread of the disease. We get:

$$\rho_0 = [M(0)]^{-1}\tilde{\rho}_0, \quad \tilde{\rho}_0 = CC - SC, \quad (5)$$

where

$$\begin{aligned} SC &= \big[P_a^{I,R} - P_a^{S,R} + \tilde{m}\big(1 - P_{b,mS}^{S,R}\big)\big] \\ &\quad \times \big[1 + \tilde{m}\big(1 - P_{b,mE}^{S,R}\big)\big[P_a^{E,I}\big]^{-1}\big] \\ &= \big[P_a^{I,R} - P_a^{S,R} + \tilde{m}\big(1 - P_{b,mS}^{S,R}\big)\big] \\ &\quad \times \left[1 + \frac{\tilde{m}\big(1 - P_{b,mE}^{S,R}\big)T_{R^c}}{1 - P_a^{E,R}}\right] \end{aligned} \quad (6)$$

represents some capacity for renewing the susceptible population in spite of the disease and is increasing with $P_a^{I,R}$ and T_{R^c}. We get (Section A.3):

$$\operatorname{sign}(\rho_0) = \operatorname{sign}(\lambda - 1),$$

which means that ρ_0 is equivalent to λ for predicting the spread of the disease.

Compare now the reproductive number R_0 and ρ_0. First we have:

$$R_0 = \frac{P_a^{E,I}}{P_a^{I,R}\big(P_a^{E,I} + P_a^{E,R}\big)}CC,$$

which implies (Section A.3):

$$\begin{aligned} &\operatorname{sign}(R_0 - 1) = \operatorname{sign}(\rho_0) \\ \Longleftrightarrow &\lim_{e_0 + i_0 = 0, N_0 \to \infty} N_{n+1} N_n^{-1} = 1, \end{aligned} \quad (7)$$

which means that in the case of a stable population size, R_0 may be used for predicting the evolution of the disease leading to the local asymptotic stability of the healthy state $(0, 0)$ when $R_0 < 1$. Therefore, the disease will die out if the total number of infected animals (including those in incubation) is small enough. The restriction of Equation (7) is due to the fact that the model concerns proportions instead of numbers.

But when $M(0) \neq 1$, then R_0 is generally not a bifurcation parameter. For example, assume $M(0) > 1$ (increasing population when healthy). Then $C_2\rho_0 < R_0 - 1$, which implies that the extinction predicted by R_0 when $R_0 < 1$ is valid because in this case $\rho_0 < 0$. But the persistence predicted by R_0 when $R_0 > 1$ may be false since we may have at the same time $\rho_0 < 0$. Conversely, assume $M(0) < 1$ (decreasing population size), then $R_0 - 1 < C_2\rho_0$. Consequently, we may have at the same time $\rho_0 > 0$, indicating the persistence of the disease, and $R_0 < 1$, which may be dangerous if the predicted extinction according to this value of R_0 leads to remove the control regulations while the disease persists.

In the semi-Markovian setting, which assumes that the incubation time distribution is a dirac law at T, since the model with intermediate states $\{E_j\}_j$ is of the Markovian type, the usual bifurcation parameter

is calculated in the same way as previously. In the particular case $P_a^{I,R} = 1$, the largest eigenvalue of the system linearized at 0 has an analytical form (which does not exist if $P_a^{I,R} \neq 1$):

$$[\lambda(\delta_T)]^{T+1} = CC\left(1 - P_a^{E,R}\right)^T M(0)^{-(T+1)}.$$

This implies that the following quantity $\tilde{\rho}_0(\delta_T)$ is also a bifurcation parameter under $P_a^{I,R} = 1$,

$$\tilde{\rho}_0(\delta_T) \overset{def.}{=} \left([\lambda(\delta_T)]^{T+1} - 1\right)\frac{M(0)^{T+1}}{\left(1 - P_a^{E,R}\right)^T}$$

$$= CC - \frac{M(0)^{T+1}}{\left(1 - P_a^{E,R}\right)^T}. \quad (8)$$

Consequently,

$$\tilde{\rho}_0(\delta_T) = \tilde{\rho}_0 + \Delta_2; \quad \Delta_2 = SC - \frac{M(0)^{T+1}}{\left(1 - P_a^{E,R}\right)^T}. \quad (9)$$

Notice that if we assumed $P_a^{I,R} \neq 1$ or another incubation law such as a gamma distribution, then in general there would no more exist any explicit analytical expression for the bifurcation parameter in the semi-Markovian setting.

Next the calculus of the reproductive ratio $R_0(\delta_T)$ in this semi-Markovian frame, done in the same way as in the Markovian one, leads to:

$$R_0(\delta_T) = \frac{\left(1 - P_a^{E,R}\right)^T}{P_a^{I,R}} CC. \quad (10)$$

Therefore, under $P_a^{I,R} = 1$ and according to Equations (8) and (10), we have (Section A.3):

$$\operatorname{sign}(R_0(\delta_T) - 1)$$

$$= \operatorname{sign}(\tilde{\rho}_0(\delta_T)) \Longleftrightarrow \lim_{e_0+i_0=0, N_0\to\infty} N_{n+1}N_n^{-1} = 1.$$

According to Equation (9), the reproductive rates $\tilde{\rho}_0, \tilde{\rho}_0(\delta_T)$ calculated in the Markovian setting or the semi-Markovian one are generally not equivalent. But Δ_2 being independent of the infection probabilities, we may determine T_{R^c} by $\Delta_2 = 0$, which leads to the same qualitative behavior in the two models, whatever the infection probabilities. We get $T_{R^c} = [(M(0))^T(1 - P_a^{E,R})^{-T} - 1](1 - P_a^{E,R})[\tilde{m}(1 - P_{b,mE}^{S,R})]^{-1}$ (see Section A.4).

3.2. Asymptotic Behavior of the Disease (See Section A.5)

In a linear model such as $(e_n, i_n) = (e_{n-1}, i_{n-1})M$, if the largest eigenvalue λ of M satisfies $\lambda < 1$, then for any value of $e_0 + i_0$, $\lim_n(e_n, u_n) = (0, 0)$ since $(e_n, i_n) = (e_0, i_0)M^n$, which implies $(e_n, i_n)u = (e_0, i_0)M^{n-1}Mu = (e_0, i_0)M^{n-1}\lambda u = \cdots = (e_0, i_0)\lambda^n u$, where $u = (u_1, u_2)^t$ is the right eigenvector of M associated to λ. But this property is no more checked in a nonlinear model, and for $\lambda < 1$, where λ is the largest eigenvalue of the system linearized at (0, 0), we get only the local stability of the healthy state (0, 0), which means that the disease dies out only when starting from a sufficiently low level of the current infection. Since this level is unknown and, moreover, the animals in incubation are nonobserved, the extinction of the disease is predicted in a sure way if the healthy state is globally asymptotically stable,[10] that is, the extinction of the disease occurs whatever the initial level of infection. But this property is generally difficult to obtain analytically in nonlinear models. In this section, we give some sufficient conditions leading to this property, which are derived from the properties of the current reproductive rate.

From now on let us assume $P_a^{I,R} = 1$, and denote $\tilde{\rho}_0$ instead of $\tilde{\rho}_0(\delta_T)$ since we assumed their equality ($\Delta_2 = 0$). Let us recall that $\tilde{\rho}_0$ is given by Equation (5), $g(i_n)$ is given by Equation (1). Let us denote $D = \gamma_I - \gamma_S$, $i_{M,0} = P_a^{E,I} D^{-1}$, and let us define some simplified functions of the reproductive rate:

$$\tilde{r}_1(i) = (g(i) - i\,D)(1 - i) - \tilde{m}b(i)iq\left(1 - P_{b,mI}^{S,R}\right) \quad (11)$$

$$\tilde{r}_2(i) = g(i) - i\,D \quad (12)$$

$$\tilde{\rho}_1 = \lim_{i\to 0} \tilde{r}_1(i)i^{-1} = g'(0) - D - \tilde{m}q\left(1 - P_{b,mI}^{S,R}\right) \quad (13)$$

$$\tilde{\rho}_2 = \lim_{i\to 0} \tilde{r}_2(i)i^{-1} = g'(0) - D. \quad (14)$$

We have $\tilde{\rho}_2 \geq \tilde{\rho}_1 \geq \tilde{\rho}_0$ with equality only in a closed population (which is not the case in the BSE setting since the spread of the disease takes a much longer time than the birth frequency).

PROPOSITION 1: *Assume* $g(\cdot) = 0$ (*no transmission of the horizontal type). Then the extinction is guaranteed in both models starting from any level of the epidemic (global asymptotic stability of* (0,0)*) and the sequence* $\{e_n + i_n\}_n$ *of the total proportion of infected animals at each time, is decreasing to* 0.

This result shows that the only vertical transmission always leads to the extinction of the epidemic.

Let $f''(i)$ and $f'''(i)$ denote the respective second and third derivatives at i of any function $f(i)$.

PROPOSITION 2: *Assume $g(\cdot) \neq 0$ (there exists a transmission of the horizontal type). Then in both models*

1. *if $\tilde{\rho}_0 > 0$, the disease is endemic ((0,0) is unstable implying that the extinction is not possible*);
2. *if $\tilde{\rho}_0 < 0$, the disease dies out when starting from a very (unknown) low level of the epidemic ((0, 0) is (locally) asymptotically stable)*;
3. *if $\tilde{\rho}_1 < 0$ with $\tilde{r}_1'''(\cdot) \geq 0$, or if $\tilde{\rho}_2 < 0$ with either $g''(\cdot) \leq 0$ or $g'''(\cdot) \geq 0$, then the disease dies out when starting from any level of the epidemic ((0,0) is globally asymptotically stable) and $\{e_n + i_n\}_n$ is decreasing to 0).*

Conditions $g''(\cdot) \leq 0$, $g'''(\cdot) \geq 0$, and $\tilde{r}_1'''(\cdot) \geq 0$ are satisfied when $\bar{a}(i) = 1 - a^i$ and $\bar{b}(i) = 1 - b^i$, for any values of all parameters, or when $\bar{b}(i) = 1 - b^i$ with $\bar{a}(\cdot)$ modeled by the sigmoid function $(1 - c * a^i)^l$, $c \in (0, 1)$, $a \in (0, 1)$, $l \geq 2$ depending on the values of b and of the other parameters.

The second item of Proposition 2 is valid only when $e_0 + i_0$ is small enough. But since the proportion e_0 of animals in incubation is unobservable and, moreover, much larger than i_0, this result is not sufficient for ensuring the future extinction of the disease based on the only observation of a low level of the infectives. The third item of Proposition 2 and the following proposition give sufficient conditions ensuring this extinction starting from any value of (e_0, i_0).

Let us define $r(i) = -a(i)(1 - i\,T_{R^c}) + (1 - i)(1 - i\,i_{M,0}^{-1})$. Then $r(\cdot)$ has the same sign as the current reproductive rate under $\bar{a}(\cdot) = \bar{b}(\cdot)$.

PROPOSITION 3: *Assume the Markovian model. Assume $\bar{a}(\cdot) = \bar{b}(\cdot)$ (identical exposure/susceptibility for the calves and the adults) with either $r'''(i) > 0$ or $r''(i) < 0$, for all $i \in]0, i_{M,0}[$. Then, for $P_{b,mI}^{S,R} \simeq 1$,*

1. *if $\tilde{\rho}_0 < 0$, the disease dies out when starting from any level of the epidemic ((0,0) is globally asymptotically stable*);

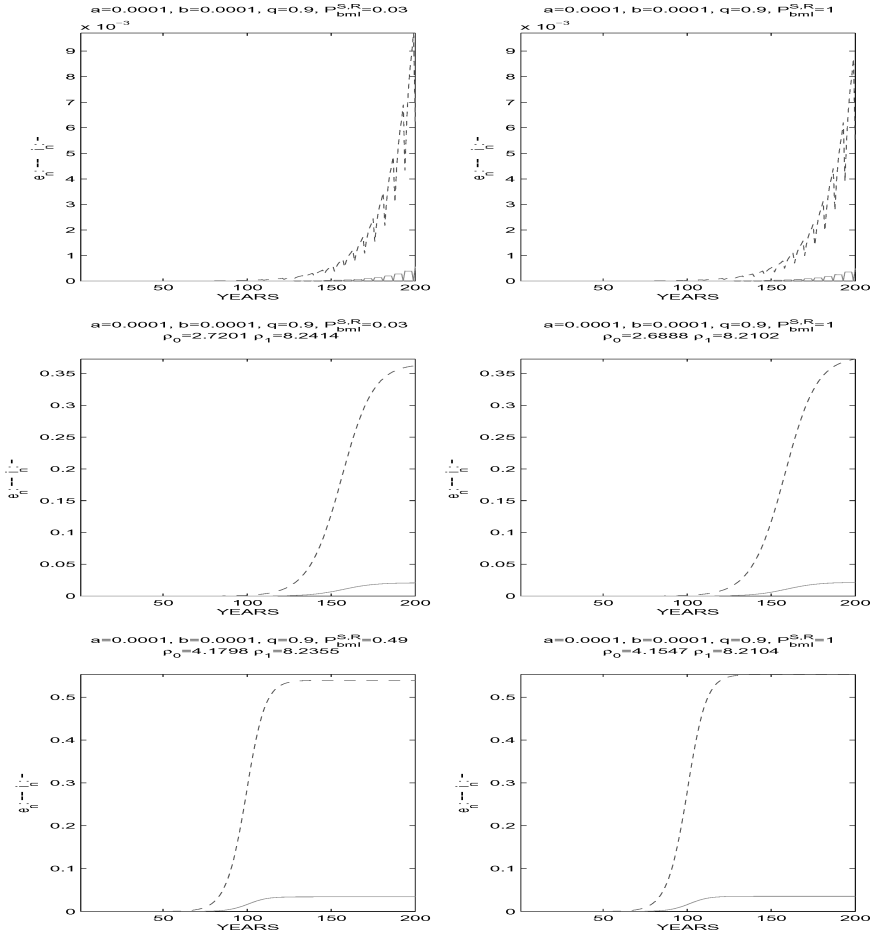

Fig. 3. For $a = b = 0.0001$, the disease persists both in Great Britain and in France, with a higher level in France than in Great Britain.

2. *if* $\tilde{\rho}_0 > 0$, *the disease is endemic with an asymptotic stationary law for any value of* $e_0 + i_0$ *provided that* $e_0 + i_0 \neq 0$ (*there exists a unique equilibrium point and it is globally asymptotically stable from any* $(e_0, i_0) \neq (0, 0)$).

The condition $r'''(i) > 0$ is satisfied at least for $\bar{b}(i) = \bar{a}(i) = 1 - a^i$, for any values of the parameters involved in $r'''(\cdot)$.

4. SIMULATIONS

Consider simulations under either the French routine slaughtering conditions or the British ones, all other conditions, $\bar{a}(\cdot)$, $\bar{b}(\cdot)$, $\bar{q}$, T_{R^c}, $M(0)$, being identical in both countries. Let in addition the following assumptions:

- We assume $P_a^{I,R} = 1$ since the duration of the clinical state is at most several months and that of the infectious incubation period is of order 6 months.
- We assume either $P_{b,mI}^{S,R} = P_{b,mS}^{S,R}$ (routine slaughtering for all calves) or $P_{b,mI}^{S,R} = 1$ (slaughtering of the calf the mother of which is infectious). Notice that this implies $P_a^{E,I} < D$ i.e., $i_{M,0} < 1$.
- Denoting $S_{a'}$ the probability for an apparently healthy animal to survive at age $A \geq a'$, the probability $1 - P_{b,mS}^{S,R}$ of surviving 1 year more for a calf the mother of which is infectious is equal to S_1/S_0, and the probability $1 - P_{a'}^{S,R}$ of surviving 1 year more for an adult aged a' is similarly $S_{a'+1}/S_{a'}$. Consequently, the probability $1 - P_a^{S,R}$ of surviving 1 year more for an adult is estimated by the expectation $E_A(S_A/S_{A-1}) \overset{def.}{=} \sum_{a' \geq 2} \times (S_{a'}/S_{a'-1})(S_{a'} - S_{a'+1})][\sum_{a' \geq 2}(S_{a'} - S_{a'+1})]^{-1}$ (equal to $S_{a'}/S_{a'-1}$, for all $a' \geq 1$ if $\{S_{a'}\}_{a' \geq 1}$ is exponential). We use estimates of the survival probabilities $\{S_a\}$ produced in Reference 4, which leads to $P_a^{S,R} = 0.3127$, $P_{b,mS}^{S,R} = 0.03$ in

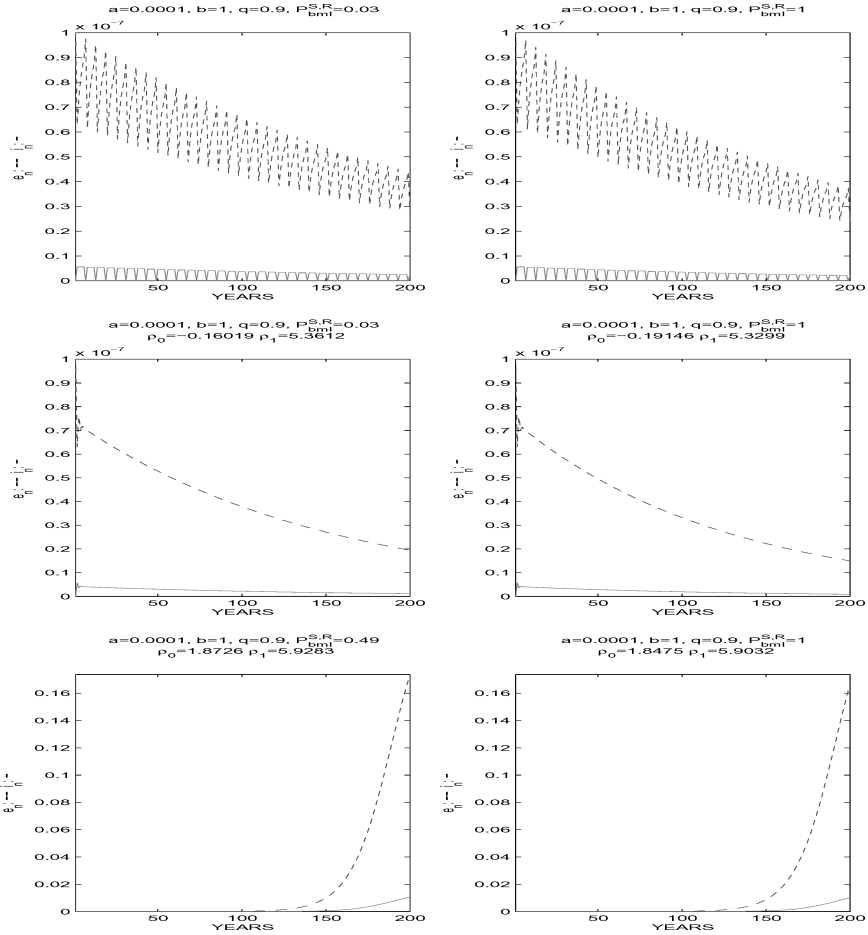

Fig. 4. For $a = 0.0001$, $b = 1$ (the calves cannot be infected via a horizontal route), the disease dies out in Great Britain (first two lines of graphs) while it persists in France (third line). The control slaughtering $P_{b,mI}^{S,R} = 1$ of the calves with infectious mothers has not a significant effect (right-hand graphs) with respect to the routine slaughtering of these calves (left-hand graphs).

Great Britain, and $P_a^{S,R} = 0.2505$, $P_{b,mS}^{S,R} = 0.49$ in France.

- We set the mean number $\tilde{m}$ of calves per dam each year in order to get a stable total size of the population in each country when this population is healthy, that is, $M(0) = 1$, which is equivalent to $\tilde{m} = P_a^{S,R}(1 - P_{b,mS}^{S,R})^{-1}$. This leads to the estimations $\widehat{\tilde{m}} = 0.32239$ in Great Britain and $\widehat{\tilde{m}} = 0.49118$ in France.
- Using (24) and the estimations of the British dynamical parameters, we get $\widehat{T_{R^e}} = 12.1346$, and then using $T_{R^e} = [P_a^{E,I}(1 - P_a^{E,R})^{-1}]^{-1}$, we get the estimations of $P_a^{E,I}$ under the British conditions and the French ones, leading to $\widehat{P_a^{E,I}} = 0.0566$ in Great Britain and $\widehat{P_a^{E,I}} = 0.0618$ in France.
- Concerning the infection probabilities, we set $\bar{q} = 0.1$, which is the maximum reasonable vertical infection probability usually assumed in BSE,[7] and we assume $\bar{a}(i) = 1 - a^i$, $\bar{b}(i) = 1 - b^i$. The values of a and b are chosen for showing different levels of infection and therefore different types of behavior, but since they are not estimated from data, they do not correspond to real situations.
- We assume the same initial conditions in all the simulations: $P_0^I = 0$ and $P_0^E = 10^{-7}$, with in addition $P_{-4}^{E_1} = P_{-3}^{E_1} = P_{-2}^{E_1} = P_{-1}^{E_1} = P_0^{E_1} = 3.693710^{-8}$ in the semi-Markovian setting (identical infection for each of the 5 years before the occurrence of the first case). The number of simulated years is 200.

In each figure, the first two lines of graphs correspond to the British conditions, the first line being relative to the semi-Markovian frame, and the second one to the Markovian frame. The third line corresponds to the French conditions in the Markovian frame. On each line, the left-hand graph corresponds to the routine slaughtering $P_{b,mI}^{S,R} = P_{b,mS}^{S,R}$ of the calf the dam of which is infectious, and the right-hand

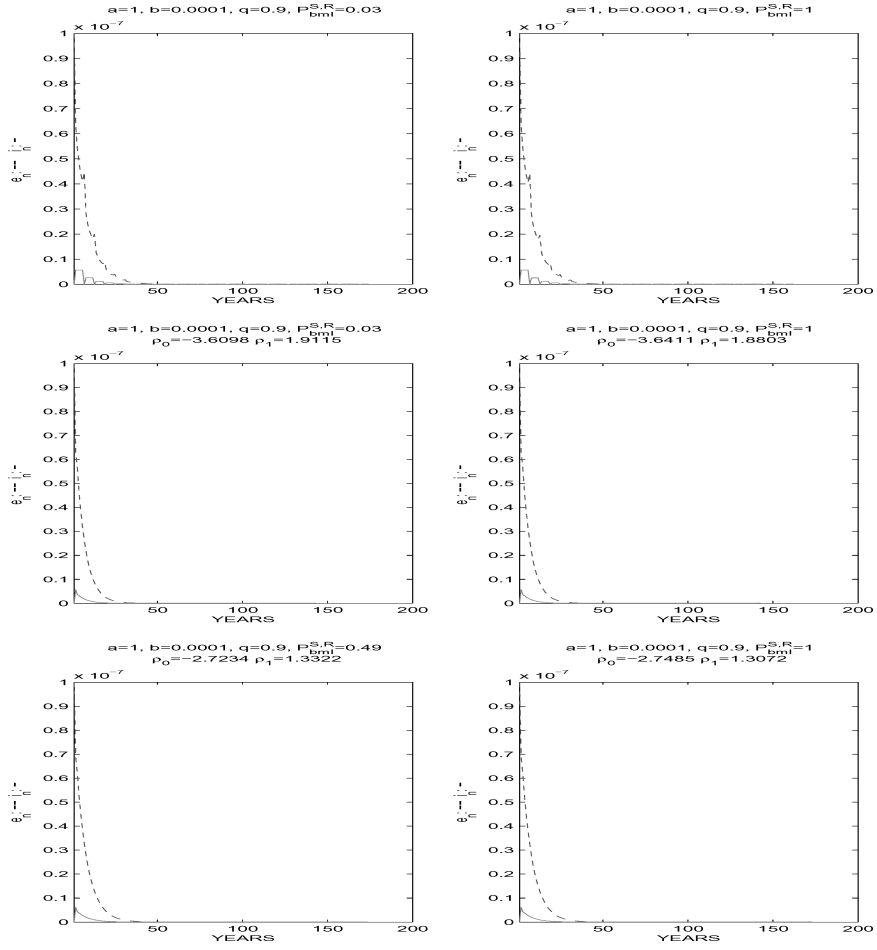

Fig. 5. For $a = 1$, $b = 0.0001$ (the adults cannot be infected), the disease dies out rapidly in Great Britain and in France. Comparing this figure to Fig. 4, we deduce that infection of the adults is much more essential than that of the calves for persistence of the disease.

graph concerns the control slaughtering $P_{b,mI}^{S,R} = 1$. In each graph, $\{e_n\}_{n\leq 200}$ is represented by a dashed line and $\{i_n\}_{n\leq 200}$ is represented by a continuous line. Above each graph in the Markovian setting, the value of $\tilde{\rho}_0$ and $\tilde{\rho}_1$ are given. Since we assume for these simulations $M(0) = 1$, then $\text{sign}(\tilde{\rho}_0) = \text{sign}(R_0)$.

Some interesting general features are highlighted by the simulations. The general tendency of the spread of the disease in the semi-Markovian setting is similar to that in the Markovian setting, but its rate of increase or decrease may be slightly different from the rate in the Markovian frame and oscillations due to the incubation distribution (dirac law) exist in the semi-Markovian setting (first line of graphs for each figure) contrary to the Markovian one. The results of global stability under $\bar{a}(\cdot) = \bar{b}(\cdot)$, which means that the disease tends to a constant level independent of the initial infection, seem to be generalizable to $\bar{a}(\cdot) \neq \bar{b}(\cdot)$. The E individuals are much more numerous than the infectives; the systematic slaughtering of calves of infectious dams has generally a negligible influence on the spread of the disease. It may lead to extinction only when the infection via a horizontal route is low enough, especially concerning the adults (Figs. 6 and 7). The routine slaughtering has a very large influence on the behavior of the disease, leading to a much easier spread of the disease under the French conditions than the English ones, when assuming in both countries the same infection parameters a, b, q, and the same value of T_{R^c}. Since this result is valid even when $a = 1$ with $b \neq 1$ or $b = 1$ with $a \neq 1$, i.e., as soon as some horizontal route exists, we conclude that its main cause is the fact that the probability to achieve the transition $E \to I$ is larger in France than in Great Britain, which is due to a smaller value of $P_a^{E,R}$ in France than in Great Britain. The adult infection parameter a has a much larger influence than the young one (Fig. 4 compared to Fig. 5). In particular, when $a = 1$ (no possible infection of the adults), the increase

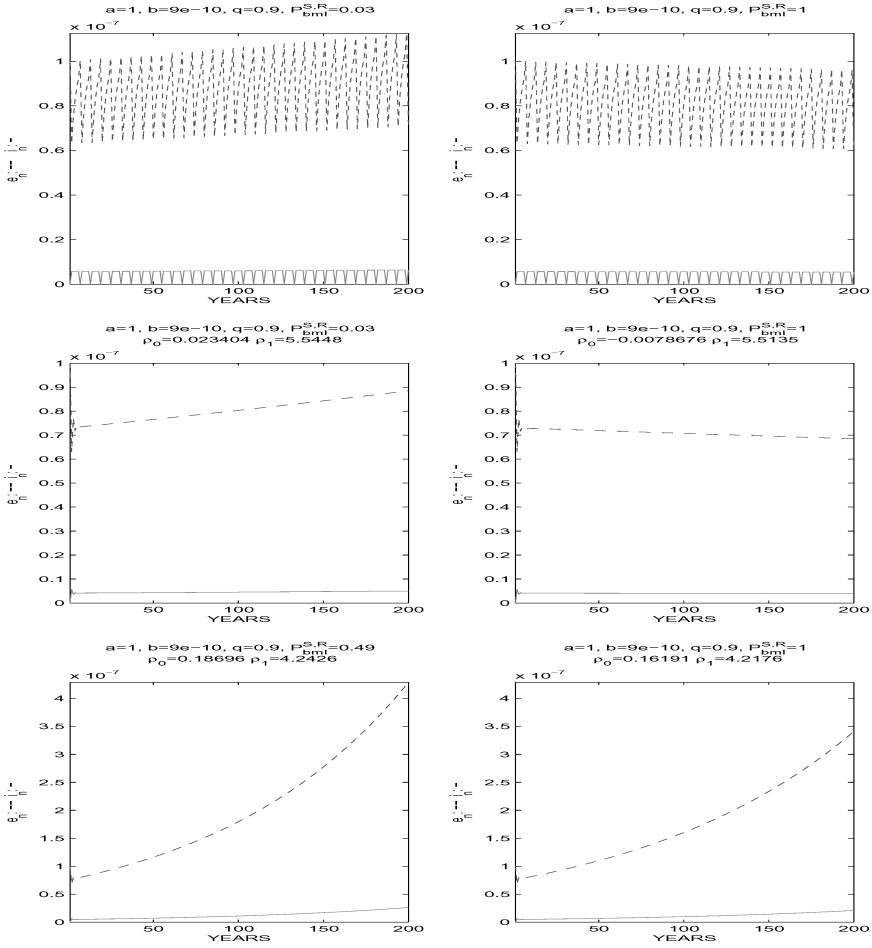

Fig. 6. For $a = 1, b = 9\,10^{-10}$ (an adult cannot be infected and the probabilty for a calf to be infected via a horizontal route is much greater here than in Fig. 5), the disease persists in Great Britain under the usual slaughtering $P_{b,mI}^{S,R} = P_{b,mS}^{S,R}$ of the calves (left graphs of the first two lines of graphs) and dies out under the control slaughtering $P_{b,mI}^{S,R} = 1$ (right-hand graphs of the first two lines of graphs), while it always persists in France (last line of graphs).

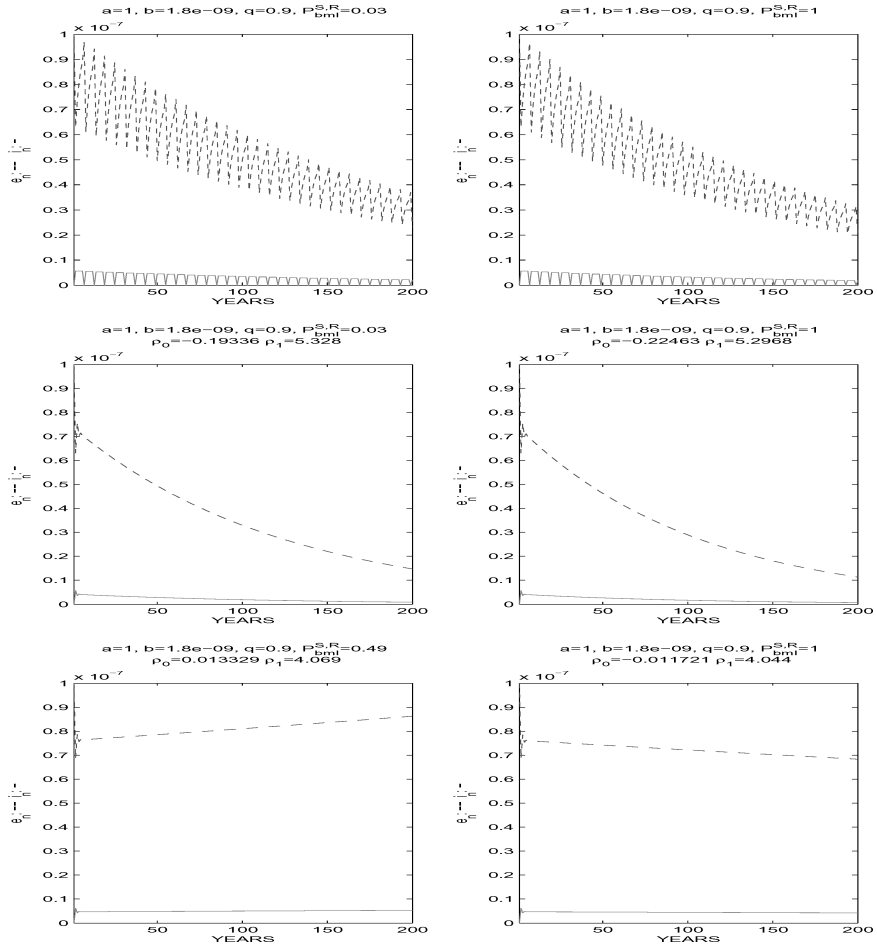

Fig. 7. For $a = 1$, $b = 1.8\,10^{-9}$ (an adult cannot be infected and the probability for a calf to be infected via a horizontal route is a bit smaller here than in Fig. 6), the disease dies out in Great Britain; it persists in France under the usual slaughtering $P^{S,R}_{b,mI} = P^{S,R}_{b,mS}$ and dies out very slowly under the control slaughtering $P^{S,R}_{b,mI} = 1$. The number of cases seems almost constant in both cases in France.

of the disease is possible in Great Britain only for $b \leq 9\,10^{-10}$ (Fig. 6) while in France it is possible for $b \leq 1.8\,10^{-9}$ (Fig. 7), which is around twice the British value. When there is no horizontal route or this one is very weak (Fig. 5), the disease dies out very quickly.

Notice that the same qualitative results are obtained assuming an identical $\tilde{m} = 0.37$ in both countries, which leads to a slowly increasing population size in Great Britain and a slowly decreasing population size in France.[1] But in this case, R_0 is not equivalent to the bifurcation parameter ρ_0.

5. CONCLUSIONS

We built a rigorous methodology allowing the study and the comparison of the potential spread of the disease at the scale of countries under different slaughtering conditions. We rigorously defined the reproductive rate behaving like a bifurcation parameter, allowing us to predict endemicity or extinction of the disease according to its sign. We also proved that this reproductive rate is equivalent to the classical reproductive ratio R_0 defined as the total number of secondary cases produced by an infective in a susceptible population[11,12] if and only the population size remains stable. This result is due to the fact that proportions instead of numbers are modeled.

Using this methodology, we showed that routine slaughtering may have an important influence on the spread of the disease, the French conditions being much more favorable to the spread of the disease than the British ones, this result being due to a smaller value of $P^{E,R}_a$ in France than in Great Britain, leading to a larger value of the probability $P^{E,I}_a$ to become infectious when infected in France than in Great Britain. Under the same infection conditions, the French routine slaughtering may lead to endemicity while the English ones lead to extinction. The control slaughtering of a calf the dam of which is infectious has generally a negligible effect, leading to a very slow extinction of the disease only when the disease when noncontrolled is already close to this extinction. The number

of animals in a noninfectious stage of incubation is much larger than the number of infectious animals, especially the equilibrium value of the first population is much larger (when nonnull) than the second one. This is due to slaughtering, which embeds a large proportion of animals in incubation to become infectious. The maternal transmission when alone always leads to a very rapid extinction but as soon as some horizontal route exists, the apparent nonincreasing number of observed cases in some countries for a given period of time is not a guarantee of the extinction of the epidemic.

APPENDIX

A.1. Transmission Probability Under the Reed-Frost Assumption

Let N_n^I be the number of infectives at time n, $\widehat{i_n} = N_n^I N_n^{-1}$, be the proportion of infectives at this time. Let γ be the expected number of infectious doses produced by an infectious animal either by excretion when alive or contained in the animal when dead, where an infectious dose is is defined here as the minimum amount of pathogenic agents such that the probability for an animal ω to become infectious after eating such a dose is is nonnull. Assuming (Reed-Frost assumption) that the events $\{\omega \textit{ is not infected by a dosis } d\}_d$ are mutually independent and have each the same probability given the survival of ω at $n+1$, we get at time $n+1$,

$$\begin{aligned} a(\widehat{i_n}) &\overset{definition}{=} P(\omega \textit{ is not infected by } \gamma N_n^I \mid \omega \\ &\qquad \textit{survives at } n+1) \\ &\overset{assumption}{=} (1 - P(\omega \textit{ is infected by a dosis} \mid \omega \\ &\qquad \textit{survives at } n+1))^{\gamma N_n^I} \\ &\overset{assumption}{=} \left(1 - \phi N_n^{-1}\right)^{\gamma \widehat{i_n} N_n} \\ &\overset{large\ N_n}{\simeq} \exp(-\phi\gamma\widehat{i_n}) = a^{\widehat{i_n}}, \end{aligned}$$

where $\ln a = -\phi\gamma < 0$ and therefore $0 < a < 1$, and similarly for $b(\cdot)$.

A.2. Elaboration of the Models[9]

Let us first consider the Markovian setting (the distributions of the times of transition are all geometric (corresponding to exponential distributions in continuous time)). The dynamical system on the probabilities $\vec{P}_n = (s_n, e_n, i_n)$ for an animal to be in S, E, and I is derived from a Markovian density-dependent branching process on the corresponding countings $\vec{N_n} = (N_n^I, N_n^E, N_n^I)$[9]: for $k \in \{S, E, I\}$,

$$N_n^k = \sum_{h \in \{S,E,I\}} \sum_{i=1}^{N_n^h} Y_{n+1,i}^{h,k}$$

$$\begin{aligned} E\left(Y_{n+1,i}^{h,k} \mid \vec{N}_n\right) &= P_a^{h,k}(\widehat{i_n}) + \tilde{m} P_b^{h,k}(\widehat{i_n}) \\ &\overset{notation}{=} Q^{h,k}(\widehat{i_n}), h \in \{S, E, I\}, \end{aligned}$$

where $Y_{n+1,i}^{h,k}$ is the number of animals in state k "produced" at time $n+1$, i.e., during the year $n+1$, by the animal i in state h at n, $\tilde{m}$ is the mean number of calves at birth per year and per cow, assumed to be independent of the state of the dam and of time, $P_a^{h,k}(\widehat{i_n})$ is the probability for an "adult" (animal existing at the previous time) to realize the transition $h \to k$, assumed to depend only on the percentage $\widehat{i_n} = N_n^I / N_n$ of infectives at n, and $P_b^{h,k}(\widehat{i_n}) = P_{b,mh}^{S,k}(\widehat{i_n})$ (see Section 2.1) is the probability for a calf with mother in state h for becoming k, also assumed to depend only on $\widehat{i_n}$.

Then using the transition probabilities given in Section 2.2, normalizing the branching process by the total size N_n of the population at each time in order to get the proportions of animals in each state, we get the limit model on probabilities, as $N_0 \to \infty$:

$$\begin{aligned} M(i_n)s_{n+1} &= s_n Q^{S,S}(i_n) + e_n Q^{E,S}(i_n) + i_n Q^{I,S}(i_n) \\ M(i_n)e_{n+1} &= s_n Q^{S,E}(i_n) + e_n Q^{E,E}(i_n) + i_n Q^{I,E}(i_n) \\ M(i_n)i_{n+1} &= s_n Q^{S,I}(i_n) + e_n Q^{E,I}(i_n) + i_n Q^{I,I}(i_n), \end{aligned}$$

where

$$\begin{aligned} M(i_n) &= \lim_{N_0 \to \infty} N_{n+1} N_n^{-1} \\ &= 1 - P_a^{S,R} + \tilde{m}\left(1 - P_{b,mS}^{S,R}\right) + i_n\left[P_a^{S,R} - P_a^{I,R}\right. \\ &\quad \left. + \tilde{m}\left(P_{b,mS}^{S,R} - P_{b,mI}^{S,R}\right)\right] \\ &= 1 + \tilde{m} - \gamma_S - i_n(\gamma_I - \gamma_S). \end{aligned} \tag{A.1}$$

Therefore, using the assumptions on $\{P_a^{h,k}(i_n)\}$ and $\{P_b^{h,k}(i_n)\}$ (Section 2.1),

$$\begin{aligned} M(i_n)s_{n+1} = s_n\left[a(i_n)\left(1 - P_a^{S,R}\right) + \tilde{m}b(i_n)\left(1 - P_{b,mS}^{S,R}\right)\right] \\ + e_n\left[\tilde{m}b(i_n)\left(1 - P_{b,mE}^{S,R}\right)\right] \\ + i_n\left[\tilde{m}qb(i_n)\left(1 - P_{b,mI}^{S,R}\right)\right] \end{aligned} \tag{A.2}$$

$$M(i_n)e_{n+1} = s_n\big[\bar{a}(i_n)\big(1 - P_a^{S,R}\big) + \tilde{m}\bar{b}(i_n)(1 - P_{b,mS}^{S,R})\big] + e_n\big[1 - P_a^{E,R} - P_a^{E,I}\tilde{m}\bar{b}(i_n)\big(1 - P_{b,mE}^{S,R}\big)\big] + i_n\big[\tilde{m}(1 - qb(i_n))\big(1 - P_{b,mI}^{S,R}\big)\big] \quad \text{(A.3)}$$

$$M(i_n)i_{n+1} = e_n P_a^{E,I} + i_n\big(1 - P_a^{I,R}\big). \quad \text{(A.4)}$$

Since $s_{n+1} + e_{n+1} + i_{n+1} = 1$, the system given by Equations (A.2), (A.3), and (A.4) is equivalent to the system given by Equations (A.3), and (A.4) when $M(i_n) > 0$:

$$(e_{n+1}, i_{n+1}) = F(e_n, i_n) = (F_1(e_n, i_n), F_2(e_n, i_n)).$$

We have $M(i_n) = 0$ if and only if $\gamma_I = 1 + \tilde{m}$ (i.e., $P_a^{I,R} = 1$ and $P_{b,mI}^{S,R} = 1$), with $i_n = 1$, which never occurs when $i_0 + e_0 < 1$.[1] Therefore, the system is always defined under $i_0 + e_0 < 1$.

Now assume the semi-Markovian setting. We elaborate the model in the same way as previously using the intermediate states $\{E_j\}_{j \le T}$ such that the transition from S to I is now obtained by the sequence of transitions $S \to \mathrm{E}_1 \to \cdots \to E_T \to I$, where E_j corresponds to the jth time in the incubation state. We assume $P_a^{E_j,E_{j+1}} = 1 - P_a^{E_j,R} = 1 - P_a^{E,R}$, $j \le T - 1$, and $P_a^{E_T,I} = 1 - P_a^{E_T,R} = 1 - P_a^{E,R}$. This implies that $P_a^{E_j,E_j} = 0$, $j \le T$, and the probability to achieve the transition $E_1 \to I$ for an E_1 animal, is the probability $(1 - P_a^{E,R})^T$ that it survives during T time units from the state E_1. So now the state variable of the dynamical system is $(\vec{e}_n, i_n)$, where $\vec{e}_n = (e_n^1, \ldots, e_n^T)$, e_n^j being the probability for an animal to be in E_j at time n. We get:

$$M(i_n)s_{n+1} = s_n Q^{S,S}(i_n) + \sum_{j'=1}^{T} e_n^{j'} Q^{E_{j'},S}(i_n) + i_n Q^{I,S}(i_n)$$

$$M(i_n)e_{n+1}^{j} = s_n Q^{S,E_j}(i_n) + \sum_{j'=1}^{T} e_n^{j'} Q^{E_{j'},E_j}(i_n) + i_n Q^{I,E_j}(i_n)$$

$$M(i_n)i_{n+1} = s_n Q^{S,I}(i_n) + \sum_{j'=1}^{T} e_n^{j'} Q^{E_{j'},I}(i_n) + i_n Q^{I,I}(i_n).$$

A.3. Bifurcation

In the Markovian setting (all the transitions, including $E \to I$, are Markovian), let λ be the largest eigenvalue of the derivative L at 0 of $F(x, y)$:

$$L \overset{def.}{=} \begin{pmatrix} \frac{\partial F_1}{\partial e}(0,0) & \frac{\partial F_1}{\partial i}(0,0) \\ \frac{\partial F_2}{\partial e}(0,0) & \frac{\partial F_2}{\partial i}(0,0) \end{pmatrix} = \frac{1}{M(0)} \begin{pmatrix} P_a^{E,E} & CC \\ P_a^{E,I} & 1 - P_a^{I,R} \end{pmatrix},$$

where

$$CC \overset{def.}{=} M(0)\frac{\partial F_1}{\partial i}(0,0) = \bar{a}'(0)\big(1 - P_a^{S,R}\big) + \tilde{m}\bar{b}'(0)\big(1 - P_{b,mS}^{S,R}\big) + \tilde{m}\bar{q}\big(1 - P_{b,mI}^{S,R}\big)$$

represents the infection capacity when the disease starts (mean number of newly infected animals produced by an infective per time unit). We get:

$$\lambda = [2M(0)]^{-1}\big[P_a^{E,E} + 1 - P_a^{I,R} + \sqrt{\big(P_a^{E,E} - \big(1 - P_a^{I,R}\big)\big)^2 + 4CCP_a^{E,I}}\big].$$

Then, according to $\mathrm{sign}(\lambda - 1)$, the healthy state $(0, 0)$ is either locally asymptotically stable or unstable.[10]

Now let $C_n = e_n + i_n$ and define the current reproductive rate by:

$$\rho(i_n) = (c_{n+1} - c_n)i_n^{-1} \text{ under the condition } i_{n+1} = i_n = (e_{n+1} - e_n)i_n^{-1} \text{ under the condition } i_{n+1} = i_n$$

and the initial reproductive rate by:

$$\rho_0 = \lim_{i_0 \to 0, i_1 = i_0} \rho(i_0) = \lim_{i_0 \to 0, i_1 = i_0} (e_1 - e_0)i_0^{-1},$$

which, according to Equation (A.4), is equivalent to:

$$\rho_0 = \lim_{i_0 \to 0, e_0 = l(i_0)} (e_1 - e_0)i_0^{-1}$$

$$l(i_0) = i_0\big[M(i_0) - \big(1 - P_a^{I,R}\big)\big]\big[P_a^{E,I}\big]^{-1}.$$

Then $\rho_0 = [M(0)]^{-1}(CC - SC)$, where $SC = [P_a^{I,R} - P_a^{S,R} + \tilde{m}(1 - P_{b,mS}^{S,R})][1 + \tilde{m}(1 - P_{b,mE}^{S,R})[P_a^{E,I}]^{-1}]$. In the particular case of a stable population size ($M(0) = 1 \iff \tilde{m} = P_a^{S,R}\big(1 - P_{b,mS}^{S,R}\big)^{-1}$), SC becomes $SC = P_a^{I,R}\big(1 - P_a^{S,R}\big)^{-1}(1 + P_a^{S,R}(T_{R^c} - 1))$. Of course, ρ_0 is function of λ. Using

$$\sqrt{\big(P_a^{E,E} - \big(1 - P_a^{I,R}\big)\big)^2 + 4CCP_a^{E,I}} = 2M(0)\lambda - \big(P_a^{E,E} + 1 - P_a^{I,R}\big)$$

and the assumption $P_a^{E,R} = P_a^{S,R}$, $P_{b,mE}^{S,R} = P_{b,mS}^{S,R}$, we get:

$$\mathrm{sign}(\rho_0) = \mathrm{sign}(\lambda - 1).$$

Let us calculate now the classical reproductive number R_0, which is defined for a starting epidemic. Consider the linearized system at $(0, 0)$ and write this

system on countings $\{E_n, I_n\}_n$ instead of probabilities. Define $E_n = N_n e_n$, $I_n = N_n i_n$. Then for $E_0 + I_0$ small enough, we have, using Taylor's development at order one, $(E_1, I_1) = M(i_0)(F_1(E_0, I_0), F_2(E_0, I_0)) \simeq (E_0, I_0)M(0)L^t$, that is:

$$E_1 \simeq P_a^{E,E}E_0 + CCI_0$$
$$I_1 \simeq P_a^{E,I}E_0 + \left(1 - P_a^{I,R}\right)I_0.$$

Then using this model, we get:

$$R_0 = \left[CC\sum_{k\geq 0}(k+1)\left(P_a^{I,I}\right)^k P_a^{I,R}\right] \times \left[\sum_{k\geq 0}\left(P_a^{E,E}\right)^k P_a^{E,I}\right]$$

since CC represents the mean number of newly infected animals produced by one infective during a time unit, $\sum_{k\geq 0}(k+1)(P_a^{I,I})^k P_a^{I,R}$ is the mean life duration of an infective (equal to 1 when $P_a^{I,R} = 1$), and $\sum_{k\geq 0}(P_a^{E,E})^k P_a^{E,I}$ represents the mean number of infectives resulting from one newly infected animal. Using $\sum_{k\geq 0}(k+1)c^k = [c\sum_{k\geq 0}c^k]'$, $\sum_{k\geq 0}c^k = (1-c)^{-1}$, for $c \in [0, 1[$, $1 - P_a^{E,E} = P_a^{E,I} + P_a^{E,R}$, and $P_a^{I,I} = 1 - P_a^{I,R}$, we get:

$$R_0 = \frac{P_a^{E,I}}{P_a^{I,R}\left(P_a^{E,I} + P_a^{E,R}\right)}CC$$

and therefore:

$$R_0 - 1 = \frac{P_a^{E,I}}{P_a^{I,R}\left(P_a^{E,I} + P_a^{E,R}\right)}(CC - SC_{R_0}), \quad \text{(A.5)}$$

where $SC_{R_0} = P_a^{I,R}(P_a^{E,I} + P_a^{E,R})(P_a^{E,I})^{-1}$. The sign of $R_0 - 1$ has to be compared to the sign of ρ_0, which is equal to the sign of $CC - SC$. Let

$$\Delta = SC - SC_{R_0} = \frac{\left[P_a^{I,R} - P_a^{S,R} + \tilde{m}\left(1 - P_{b,mS}^{S,R}\right)\right]\left[P_a^{E,I} + \tilde{m}\left(1 - P_{b,mE}^{S,R}\right)\right] - P_a^{I,R}\left(P_a^{E,I} + P_a^{E,R}\right)}{P_a^{E,I}}. \quad \text{(A.6)}$$

Then using Equations (5), (A.5), and (A.6), we get:

$$R_0 - 1 = \frac{P_a^{E,I}}{P_a^{I,R}\left(P_a^{E,I} + P_a^{E,R}\right)}[M(0)\rho_0 + \Delta] = C_2\rho_0 + \frac{P_a^{E,I}}{P_a^{I,R}\left(P_a^{E,I} + P_a^{E,R}\right)}\Delta$$
$$C_2 = M(0)\frac{P_a^{E,I}}{P_a^{I,R}\left(P_a^{E,I} + P_a^{E,R}\right)}.$$

Using $P_a^{E,R} = P_a^{S,R}$ with $P_{b,mE}^{S,R} = P_{b,mS}^{S,R}$, and defining $\mu = M(0) - 1 = -P_a^{S,R} + \tilde{m}\left(1 - P_{b,mS}^{S,R}\right)$, we get:

$$\Delta = \frac{\mu\left(\mu + P_a^{E,I} + P_a^{S,R} + P_a^{I,R}\right)}{P_a^{E,I}}. \quad \text{(A.7)}$$

We have $\mu + P_a^{E,I} + P_a^{S,R} + P_a^{I,R} = \tilde{m}\left(1 - P_{b,mS}^{S,R}\right) + P_a^{E,I} + P_a^{I,R} > 0$. Therefore, we have $\text{sign}(\Delta) = \text{sign}(\mu)$ with $\Delta = 0$ if and only if $\mu = 0$.

In the semi-Markovian setting the usual bifurcation parameter is calculated in the same way as previously as the largest eigenvalue $\lambda(\delta_T)$ of $L(\delta_T)$, which is the derivative at 0 of $G(\vec{e}, y)$:

$$L(\delta_T) = \begin{pmatrix} \frac{\partial G_1}{\partial e^1}(0,0) & \dots & \frac{\partial G_1}{\partial i}(0,0) \\ \dots & & \dots \\ \frac{\partial G_{T+1}}{\partial e^1}(0,0) & \dots & \frac{\partial G_{T+1}}{\partial i}(0,0) \end{pmatrix}.$$

The first line of $M(0)L(\delta_T)$ is $(\tilde{P}_a^{E,E}, \dots, \tilde{P}_a^{E,E}, CC)$, the diagonal below the main diagonal is $(\tilde{P}_a^{E,I}, \dots, \tilde{P}_a^{E,I})$, and the term at the intersection of the last line and last column is $1 - P_a^{I,R}$, where $\tilde{P}_a^{E,I} = 1 - P_a^{E,R}$ and $\tilde{P}_a^{E,E} = 1 - \tilde{P}_a^{E,I} - P_a^{E,R} = 0$; the other terms of the matrix are null. We get:

$$[\lambda(\delta_T)]^T\frac{\left(1 - P_a^{I,R}\right)}{m - \gamma_S} - [\lambda(\delta_T)]^{T+1} + CC\frac{\left(1 - P_a^{E,R}\right)^T}{(m - \gamma_S)^{T+1}} = 0,$$

which has generally no explicit solution. But in our particular case $P_a^{I,R} = 1$, we get the explicit solution:

$$[\lambda(\delta_T)]^{T+1} = CC\left(1 - P_a^{E,R}\right)^T M(0)^{-(T+1)}.$$

Since the sign of $\lambda(\delta_T) - 1$, and therefore the sign of $([\lambda(\delta_T)]^{T+1} - 1)\alpha$, are the only quantities determinating the asymptotic behavior of the model, for any $\alpha > 0$, then under $([\lambda(\delta_T)]^{T+1} - 1)\alpha > 0$, $(0,0)$ is unstable, and under $([\lambda(\delta_T)]^{T+1} - 1)\alpha < 0$, $(0,0)$ is locally asymptotically stable.[10]

In the same way as previously, the basic reproductive number is:

$$R_0(\delta_T) = \left[CC\sum_{k\geq 0}(k+1)\left(1 - P_a^{I,R}\right)^k P_a^{I,R}\right]\left(1 - P_a^{E,R}\right)^T = \frac{\left(1 - P_a^{E,R}\right)^T}{P_a^{I,R}}CC. \quad \text{(A.8)}$$

Therefore, under $P_a^{I,R} = 1$ and according to Equations (8) and (A.8),

$$\tilde{\rho}_0(\delta_T) = \left[1 - P_a^{E,R}\right]^{-T}\left[R_0(\delta_T) - M(0)^{T+1}\right],$$

and as in the Markov setting, we have

$$\begin{aligned}\operatorname{sign}(R_0(\delta_T) - 1) &= \operatorname{sign}(\tilde{\rho}_0(\delta_T)) \\ &\Longleftrightarrow \lim_{e_0+i_0=0,\, N_0\to\infty} N_{n+1}N_n^{-1} = 1.\end{aligned}$$

A.4. Intrinsic Incubation Time

Define the censored transition $E \to I$ such that $E \to R$ is forbidden. Then the probability $P_{a,c}^{E,I}$ of this transition is equal to $P_{a,c}^{E,I} = P_a^{E,I}(1 - P_a^{E,R})^{-1}$. Define in the same way $P_{a,c}^{E,E} = P_a^{E,E}(1 - P_a^{E,R})^{-1}$. Then the expectation T_{R^c} of the transition time of this censored transition is:

$$\begin{aligned}T_{R^c} &= \sum_{k\geq 0}(k+1)\left(P_{a,c}^{E,E}\right)^k P_{a,c}^{E,I} \\ &= \frac{P_{a,c}^{E,I}}{\left(1 - P_{a,c}^{E,E}\right)^2} = \left[P_{a,c}^{E,I}\right]^{-1}.\end{aligned}$$

Since T_{R^c} and $P_a^{E,I}$ are both unobervable and moreover in order to validate the prediction given in the Markovian setting from that given in the semi-Markovian one, at least from a qualitative point of view, we determine T_{R^c} in order that both models have the same qualitative behavior, that is:

$$\tilde{\rho}_0 = \tilde{\rho}_0(\delta_T). \tag{A.9}$$

Therefore, using Equations (5), (6), (8), and (A.9), we get T_{R^c} as a function of the dynamical parameters, which are estimable:

$$\begin{aligned}T_{R^c} = &\left[(M(0))^T\left(1 - P_a^{E,R}\right)^{-T} - 1\right] \\ &\left(1 - P_a^{E,R}\right)\left[\tilde{m}\left(1 - P_{b,mE}^{S,R}\right)\right]^{-1}.\end{aligned} \tag{A.10}$$

When the population size is stable, i.e., $M(0) = 1$, equivalent to $\tilde{m} = P_a^{S,R}(1 - P_{b,mS}^{S,R})^{-1}$, using the assumption $P_a^{E,R} = P_a^{S,R}$ with $P_{b,mE}^{S,R} = P_{b,mS}^{S,R}$, then T_{R^c} is reduced to $T_{R^c} = [(1 - P_a^{E,R})^{-T} - 1](1 - P_a^{S,R})(P_a^{S,R})^{-1}$.

A.5. Asymptotic Behavior

Let us define $\tilde{r}_1(\cdot)$ and $\tilde{r}_2(\cdot)$ according to Equations (11) and (12). Then:

$$\begin{aligned}&\tilde{r}_1''(i) \\ &\quad = g''(i)(1-i) - 2(g'(i) - D) - \tilde{m}b''(i) \\ &\qquad \times iq\left(1 - P_{b,mI}^{S,R}\right) - 2\tilde{m}b'(i)q\left(1 - P_{b,mI}^{S,R}\right) \\ &\quad = \bar{a}''(i)\left(1 - P_a^{S,R}\right)(1-i) + \tilde{m}\bar{b}''(i) \\ &\qquad \times \left[\left(1 - P_{b,mS}^{S,R}\right)(1-i) + iq\left(1 - P_{b,mI}^{S,R}\right)\right] \\ &\qquad - 2\left[\bar{a}'(i)\left(1 - P_a^{S,R}\right) + \tilde{m}\bar{b}'(i)\left[\left(1 - P_{b,mS}^{S,R}\right)\right.\right. \\ &\qquad \left.\left. - q\left(1 - P_{b,mI}^{S,R}\right)\right]\right] + 2D \\ &\tilde{r}_1'''(i) \\ &\quad = g'''(i)(1-i) - 3g''(i) - \tilde{m}b'''(i)iq\left(1 - P_{b,mI}^{S,R}\right) \\ &\qquad - 3\tilde{m}b''(i)q\left(1 - P_{b,mI}^{S,R}\right) \\ &\quad = \bar{a}'''(i)\left(1 - P_a^{S,R}\right)(1-i) + \tilde{m}\bar{b}'''(i) \\ &\qquad \times \left[\left(1 - P_{b,mS}^{S,R}\right)(1-i) + iq\left(1 - P_{b,mI}^{S,R}\right)\right] \\ &\qquad - 3\left[\bar{a}''(i)\left(1 - P_a^{S,R}\right) + \tilde{m}\bar{b}''(i)\left[\left(1 - P_{b,mS}^{S,R}\right)\right.\right. \\ &\qquad \left.\left. - q\left(1 - P_{b,mI}^{S,R}\right)\right]\right].\end{aligned}$$

Concerning the Markovian setting, the proofs of Proposition 1 and Item 3 of Proposition 2 are done in the equivalent model giving (i_{n+1}, c_{n+1}) as a function of (i_n, c_n), where $c_n = e_n + i_n$, and are direct consequences of the negative sign of $M(i_n)(c_{n+1} - c_n)$ expressed as a function of (i_n, c_n). Since this quantity has also exactly the same expression in the semi-Markovian model as in the Markovian model, the results are also valid in the semi-Markovian setting. The first two items of Proposition 2 are just applications of classical results on dynamical systems.[10]

Let us define $r(i_n) = -a(i_n)(1 - i_n T_{R^c}) + (1 - i_n)(1 - i_n i_{M,0}^{-1}) = G(i_n)[c_{n+1} - c_n]$, where $G(i) > 0$ for all i. Then $r(\cdot)$ has the same sign as the current reproductive rate, and we have:

$$\begin{aligned}r''(i) &= \bar{a}''(i)(1 - i\,T_{R^c}) - 2\bar{a}'(i)T_{R^c} + 2i_{M,0}^{-1} \\ r'''(i) &= \bar{a}'''(i) - 3\bar{a}''(i)T_{R^c}(1 - i\,T_{R^c})^{-1}.\end{aligned}$$

Notice that $1 - i\,T_{R^c} \geq 0$ and $1 - ii_{M,0}^{-1}$, for all $i < i_{M,0}$.

The detailed proof of Proposition 3 is given in References 1 and 2 and is based on some monotony properties of the model written as a system giving (i_{n+1}, i_n) from (i_n, i_{n-1}) and on the unicity of the fixed point of the system, which is guaranteed under the assumption on $\bar{a}(\cdot)$ given in this proposition, thanks to the properties of $r(i_n)$.

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