Journal de la Société Française de Statistique
Vol. 157 No. 1 (2016)

The BSE epidemic in Great-Britain: a generic example of risk assessment during the growth and decay phases

Titre: L'épidémie d'ESB en Grande-Bretagne : un exemple générique d'évaluation des risques au cours des phases de croissance et de déclin

Christine Jacob[1] and Sophie Pénisson[2]

Abstract: In this paper we provide a comprehensive analysis of the Bovine spongiform encephalopathy (BSE) epidemic evolution in Great-Britain. Our study is based on a multi-type branching process model and on different stochastic and statistical tools. We first focus on the growth phase until the first sanitary control measure in 1988, and provide an estimation of the unknown parameters of our model, using a Bayesian approach. We then consider the decay phase of the epidemic and estimate its new infection parameter using a frequentist approach, which enables us to predict the future incidences of cases, the epidemic extinction time and the total epidemic size. We finally evaluate the risks that would be caused by a very long decay phase. For this purpose we condition the process on a very late extinction, and thanks to an estimation of the infection parameter, we predict the evolution of the epidemic in this worst-case scenario.

Résumé : Dans cet article nous proposons une analyse complète de l'évolution de l'épidémie d'encéphalopathie spongiforme bovine en Grande-Bretagne. Notre étude est basée sur un modèle de processus de branchement multitype et sur différents outils probabilistes et statistiques. Nous nous focalisons en premier lieu sur la phase de croissance jusqu'à la première mesure de contrôle sanitaire en 1988, pour laquelle nous proposons une estimation des paramètres inconnus de notre modèle via une approche bayésienne. Nous considérons ensuite la phase de déclin et estimons par une approche fréquentiste le paramètre d'infection afférent, ce qui nous permet de prédire l'incidence des cas à venir, le temps d'extinction de l'épidémie ainsi que sa taille totale. Pour finir, nous évaluons les risques qui seraient conséquents à une très longue phase de déclin. Dans ce but nous conditionnons le processus à une extinction très tardive, et prédisons grâce à une estimation du paramètre d'infection l'évolution de l'épidémie dans le cas de ce scénario le plus défavorable.

Keywords: BSE, stochastic epidemic, SEI, branching process, Q-process, worst-case scenario, Bayesian inference, CLSE, consistency and asymptotic normality

Mots-clés : ESB, modèle épidémique stochastique, SEI, processus de branchement, Q-processus, pire scénario, inférence bayésienne, estimateur des moindres carrés conditionnels, consistance et normalité asymptotique

AMS 2000 subject classifications: 60J80, 60J85, 62F12, 62F15, 62M05, 62M20, 62P10, 62P12

[1] MaIAGE, INRA, Université Paris-Saclay,
78350 Jouy-en-Josas, France.
E-mail: cjacob@jouy.inra.fr

[2] Université Paris-Est, LAMA (UMR 8050), UPEMLV, UPEC, CNRS,
94010 Créteil, France.
E-mail: sophie.penisson@u-pec.fr

 ISSN: 2102-6238

1. Introduction

BSE (Bovine Spongiform Encephalopathy), also known as "mad cow disease", was first officially identified in 1986 (Wells et al., 1987) reached its peak in 1992 (36682 cases) and is obviously now in its decay phase. This disease, the epidemiology of which is now well-known (see e.g. Anderson et al., 1996) is due to a change in the early 1980s of the rendering process by which livestock carcasses are converted to protein supplements for livestock feed. It is a fatal neurodegenerative transmissible disease in cattle due to the abnormal form of the protein prion. It causes a spongy degeneration in the brain and spinal cord leading to death. The main routes of transmission are horizontal via the oral route by protein supplements (MBM (Meat and Bone Meal), milk replacers) and maternal from a cow to its calf (Donnelly, 1998). It may be transmitted to human by the food route. The human disease, called vCJD, was first detected in 1995 and caused 177 deaths in the United Kingdom until July 31th, 2014. The key measure for controlling BSE was the ban of feeding ruminants with ruminant-derived proteins in July 1988. This measure was then extended in 1996 to mammalian-derived proteins and to all farmed livestock (HMSO, 1996).

Our goal is to provide a methodology taking into account the randomness of the main factors of propagation of the disease over time, and which would enable to quantify the infection over time according to the different sources (feed, maternal, excretion). This should allow to evaluate the efficiency of the key feed ban law (July 1988). Moreover even if now the disease should obviously soon come to an end (2 cases in 2012, 3 in 2013, and 1 in 2014, World Organisation for Animal Health, 2014), this methodology should lead to more accurate and longer-term predictions than those given by the classical back-calculation methods. More generally, the methodology that we intend to develop should be useful to analyze and predict any epidemic in a large population with a large incubation period respectively to the population dynamics.

These purposes suppose a stochastic modeling that takes into account the population dynamics (births and deaths) and the disease dynamics, and allows an estimation of the unknown parameters based only on the yearly notified infectives (observations given in Subsection 2.1). To this end, we first build in Subsection 2.2 a non classical multitype branching process in discrete time which describes more particularly the time evolution of the subpopulation of infectives within a finite population, and which takes into account their time of infection. Then, in Subsection 2.3, assuming a rare disease at the initial time and the probability for an animal to be exposed to a given infective inversely proportional to the population size, we recursively derive from this process, as the initial size of the population increases to infinity, a limit process on the incidence of clinical cases. We show that this limit process may be written either as a single-type Markovian process with a Poissonian transition distribution whose order d depends on the largest potential incubation time, or as a multitype branching process with d types and Poisson offspring distributions. The limit process has the advantage of depending only on the incidence of clinical cases at successive times, which corresponds to the observations. We then estimate in Subsection 2.4, thanks to a Bayesian approach using the whole epidemic until 2007, the unknown parameters of the limit process (the efficiency of the MBM ban in 1988, the infection parameters via the horizontal route, the incubation period distribution, and the initial cases numbers from 1982 to 1986. Due to the time-inhomogeneity of the process and the number of unknown and heterogeneous parameters including initial data, the Bayesian approach is here the most convenient approach. We show in particular the good efficiency of the MBM ban in 1988, which leads to a single remaining infection

 ISSN: 2102-6238

parameter θ corresponding to the mean number of infectious aggregates of prion produced by an infectious alive animal.

We then focus in Section 3 on the decay phase starting from 1989, and during which the limit process can be considered to be time-homogeneous. It then belongs to the general class of multitype BGW (Bienaymé-Galton-Watson) processes. This section is aimed at predicting the future spread of the disease. For this purpose we first provide in Subsection 3.2 an estimation of θ, the other parameters being deduced from the estimations presented in Section 2. Due to the time-homogeneity of the process and the single dimension of the parameter, we choose here the frequentist approach, namely a WCLSE (Weighted Conditional Least Squares Estimator). Combined with the numerous theoretical properties of the multitype BGW process describing the epidemic in this phase, this enables us to provide the asymptotic properties of the estimator as the number of cases from 1989 to 1997 grows to infinity (strong consistency and asymptotic normality) and to accurately predict the future spread of the epidemic from 2014, namely its speed of extinction, its extinction time distribution, the future incidences of cases and of infected cattle, and the total epidemic size (Subsection 3.3).

Then, in order to investigate the worst-case scenario of an extremely late extinction of the epidemic, we introduce in Section 4 the so-called Q-process, obtained by conditioning the epidemic process on a very late extinction. In the frame of this Q-process, we estimate θ by a WCLSE (Subsection 4.2). Then thanks to its asymptotic properties as time tends to infinity (strong consistency and asymptotic normality), we predict by simulations of the estimated Q-process the behavior of the "most dangerous" evolution of the epidemic, namely the future incidences of infectives and infected cattle (Subsection 4.3).

2. Modeling the whole epidemic: time-inhomogeneous setting

2.1. Observations

They consist in the number of cases of BSE per year reported in Great Britain until 2013 by the World Organisation for Animal Health (2014) (see Table 1), where we detail the observations until 1987, attributing 9 cases in 1986, 1 case in 1985 and 0 case before 1985. Recall that the disease was notifiable from 1988, and that different types of active surveillance began since 1999, in particular the most efficient one required by the European Union that started in 2001 (Department for Environment, Food & Rural Affairs, 2014). Hence the accuracy of the observations increases with time. In particular, the first observations simply concern the clinical status while the current observations from 2001 concern the infectious stage including the clinical status. However we will not take into account this accuracy evolution when estimating unknown parameters.

2.2. Epidemic branching process in a finite population

The disease propagates within each animal according to the steps described in Figure 1, where an animal E^1 has just been infected and an animal I^1 has just been infectious. Contrary to the usual Markovian approach which forgets the time already spent in the state E, the steps E^1 and I^1 are crucial for a general modeling approach of the incubation process when the distribution of the incubation time is a priori unknown. While the infection process may be assumed instantaneous

 ISSN: 2102-6238

TABLE 1. *Yearly number of cases of BSE reported in Great-Britain from 1981 to 2013.*

n	1981	1982	1983	1984	1985	1986	1987	**1988**	1989	1990	1991
i_n	0	0	0	0	1	9	432	2469	7137	14181	25032
n	1992	1993	1994	1995	**1996**	1997	1998	1999	2000	2001	2002
i_n	36682	34370	23945	14302	8016	4312	3179	2274	1355	1113	1044
n	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
i_n	549	309	203	104	53	33	9	11	5	2	3

and while it is commonly accepted that the infectious stage, including the clinical state, should last a few months and no more than a year, the incubation process itself can last several years.

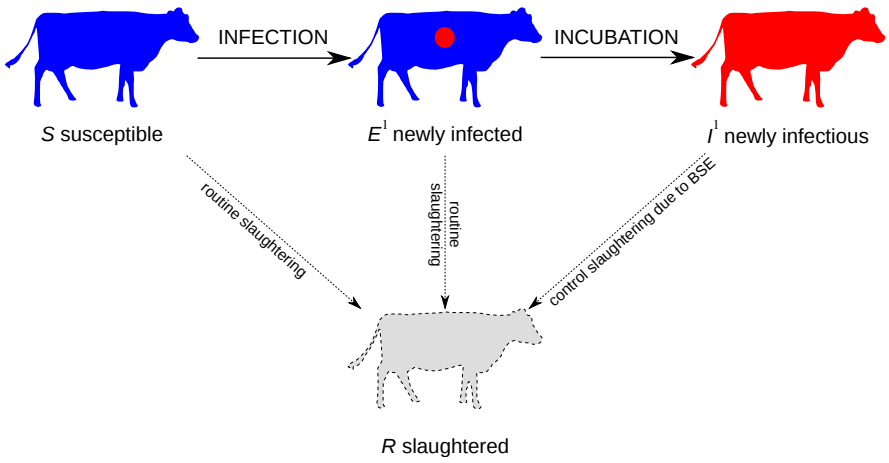


Figure 1: Evolution of health status in the BSE epidemic.

We choose a discrete time approach with a time unit of one year for consistency with the observations and the duration of the infectious state. In addition this unit removes the seasonal effects.

Let $N_n^{I^1}$ (resp. N_n^I) be the number of new infectives (resp. total number of infectives) at time $n \in \mathbb{N}$. Due to the chosen unit time, we have $N_n^I = N_n^{I^1}$. Let similarly $N_n^{E^1}$ be the number of newly infected animals and N_n the total population size at time n.

We define for any pair of health states $(H_0, H_1) \in \{(S,E^1),(S,R),(E^1,I^1),\ldots\}$, $a' \geqslant 1$ and $n', n \in \mathbb{N}$, $n' < n$, the Bernoulli variable $\delta_{a',n';n,i}^{H_0,H_1}$ equal to 1 if animal i aged a' and in state H_0 at time n', undergoes during the interval (n', n) the single transition $H_0 \to H_1$. Moreover denoting by $R^c = S \cup E \cup I$ the alive state, we define $\delta_{a',n';n,i}^{H_0,R^c}$ the Bernoulli variable equal to 1 if animal i aged a' and in state H_0 at time n', is still alive at time n. Finally, let $\delta_{n,i}^{(H,a)}$ be the Bernoulli variable equal to 1 if animal i is H and aged a at time n.

Then the evolution of the populations in each of the health states $\{S,E,I\}$ could be described by a classical (Markovian of order 1) multitype age, health, and population dependent branching process. However this kind of process has a large number of types, especially here since the

 ISSN: 2102-6238

distribution of the incubation time cannot be considered as a geometric law. Moreover we aim to build a model essentially based on the set of variables $\{N_n^I\}_n$ which are the only observed variables. Therefore we describe N_n^I as the sum of all the infectives at time n that have been infected at any previous time $n-k$ by infectives of this time. Thus

$$N_n^I = \sum_{k=1}^{a_m-1} \sum_{a=k+1}^{a_m} \sum_{i=1}^{N_{n-k}} \delta_{n-k,i}^{(E^1,a-k)} \delta_{a-k,n-k;n,i}^{E^1,I^1}, \tag{2.1}$$

where $a_m \leqslant +\infty$ is the largest theoretical animal survival age and the process $\{N_n\}_n$ has the branching property: defining $Y_{n,i}$ as the number of newborn animals of dam i born at time $n-1$, which are therefore aged 1 at time n if they are still alive, and denoting $N_{a,n}$ the number of animals aged a at time n, then

$$N_n = \sum_{a=1}^{a_m} N_{a,n}, \text{ where } N_{a,n} = \sum_{i=1}^{N_{n-1}} \mathbf{1}_{\{a\geqslant 2\}} \delta_{n-1,i}^{(R^c,a-1)} \delta_{a-1,n-1;n,i}^{R^c,R^c} + \mathbf{1}_{\{a=1\}} \sum_{j=1}^{Y_{n,i}} \delta_{n,i,j}^{(R^c,1)}, \tag{2.2}$$

the variables $\{Y_{n,i}\}_{i,n}$ being independent and identically distributed with a finite population and time independent expectation m and finite variance.

In addition, the number of newly infected animals at time n is given by

$$N_n^{E^1} = \sum_{i=1}^{N_n} \sum_{a=1}^{a_m} \delta_{n,i}^{(E^1,a)}. \tag{2.3}$$

The random variables $\{\delta_{n,i}^{(H,a)}\}_i$ are identically distributed, and so are the other sets of Bernoulli random variables. We assume that the set of variables $(N_n^I, N_n^{E^1}, \{N_{a,n}\}_{a=1}^{a_m})$ depend on the past through $\{\{N_{a,n-k}\}_{a=1}^{a_m}, N_{n-k}^I\}_{k=1}^{a_m-1}$ at most, and we denote $\sigma(\{\{N_{a,n-k}\}_{a=1}^{a_m}, N_{n-k}^I\}_{k=1}^{a_m-1}) =: \mathscr{F}_{n-1}$. As a consequence, $a_m - 1$ is the largest memory length of N_n^I. The time origin 0 may be defined by any time such that $N_0^I \neq 0$. The time indices before the origin are then denoted by $-1, -2, \ldots$ and the corresponding values of the process define the initial conditions.

Finally, in order to achieve to define the process $\{(N_n^I, N_n^{E^1}, \{N_{a,n}\}_{a=1}^{a_m})\}_n$ given by (2.1)-(2.3), we have to define, for each n, the conditional distributions given $\mathscr{F}_{n-1}$ of the Bernoulli variables involved in (2.1)-(2.2) and the conditional distribution given $\mathscr{F}_n$ of $\delta_{n,i}^{(E^1,a)}$. For this purpose, we shall make the following assumptions relating to the population dynamics characteristics and the disease propagation process.

(AS) - *Characteristics of the non infectious population dynamics.*

- (AS_1) - *Survival probability for the S animals.* In absence of any disease, the animals all have the same time-homogeneous probability $S(a)$ to survive at least until age $1 \leqslant a \leqslant a_m$. We set $S(0) = 1$, the survival probability at birth.
- (AS_2) - *Survival probability at each time for the E animals.* Since the E animals cannot be distinguished from the S animals, we assume that they have the same probability to die at each time, that is, for each $a \geqslant 2$ and $n' \geqslant n-1$,

$$\mathbb{E}\left(\delta_{a-1,n-1;n,i}^{E,R^c} \mid \mathscr{F}_{n'}\right) = \mathbb{E}\left(\delta_{a-1,n-1;n,i}^{S,R^c} \mid \mathscr{F}_{n'}\right) = \frac{S(a)}{S(a-1)} + \mathbf{1}_{\{n'\geqslant n\}} e_{a-1,n-1;n|n'}, \tag{2.4}$$

 ISSN: 2102-6238

where $e_{a-1,n-1;n|n'}$, which represents the influence of the future on the mortality of i at n, may be assumed to satisfy $\lim_{N_{n-1}\to\infty} e_{a-1,n-1;n|n'} \overset{a.s.}{=} 0$ (this influence on a given animal at time $n-1$ decreases as the population size at $n-1$ increases), or equivalently, under (AS_3), $\lim_{\mathbf{N}_0\to\infty} e_{a-1,n-1;n|n'} \overset{a.s.}{=} 0$.

(AS_3) - *Stability of the population. Until time 0, the infectious population size is assumed negligible with respect to the whole population size, and the population size and the distribution of ages are assumed stable over time, that is, for all* $1 \leqslant a \leqslant a_m$ *and* $-a_m+2 \leqslant n \leqslant 0$,

$$\lim_{\mathbf{N}_0\to\infty} \frac{N_{n+1}}{N_n} \overset{a.s.}{=} 1, \quad \lim_{\mathbf{N}_0\to\infty} \widehat{P}_{age,n}(a) \overset{a.s.}{=} mS(a) = \frac{S(a)}{\sum_{a'\geqslant 1} S(a')} =: P_{age}(a),$$

where $\{\mathbf{N}_0 \to \infty\} := \{N_n \to \infty, -a_m+2 \leqslant n \leqslant 0\}$ *and for all* $n' \geqslant n$,

$$\widehat{P}_{age,n}(a) := \frac{N_{a,n}}{N_n} = \mathbb{E}\left(\delta_{n,i}^{(R^c,a)} \mid \mathscr{F}_{n'}\right).$$

(AI) - *Infection process.*

(AI_1) - *Infection probability.* This assumption concerns $\delta_{n-k,i}^{(E^1,a-k)} \mid \mathscr{F}_{n-\mathbf{1}_{\{k\geqslant 1\}}}$, $k \geqslant 0$. We denote this quantity by $\delta_{n,i}^{(E^1,a)} \mid \mathscr{F}_{n'}$, where $n' \geqslant n$. There exists at each time n for each living animal at this time, a possible horizontal infection due to the ingestion of prion either excreted from the N_n^I infectives, or present in the MBM or milk replacers. The latter results from the $N_{n-1,n}^{E^{last},R} := N_{n-1}^{E^{last}} - N_n^I$ animals that were in the last stage E^{last} of the non infectious incubation period at time $n-1$ and are slaughtered at time n. Moreover a calf may be infected by its dam with a probability p_{mat} which is assumed to be constant over time (maternal infection). Finally, we assume that the infection probability of an S animal follows a model of Reed-Frost's type. We define $\widehat{p}_{n|n'}^{a,R^c}$ (resp. $\widehat{p}_{n|n'}^{a,R}$) as the probability given $\mathscr{F}_{n'}$ and the survival of the animal at n, that an animal aged a at n is infected at this time by a given infectious aggregate set of prion excreted by an I animal (resp. produced in the environment by a dead infectious animal). We denote by $\gamma^{R^c} N_n^I$ (resp. $\gamma^R N_{n-1,n}^{E^{last},R}$), the number at time n of the corresponding prion sets. We define $\phi_n \in [0,1]$ as the efficiency of the control measure on the exposition of an S animal to the prion coming from the $N_{n-1,n}^{E^{last},R}$ animals at time n, where $\phi_n = 0$ expresses a total efficiency. We then assume that, for each $1 \leqslant a \leqslant a_m$,

$$\begin{aligned}&\mathbb{P}\left(\delta_{n,i}^{(E^1,a)} = 1 \mid N_{n-1,n}^{E^{last},R},\ \delta_{n,i}^{(R^c,a)} = 1,\ \mathscr{F}_{n'}\right)\\ &\quad\overset{a.s.}{=} 1 - \left(1-\widehat{p}_{n|n'}^{a,R^c}\right)^{\gamma^{R^c} N_n^I} \left(1-\widehat{p}_{n|n'}^{a,R}\right)^{\gamma^R N_{n-1,n}^{E^{last},R}} \left(1 - \mathbf{1}_{\{a=1\}} \widehat{p}_{mat,n|n'} \frac{N_n^I}{N_n}\right), \quad (2.5)\end{aligned}$$

where similarly to (2.4), we may assume that $\widehat{p}_{n|n'}^{a,u} = \widehat{p}_{n|n}^{a,u} + \mathbf{1}_{n'>n} e_{a,n|n'}^u$, $u \in \{R, R^c\}$, and $\widehat{p}_{mat,n|n'} = p_{mat} + \mathbf{1}_{n'>n} e_{1,n|n'}^{mat}$ with, under (AS_3), $\lim_{\mathbf{N}_0\to\infty} e_{a,n|n'}^u \overset{a.s.}{=} 0$ for each $u \in$

 ISSN: 2102-6238

$\{R^c, R, mat\}$ and $a = 1, \ldots, a_m$. Therefore (2.5) implies that

$$\mathbb{P}\left(\delta_{n,i}^{(E^1,a)} = 1 \mid \delta_{n,i}^{(R^c,a)} = 1,\ \mathscr{F}_{n'}\right) \overset{a.s.}{=} \left(\widehat{p}_{n|n}^{a,R^c} N_n \gamma^{R^c} + \widehat{p}_{n|n}^{a,R} N_n \gamma^R \widehat{\lambda}_{n|n'} \phi_n + \mathbf{1}_{\{a=1\}} p_{mat}\right) \frac{N_n^I}{N_n} + \varepsilon_{a,n|n'}, \quad (2.6)$$

where

$$\widehat{\lambda}_{n|n'} := \mathbf{1}_{\{N_n^I \neq 0\}} \frac{\mathbb{E}\left(N_{n-1,n}^{E^{last},R} \mid \mathscr{F}_{n'}\right)}{N_n^I} = \mathbf{1}_{\{N_n^I \neq 0\}} \left(\frac{\mathbb{E}\left(N_{n-1}^{E^{last}} \mid \mathscr{F}_{n'}\right)}{N_n^I} - 1\right) \quad (2.7)$$

is the mean ratio given $\mathscr{F}_{n'}$ of the animals among the population of size $N_{n-1}^{E^{last}}$ that are dead at time n, relatively to those still alive, and $\varepsilon_{a,n|n'}$ is the error term. Denoting

$$\widehat{\theta}_n^{a,R^c} := \widehat{p}_{n|n}^{a,R^c} N_n \gamma^{R^c}, \quad \widehat{\theta}_n^{a,R} := \widehat{p}_{n|n}^{a,R} N_n \gamma^R, \quad (2.8)$$

we assume that $\widehat{\theta}_n^{a,R^c}$ and $\widehat{\theta}_n^{a,R}$ are continuous functions of $\{\widehat{P}_{age,n}(a)\}_{1 \leqslant a \leqslant a_m}$ only. Under this assumption, $\varepsilon_{a,n|n'} = O\left(\left(N_n^I/N_n\right)^2\right)$ as $\mathbf{N}_0 \to \infty$. For example , for $u \in \{R, R^c\}$, $\widehat{p}_{n|n}^{a,u} = \nu^{a,u}\mu^{a,u}/\sum_{a'} c_{a'}^{a,u} N_{a',n}$, where $\nu^{a,u}$ is the probability for an S animal to be infected when exposed to a given aggregate set of prions while $\mu^{a,u}/\sum_{a'} c_{a'}^{a,u} N_{a',n}$ is the probability for the animal to be exposed to this set. The quantity $\widehat{\theta}_n^{a,R^c}$ (resp. $\widehat{\theta}_n^{a,R}$) is the mean number of animals aged a infected at time n by a given I animal (resp. a slaughtered E^{last} animal).

(AI_2) - *Incubation time.* Let $\{\mathbb{P}\left(\delta_{a",n";n,i}^{E^1,I^1} = 1 \mid \delta_{a",n";n,i}^{E^1,R^c} = 1, \mathscr{F}_{n"}\right)\}_{1 \leqslant n-n" \leqslant a_m - a"}$ be the intrinsic incubation time distribution for an animal aged $a"$ at its infection time $n"$. We assume that there is no overcontamination during the incubation time and that the incubation time is independent of the population, of the time, and of the age of i at its infection time. This means that, for each $1 \leqslant a" \leqslant a_m - 1$, there exists a probability distribution $P_{inc}(.)$ such that

$$\mathbb{P}\left(\delta_{a",n";n,i}^{E^1,I^1} = 1 \mid \delta_{a",n";n,i}^{E^1,R^c} = 1, \mathscr{F}_{n'}\right) = P_{inc}(n - n") + \mathbf{1}_{\{n' > n"\}} e_{a",n";n|n'}^{inc},$$

where $\lim_{\mathbf{N}_0 \to \infty} e_{a",n";n|n'}^{inc} \overset{a.s.}{=} 0$, and $P_{inc}(k) = 0$, if $k \leqslant 0$ or $k > a_m - a''$.

(AI_3) - *Asymptotic independence.* We assume that there exists for each animal i a bounded neighborhood B_i such that any animal i' not belonging to B_i is independent from i, which is not the case if $i' \in B_i$. More precisely, there exists $x > 1$ such that for any $i, i' \in B_i$ and any $k, k' \geqslant 1$,

$$\mathbb{E}\left(\delta_{n-k,i}^{(E^1,a-k)} \delta_{a-k,n-k;n,i}^{E^1,I^1} \delta_{n-k',i'}^{(E^1,a'-k')} \delta_{a'-k',n-k';n,i'}^{E^1,I^1} \mid \mathscr{F}_{n-1}\right) \overset{a.s.}{=} O\left(\max_{l \leqslant n-1} \left(\frac{N_l^I}{N_l}\right)^x\right), \quad (2.9)$$

as $\mathbf{N}_0 \to \infty$, and similarly concerning $\mathbb{E}\left(\delta_{n,i}^{(E^1,a)} \delta_{n,i'}^{(E^1,a')} \mid \mathscr{F}_n\right)$. For example, since a given set of prions cannot infect two different animals, then B_i could be the herd or a group of herds to which i belongs.

 ISSN: 2102-6238

Remark 2.1.

1. Thanks to Lemma 6.1 (see Appendix), *(AS)* implies that the whole population size and the distribution of ages in the population are stable over time provided that the infectives population is negligible with respect to the whole population when the size of the latter tends to infinity, i.e., for any $n \geqslant 0$,

$$\lim_{\mathbf{N}_0 \to +\infty} \frac{N_{n+1}}{N_n} \overset{a.s.}{=} 1 \text{ with } \lim_{\mathbf{N}_0 \to +\infty} \widehat{P}_{age,n}(a) := \lim_{\mathbf{N}_0 \to +\infty} \frac{N_{a,n}}{N_n} \overset{a.s.}{=} P_{age}(a).$$

2. Due to *(AS)-(AI)*, the memory length of $\{(N_n^I, N_n^{E^1})\}_n$ is $d = \min\{t_{inc}, a_m - 1\}$, where $t_{inc} := \sup\{k : P_{inc}(k) \neq 0\}$ is the largest incubation time.
3. In order to obtain the limit process of Proposition 2.2, we could assume a more complex model than (2.5) provided that it satisfies (2.6) with $\varepsilon_{a,n|n'} = O\left(\left(N_n^I/N_n\right)^u\right)$, $u > 1$.

Thanks to these assumptions, the processes $\{N_n^I, \{N_{a,n}\}_a\}_n$ and $\{N_n^I, N_{n-1}^{E^1}, \{N_{a,n}\}_a\}_n$ are population-dependent and non Markovian multitype branching processes.

2.3. *Limit process as the initial population size tends to infinity*

The epidemic model presented in Subsection 2.2 is built for a finite population. Yet it is neither theoretically nor practically usable for large populations such as the cattle population in Great-Britain (around 9 million). However, comparing the number of BSE cases with the total population, it seems reasonable to assume that even at its peak time, this epidemic remains a rare disease in a large population. We shall therefore study the limit in distribution of $\{N_n^I, N_n^{E^1}\}_n$ as the initial population size tends to infinity, under the assumptions *(AS)-(AI)*. We denote by $\{I_n, E_n^1\}_n$ the limit process, and define $\mathscr{F}_n^I := \sigma\left(\{I_h\}_{h \leqslant n}\right)$, $\mathscr{F}_n(\{I_h\}) = \mathscr{F}_n \cap \{N_h^I = I_h\}_{h \leqslant n}$. Recall also that $\{\mathbf{N}_0 \to \infty\} := \{N_n \to \infty, -a_m + 2 \leqslant n \leqslant 0\}$.

Proposition 2.2. *Let us assume (AS)-(AI), $d < +\infty$, and that for all $0 \leqslant n \leqslant d-1$,*

$$\lim_{\mathbf{N}_0 \to \infty} N_{-n}^I \overset{a.s.}{=} I_{-n}, \quad \lim_{\mathbf{N}_0 \to \infty} \widehat{\lambda}_{-n} \overset{a.s.}{=} \lambda_{-n}.$$

Then for each $n \geqslant 1$, $N_n^I \mid \mathscr{F}_{n-1}(\{I_h\})$ and $N_n^{E^1} \mid \mathscr{F}_n(\{I_h\})$ converge in distribution as $\mathbf{N}_0 \to \infty$ to $I_n \mid \mathscr{F}_{n-1}^I$ and $E_n^1 \mid \mathscr{F}_n^I$ given by

$$I_n \mid \mathscr{F}_{n-1}^I \overset{\mathscr{D}}{:=} \mathscr{P}oiss\left(\sum_{k=1}^{d} \Psi_{k|n-k} I_{n-k}\right), \tag{2.10}$$

$$E_n^1 \mid \mathscr{F}_n^I \overset{\mathscr{D}}{:=} \mathscr{P}oiss\left(\Psi_{0|n} I_n\right), \tag{2.11}$$

where for each $0 \leqslant k \leqslant d$ and $u \in \{R, R^c\}$,

$$\Psi_{k|n-k} := \sum_{a=k+1}^{a_m} \Psi_{n-k}^{a-k} P_{age}(a) P_{inc}(k), \tag{2.12}$$

 ISSN: 2102-6238

$$\Psi_{n-k}^{a-k} := \theta^{a-k,R^c} + \theta^{a-k,R}\lambda_{n-k}\phi_{n-k} + \mathbf{1}_{\{a=1\}}p_{mat}, \tag{2.13}$$

$$\theta^{a-k,u} :\overset{a.s.}{=} \lim_{\mathbf{N}_0\to\infty} \widehat{\theta}_{n-k}^{a-k,u},$$

$$\lambda_{n-k} \overset{a.s.}{=} \lim_{\mathbf{N}_0\to\infty} \widehat{\lambda}_{n-k|n-\mathbf{1}_{\{k\geqslant 1\}}}$$
$$= \mathbf{1}_{\{I_n\neq 0\}} \left(\frac{\sum_{l\geqslant I_n} l\mathscr{B}in\left(l, 1-P_{age}(1)\right)(I_n)\,\mathscr{P}oiss\left(\sum_{k=1}^{d}\Psi_{k|n-1-k}^{E^{last}} I_{n-1-k}\right)(l)}{I_n \sum_{l\geqslant I_n}\mathscr{B}in\left(l, 1-P_{age}(1)\right)(I_n)\,\mathscr{P}oiss\left(\sum_{k=1}^{d}\Psi_{k|n-1-k}^{E^{last}} I_{n-1-k}\right)(l)} - 1 \right), \tag{2.14}$$

and

$$\Psi_{k|n-1-k}^{E^{last}} := \sum_{a=k+1}^{a_m} \Psi_{n-1-k}^{a-k} P_{age}(a)\, P_{inc}(k+1).$$

Moreover, if $\lambda_n\phi_n$ depends on n only, then the processes $\{N_n^I\}_n$ and $\{N_n^I, N_n^{E^1}\}_n$ converge in distribution as $\mathbf{N}_0 \to \infty$ to the respective Markovian processes $\{I_n\}_n$, $\{I_n, E_n^1\}_n$ whose transition laws are defined by (2.10)-(2.11). If in addition $\phi_n = 0$, then these processes are time-homogeneous.

The proof of this proposition is postponed in Section 6.

Remark 2.3.

1. The quantity $\Psi_{k|n-k}$ (resp. $\Psi_{k|n-k}^{E^{last}}$) represents the mean number of new infectives (resp. E^{last} animals) produced at time n with a delay k by an animal that is infectious at time $n-k$, while $\Psi_{0|n}$ represents the mean number of new infected animals produced at time n by an animal infectious at this time. Moreover, $\theta^{a,R^c}P_{age}(a)$ (resp. $\theta^{a,R}P_{age}(a)$) represents the mean number of newly infected animals aged a at each time, produced by an I animal at this time (resp. by a slaughtered E^{last} animal). Recall also that $P_{age}(a) = S(a)/\sum_{a'\geqslant 1} S(a')$ (probability for a S animal to be aged a at any time n, see Lemma 6.1) and that $P_{inc}(\cdot)$ is the probability law of the incubation time given survival (see (AI_2)).
2. In the general case when $\phi_n \neq 0$, since I_n depends on $\{I_k\}_{k=n-d}^{n-1}$ and $\{\lambda_k\}_{k=n-d}^{n}$ by (2.10) and (2.13), and since λ_n depends on $\{I_k\}_{k=n-1-d}^{n}$ by (2.14), then I_n depends on $\{I_k\}_{k\leqslant n-1}$.

Note that by (2.10), if $\lambda_n\phi_n$ depends on n only, then we may also write $I_n = \sum_{k=1}^{d}\sum_{j=1}^{I_{n-k}} Y_{n,j}^{(k,1)}$, where the $\{Y_{n,j}^{(k,1)}\}_{k,j}$ are independent, and the $\{Y_{n,j}^{(k,1)}\}_j$ are identically distributed with

$$Y_{n,j}^{(k,1)} \overset{\mathscr{D}}{=} \mathscr{P}oiss(\Psi_{k|n-k}). \tag{2.15}$$

This variable represents the incidence of infectives generated at time n with a delay k by animal j infectious at time $n-k$.

We may then represent the limit process $\{I_n\}_n$ by a multitype Markovian branching process with d types. Let us define, for each $n \geqslant 0$, the d-dimensional vector $\mathbf{I}_n := (I_{n,1},,\ldots,I_{n,d}) := \left(I_n,\ldots,I_{n-(d-1)}\right)$. Thus, for each $i = 1,\ldots,d$, $I_{n,i} = I_{n-(i-1)} = I_{n-1,i-1}$.

 ISSN: 2102-6238

Proposition 2.4 (Jacob et al., 2010)**.** *If $\lambda_n\phi_n$ depends on n only, the process $\{\mathbf{I}_n\}_n$ is a time-inhomogeneous multitype Markovian branching process satisfying for each $i = 1 \dots d$,*

$$I_{n,i} = \sum_{k=1}^{d} \sum_{j=1}^{I_{n-1,k}} Y_{n,j}^{(k,i)},$$

where the $\{Y_{n,j}^{(k,i)}\}_{k,i,j}$ are independent given $\mathscr{F}_{n-1}^{I}$, and for each n,k,i, the $\{Y_{n,j}^{(k,i)}\}_j$ are identically distributed with $Y_{n,j}^{(k,1)}$ defined by (2.15), and for $i = 2 \dots d$, $Y_{n,j}^{(k,i)} = \delta_{k,i-1}$ (δ stands here for the Kronecker delta).

Remark 2.5. If $\lambda_n\phi_n$ is constant over time, then $\Psi_{k|n-k} =: \Psi_k$ depends on k only, and $\{\mathbf{I}_n\}_n$ is a classical multitype BGW process. Denoting by $\mathbf{e}_i$ the i-th basis vector of $\mathbb{R}^d$, its offspring generating function $\mathbf{f} = (f_1, \dots, f_d)$ defined on $[0,1]^d$ by $f_i(\mathbf{r}) = \mathbb{E}\left[r_1^{I_1} \dots r_d^{I_d} \mid \mathbf{I}_0 = \mathbf{e}_i\right]$ then satisfies

$$\begin{cases} f_i(\mathbf{r}) = e^{-(1-r_1)\Psi_i} r_{i+1}, \quad i = 1 \dots d-1, \\ f_d(\mathbf{r}) = e^{-(1-r_1)\Psi_d}. \end{cases} \tag{2.16}$$

Moreover the mean matrix $\mathbf{M}$, defined by $\mathbb{E}(\mathbf{I}_n | \mathscr{F}_{n-1}^{I}) = \mathbf{I}_{n-1}\mathbf{M}$, is given by

$$\mathbf{M} = \begin{pmatrix} \Psi_1 & 1 & 0 & \dots & 0 \\ \Psi_2 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & & \ddots & \vdots \\ \Psi_{d-1} & 0 & \dots & \dots & 1 \\ \Psi_d & 0 & \dots & \dots & 0 \end{pmatrix}. \tag{2.17}$$

2.4. Estimation

This subsection is detailed in Jacob et al. (2008) and Jacob et al. (2010). We give in Subsection 2.4.1 some constraints on the parameters which are consistent with the epidemiological problem and which allow to decrease the number of unknown parameters.

2.4.1. Model and parameters

Given that the number of observed BSE cases are relatively small compared to the cattle population size (see Subsection 2.1), the epidemic is here assumed to follow the limit model described in Subsection 2.3. Thanks to item 2 of Remark 2.3 and in order to simplify the estimation procedure, we assume in addition that $\lambda_n\phi_n$ depends on n only and is a constant piecewise function. We assume that $\lambda_n\phi_n = 1$ for $n \leqslant 1988$, $\lambda_n\phi_n = \phi \in [0,1]$ for $1989 \leqslant n \leqslant 1996$, and $\lambda_n\phi_n = 0$ for $n \geqslant 1997$. The parameter ϕ depends on the efficiency of the feed ban of 1988. Moreover we assume that for each $a \geqslant 2$, $\theta^{a,R} = \theta^{2,R}$ and that θ^{a,R^c} is independent of the age a and we denote $\theta^{a,R^c} =: \theta$ for all a. Because of an identifiability problem concerning (θ, p_{mat}), we set $p_{mat} = 0.1$ which is the largest admitted value based on observations. We choose for the distribution of the incubation

 ISSN: 2102-6238

time a discretized Weibull distribution of parameters (γ, α) with density $x \mapsto \gamma\alpha x^{\alpha-1} e^{-\gamma x^{\alpha}} \mathbf{1}_{x \geqslant 0}$, where $\gamma = (\alpha - 1)/(\alpha\beta^{\alpha})$. The parameter α (resp. β) is the shape parameter (resp. mode) of the Weibull probability density. Note for instance that $\alpha > 2$ for convex densities in a neighborhood of 0. Our choice is justified by the fact the Weibull distribution covers a very large set of uni-modal probability densities. The discretization of this distribution leads to the following definition of the incubation time distribution: for each $k \in \mathbb{N}^*$,

$$P_{inc}(k) = e^{-\gamma(k-1)^{\alpha}} - e^{-\gamma k^{\alpha}}. \tag{2.18}$$

The estimations of the survival probabilities $\{S(a)\}_{1 \leqslant a \leqslant a_m}$ are drawn from Supervie and Costagliola (2004), where $\widehat{a}_m = 10$. We then set $a_m = 10$ and $d = a_m - 1 = 9$.

The disease was unknown until 1986 and it is admitted that it did not start before 1982. We thus choose as initial time the year 1982 and the unknown multidimensional parameter that we plan to estimate is

$$\boldsymbol{\theta} := (\theta_1, \ldots, \theta_{11}) = \left((i_{1982}, ..., i_{1986}), (\alpha, \beta), \phi, \left(\theta^{1,R}, \theta^{2,R}, \theta\right)\right).$$

Because of the large dimension of $\boldsymbol{\theta}$ and the presence of numbers of cases as unknown parameters, we choose a Bayesian approach for estimating $\boldsymbol{\theta}$, which enables us to get exact credibility intervals from the posterior marginal distributions of the parameters and to get the correlation between the parameters. However this approach depends on the prior distributions which represent the lack of information (uncertainty) about each individual parameter. Assuming that these parameters are a priori independent, then the posterior distribution $\mathbb{P}(\boldsymbol{\theta} \mid i_{1981}, i_{1987}, ..., i_{2007})$ satisfies

$$\mathbb{P}(\boldsymbol{\theta} \mid i_{1981}, i_{1987}, ..., i_{2007}) \propto \prod_{j=1}^{11} \mathbb{P}(\theta_j)\, \mathbb{P}(i_{1981}, i_{1987}, ..., i_{2007} \mid \boldsymbol{\theta}), \tag{2.19}$$

where $\mathbb{P}(i_{1981}, i_{1987}, ..., i_{2007} \mid \boldsymbol{\theta})$ is the likelihood of the process of infectives at these observations, deduced from (2.10).

2.4.2. *Prior distributions*

Due to the lack of knowledge of the parameters values, we assume that all prior distributions are uniform distributions:

- $i_n \sim \mathscr{U}(0, 1000)$, for $1982 \leqslant n \leqslant 1986$;
- $\alpha \sim \mathscr{U}(1, 5)$, $\beta \sim \mathscr{U}(3, 10)$;
- $\phi \sim \mathscr{U}(0, 1)$;
- $\theta^{1,R} \sim \mathscr{U}(0, 100000)$ (calves), $\theta^{2,R} \sim \mathscr{U}(0, 100000)$ (cows);
- $\theta \sim \mathscr{U}(0, 100)$.

2.4.3. *Algorithm and software*

All calculations are performed with the software OpenBUGS (2009). BUGS stands for Bayesian inference Using Gibbs Sampling. This software mainly developed at the MRC Biostatistics Unit, Cambridge, UK, automatically implements MCMC algorithms for a very wide variety of models.

 ISSN: 2102-6238

2.4.4. *Parameters estimation*

We shall present here the main results. More details can be found in Jacob et al. (2008). The empirical marginal posterior distributions for each θ_j, $j = 1, \ldots, 11$, are computed from $N = 26000$ simulations of $\boldsymbol{\theta}$ done with the Markov Chain leading to the posterior distribution. We use here the observations until 2007 (Table 1). Note that since the observations from 2008 until 2013 are in small numbers and in the decay phase of the epidemic, they should not have a significant influence on the estimations. The MAP (Maximum A Posteriori) Bayesian estimation of $\boldsymbol{\theta}$ based on $(i_{1981}, i_{1987}, \ldots, i_{2007})$ is, for $a_m = 10$,

$$\widehat{\boldsymbol{\theta}}^{obs}_{MAP} = ((0,0,0,181,545), (3.84, 7.46), 0, (838, 1200, 2.43)). \tag{2.20}$$

Note that if we take into account the few cows that are still living at a larger age than 10 years and that do not contribute to the survival probability estimation given in Supervie and Costagliola (2004), we obtain, for example, by an extrapolation of the observed survival law until $a_m = 19$,

$$\widehat{\boldsymbol{\theta}}^{obs}_{MAP} = ((0,0,0,236,540), (4.14, 5.95), 0, (233, 616, 1.056)),$$

which roughly stays in the same order of magnitude as for $a_m = 10$. From now on we shall only provide the results for $a_m = 10$. According to Table 3, the mode of the incubation distribution is correlated with the infection parameters. Hence these estimations must be interpreted with caution.

TABLE 2. *Empirical statistics computed from the empirical marginal posterior distributions corresponding to each parameter using $a_m = 10$; s.d. stands for empirical standard deviation, MC_error $= s.d./\sqrt{N}$ is the Monte Carlo standard error for the mean, and q_p is the p-quantile defined by $\widehat{\mathbb{P}}(\theta_j \leqslant q_p \mid i_{1981}, i_{1987}, \ldots, i_{2007}) = p$, where $\widehat{\mathbb{P}}(.)$ is the empirical probability.*

Parameter	mean	s.d.	MC_error	$q_{0.025}$	median	$q_{0.975}$
i_{1982}	0.6955	0.6921	0.004654	0.01762	0.4899	2.543
i_{1983}	0.9755	0.967	0.006083	0.02544	0.6809	3.589
i_{1984}	2.541	2.519	0.01526	0.06208	1.778	9.255
i_{1985}	177.4	13.42	0.09923	149.5	178.0	202.3
i_{1986}	545.1	35.19	0.2557	478.2	544.6	616.8
α	3.84	0.03425	4.527E-4	3.772	3.841	3.907
β	7.46	0.1347	0.003829	7.204	7.457	7.737
ϕ	7.75E-5	6.079E-5	5.99E-7	2.76E-6	6.381E-5	2.251E-4
$\theta^{1,R}$	842.8	34.29	0.5332	775.7	842.6	910.9
$\theta^{2,R}$	1202.0	134.2	3.836	949.6	1198.0	1479.0
θ	2.464	0.1266	0.003252	2.231	2.458	2.728

From Tables 2 and 3, we see the good efficiency of the MBM ban, which leads from 1989 to the single remaining infection parameter θ via the horizontal route (i.e. the horizontal route is the only route allowing an eventual exponential evolution of the disease). Its estimation is $\widehat{\theta}^{obs}_{MAP} = 2.43$.

Note that model (2.10)-(2.11), where $\boldsymbol{\theta}$ is distributed according to the posterior distribution (2.19), allows to obtain, for any n, empirical credibility bands of $\{I_k(\boldsymbol{\theta})\}_{1 \leqslant k \leqslant n}$ and $\{E^1_k(\boldsymbol{\theta})\}_{1 \leqslant k \leqslant n}$

 ISSN: 2102-6238

TABLE 3. *Empirical correlations between the parameters for* $a_m = 10$.

	i_{1982}	i_{1983}	i_{1984}	i_{1985}	i_{1986}	α	β	ϕ	$\theta^{1,R}$	$\theta^{2,R}$	θ
i_{1982}	1.00	-0.02	0.00	-0.20	0.17	0.06	0.06	0.02	-0.02	0.04	0.05
i_{1983}	-0.02	1.00	-0.02	-0.27	0.20	0.06	0.05	0.02	-0.01	0.03	0.04
i_{1984}	0.00	-0.02	1.00	-0.49	0.26	0.07	0.05	0.02	-0.01	0.03	0.04
i_{1985}	-0.20	-0.27	-0.49	1.00	-0.54	0.17	-0.17	0.00	-0.21	-0.05	-0.15
i_{1986}	0.17	0.20	0.26	-0.54	1.00	0.53	0.16	0.08	-0.10	0.10	0.15
α	0.06	0.06	0.07	0.17	0.53	1.00	0.31	0.22	-0.76	0.46	0.27
β	0.06	0.05	0.05	-0.17	0.16	0.31	1.00	0.25	-0.35	0.96	0.89
ϕ	0.02	0.02	0.02	0.00	0.08	0.22	0.25	1.00	-0.29	0.29	-0.17
$\theta^{1,R}$	-0.02	-0.01	-0.01	-0.21	-0.10	-0.76	-0.35	-0.29	1.00	-0.58	-0.31
$\theta^{2,R}$	0.04	0.03	0.03	-0.05	0.10	0.46	0.96	0.29	-0.58	1.00	0.86
θ	0.05	0.04	0.04	-0.15	0.15	0.27	0.89	-0.17	-0.31	0.86	1.00

from simulations of these processes (Jacob et al., 2010). However, we intend to focus on an accurate prediction of the future evolution of these processes which is based on an estimator of θ with good properties (at least strong consistency for an appropriate asymptotic).

3. Focus on a specific period: time-homogeneous setting

In this section, which is aimed at predicting in a comprehensive way the future spread of the disease, we focus on the process from 1989 to 2013, i.e. from the first feed ban law to the time of the last available data (see Table 1). The assumptions on the parameters are the same as in Subsection 2.4.1. The study exposed in Section 2, which is based on the epidemic data from 1981 to 2007, concludes to a full efficiency of the 1988 feed ban law ($\phi_n = 0$ for $n \geqslant 1989$), and provides the Bayesian estimations $(\widehat{\alpha}^{obs}_{MAP}, \widehat{\beta}^{obs}_{MAP}) = (3.84, 7.46)$ (see (2.20)) of the parameters (α, β) of the incubation time distribution (see (2.18)). Although these estimations are not based on the whole epidemic data, they take into account a relatively large portion of the epidemic (including the peak in 1992 which contains the maximal information about the incubation period distribution). This leads us to consider them as relevant enough to be used in the following as known parameters. However, we reckon that the infection parameter θ (mean number of newly infected animals produced by an infective) should be estimated by taking into account the new available data from 2008 to 2013 as well, since they could play a significant role in the evolution of the epidemic from 1989.

The setting of this section is thus the following. The multitype branching process $\{\mathbf{I}_n\}_n$ is assumed to be time-homogeneous (see Remark 2.5), and the Ψ_k defined by (2.12) only depend on the unknown parameter θ. We write for each $k = 1 \dots d$,

$$\Psi_k(\theta) = \theta P_{inc}(k) \sum_{a=1}^{a_m - k} P_{age}(a+k) + p_{mat} P_{age}(k+1) P_{inc}(k) =: a_k \theta + b_k, \tag{3.1}$$

and denote by $\mathbf{\Psi}(\theta)$, $\mathbf{a}$ and $\mathbf{b}$ the corresponding d-dimensional vectors. The vectors $\mathbf{a}$ and $\mathbf{b}$ are known by setting $p_{mat} = 0.1$, $(\alpha, \beta) = (3.84, 7.46)$ and by deducing as previously the survival probabilities from Supervie and Costagliola (2004).

 ISSN: 2102-6238

In Subsection 3.1 we first recall important theoretical results regarding the epidemic process $\{\mathbf{I}_n\}_n$. In Subsection 3.2, we provide a least squares estimation of the infection parameter θ based on $(i_{1989},\dots,i_{2013})$, which combined with the theoretical properties of $\{\mathbf{I}_n\}_n$ enables us to predict in Subsection 3.3 the future spread of the epidemic from 2014, namely its speed of extinction and extinction year, the future incidences of cases and of infected cattle, and the total epidemic size.

3.1. Theoretical results

3.1.1. Extinction of the epidemic

Almost sure extinction. The d-dimensional process $\{\mathbf{I}_n\}_n$ becomes extinct when it reaches the d-dimensional null vector $\mathbf{0}$ (or equivalently when $\{I_n\}_n$ is null at d successive times). According to the theory of multitype positive regular and nonsingular BGW processes (Athreya and Ney, 1972), the extinction of $\{\mathbf{I}_n\}_n$ occurs almost surely (a.s.), if and only if $\rho \leqslant 1$, where ρ is the dominant eigenvalue (Perrons root) of the mean matrix $\mathbf{M}$ defined by (2.17). Thus ρ is solution of $\sum_{k=1}^{d} \Psi_k \rho^{-k} = 1$. In general for $d > 1$, ρ has no explicit expression. We nevertheless obtain the following explicit threshold criteria.

Proposition 3.1. *The epidemic becomes extinct almost surely if and only if $R_0 \leqslant 1$, where the so-called basic reproduction number $R_0 := \sum_{k=1}^{d} \Psi_k$ is the total mean number of new infectives generated by one infective. Moreover, assuming $d > 1$, then $\rho < 1$ (resp. $\rho = 1$, $\rho > 1$) implies $R_0 < \rho$ (resp. $R_0 = \rho$, $R_0 > \rho$).*

Note that when $d > 1$, R_0 only provides information about the threshold level, whereas ρ provides an additional information about the speed of extinction of the process, as shown in the next two paragraphs.

Speed of extinction. Thanks to the Perron-Frobenius theorem (see e.g. Athreya and Ney, 1972), we can deduce the expected incidence of infectives in the population at time n, for n large. Denoting by $\mathbf{u}$ and $\mathbf{v}$ the right and left eigenvectors of $\mathbf{M}$ associated to the Perron's root ρ, that is, $\mathbf{M}\mathbf{u}^T = \rho\mathbf{u}^T$ and $\mathbf{v}\mathbf{M} = \rho\mathbf{v}$, with the normalization convention $\mathbf{u}\cdot\mathbf{1} = \mathbf{u}\cdot\mathbf{v} = 1$, where $\mathbf{u}\cdot\mathbf{v}$ stands for the usual scalar product in $\mathbb{R}^d$ and where the superscript ^{T} denotes the transposition, then $\mathbb{E}(\mathbf{I}_n \mid \mathbf{I}_0) = \mathbf{I}_0\mathbf{M}^n \sim \rho^n \mathbf{I}_0\mathbf{u}^T\mathbf{v}$ as $n \to \infty$. Hence if $\rho < 1$ the mean number of infectives decreases exponentially at the rate ρ. More precisely, computing explicitly $\mathbf{I}_0\mathbf{u}^T\mathbf{v}$, we (Pénisson and Jacob, 2012),

$$\mathbb{E}_\theta(I_n \mid \mathbf{I}_0) \underset{n\to\infty}{\sim} \rho^n \frac{\sum_{i=1}^{d} I_{-i+1} \sum_{k=i}^{d} \Psi_k(\theta)\rho^{-k+i-1}}{\sum_{j=1}^{d}\sum_{k=j}^{d} \Psi_k(\theta)\rho^{-k}}. \tag{3.2}$$

In the following section, we provide a more refined result on the estimation of the disease extinction time in the population.

Extinction time of the epidemic. The extinction time distribution can be derived as a function of the offspring generating function. This quantity is calculated conditionally on the initial value of the vector $\mathbf{I}_0$, which since we are building tools for the prediction of the spread of the disease would correspond here to the time of the last available data, in our case 2013. Let $T^I := \inf\{n \geqslant 1, \mathbf{I}_n = \mathbf{0}\}$ denote the extinction time of the process $\{\mathbf{I}_n\}_n$, and $T = T^I - d$ the last

 ISSN: 2102-6238

appearance time of a clinical case. Let $\mathbf{f}_n = (f_{n,1}, \ldots, f_{n,d})$ be the n-th iterate of the generating function $\mathbf{f}$ given by (2.16). Then, by the branching property of the process, the probability of a last appearance of a clinical case before time n is given by

$$\mathbb{P}(T \leqslant n \mid \mathbf{I}_0) = \mathbb{P}(\mathbf{I}_{n+d} = \mathbf{0} \mid \mathbf{I}_0) = (f_{n+d,1}(\mathbf{0}))^{I_0} \ldots (f_{n+d,d}(\mathbf{0}))^{I_{-d+1}}. \tag{3.3}$$

It can be immediately deduced from convergence results for $\mathbf{f}_n(\mathbf{0})$ as $n \to \infty$ (Joffe and Spitzer, 1967), that if $\rho = 1$, $\mathbb{P}(T \leqslant n \mid \mathbf{I}_0) \sim 1 - ((n+d)\eta)^{-1} \mathbf{I}_0 \cdot \mathbf{u}$, while if $\rho < 1$, $\mathbb{P}(T \leqslant n \mid \mathbf{I}_0) \sim 1 - \rho^{n+d} \gamma \mathbf{I}_0 \cdot \mathbf{u}$, for some constants $\eta, \gamma > 0$. As a consequence, the closer ρ is to unity, the longer the time to extinction will be in most realizations. More specifically, formula (3.3) enables the exact computation (resp. estimation) of $\mathbb{P}(T \leqslant n \mid \mathbf{I}_0)$ for any n by the iterative computation of $\mathbf{f}_n$, $\mathbf{I}_0$ being given, when the parameters of $\boldsymbol{\Psi}(\theta)$ defined by (3.1) are known (resp. estimated). Moreover, under the assumption $\rho \leqslant 1$, then $\mathbb{P}(T < +\infty \mid \mathbf{I}_0) = 1$ and formula (3.3) consequently enables us to compute for any given probability $p \in [0,1[$ the p-quantile n_p^T of T, defined by

$$n_p^T := \min\{n \geqslant 0 : \mathbb{P}(T \leqslant n \mid \mathbf{I}_0) \geqslant p\}. \tag{3.4}$$

3.1.2. Total size of the epidemic

Under the assumption $\rho \leqslant 1$ and the independence of the $\{Y_{n,j}^{(k,i)}\}_{n,k,i,j}$, we derive the distribution of the future total size $N := \sum_{n=1}^{T} I_n$ of the epidemic until its extinction, i.e. the future total number of infectives. It can be shown that, given the initial value $\mathbf{I}_0$, N is distributed as the sum of Borel-Tanner variables. Its probability distribution is given by (Devroye, 1992; Consul and Famoye, 2006):

$$\mathbb{P}(N = n \mid \mathbf{I}_0) = \sum_{\substack{\{0 \leqslant y_{k,i} \leqslant n, \{1 \leqslant n_{k,i,j} \leqslant n\}_j\}_{i,k}: \\ \sum_{k=1}^{d} \sum_{i=1}^{I_{-k+1}} \sum_{j=1}^{y_{k,i}} n_{k,i,j} = n}} \prod_{k=1}^{d} \prod_{i=1}^{I_{-k+1}} e^{-\sum_{l=k}^{d} \Psi_l} \frac{\left(\sum_{l=k}^{d} \Psi_l\right)^{y_{k,i}}}{y_{k,i}!} \times \prod_{j=1}^{y_{k,i}} e^{-n_{k,i,j} \sum_{l=1}^{d} \Psi_l} \frac{\left(n_{k,i,j} \sum_{l=1}^{d} \Psi_l\right)^{n_{k,i,j}-1}}{n_{k,i,j}!}. \tag{3.5}$$

Hence it can be explicitly calculated (resp. estimated), replacing the $\Psi_k(\theta)$ by their values (resp. estimations). In practice, for any $p \in [0,1[$, we are then able to compute the p-quantile n_p^N of the total epidemic size,

$$n_p^N := \min\{n \geqslant 0 : \mathbb{P}(N \leqslant n \mid \mathbf{I}_0) \geqslant p\}. \tag{3.6}$$

We obtain moreover an explicit formula for the mean value and variance of the size of the epidemic,

$$\mathbb{E}(N \mid \mathbf{I}_0) = \frac{\sum_{k=1}^{d} I_{-k+1} \sum_{i=k}^{d} \Psi_i(\theta)}{1 - \sum_{k=1}^{d} \Psi_k(\theta)}, \quad \mathrm{Var}(N \mid \mathbf{I}_0) = \frac{\sum_{k=1}^{d} I_{-k+1} \sum_{i=k}^{d} \Psi_i(\theta)}{\left(1 - \sum_{k=1}^{d} \Psi_k(\theta)\right)^3}. \tag{3.7}$$

 ISSN: 2102-6238

3.1.3. Exposed population

It is also crucial to study and predict the evolution of the incidence of infected cattle, which is here unobservable. This information is given by the process $\{E_n^1\}_n$ defined by the conditional distribution $E_n^1 \mid I_n \overset{\mathscr{D}}{=} \mathscr{P}oiss\left(\Psi_0\left(\theta\right) I_n\right)$ where $\Psi_0\left(\theta\right) = \theta + p_{mat} P_{age}\left(1\right)$ (see (2.11)-(2.13)). This property enables on the one hand to reconstruct the whole past epidemic (i.e. the incidence of infectives as well as of infected cattle) thanks to the observable data. On the other hand, it allows to simulate the evolution of the incidence of infected cattle in the future, based on predictions of the evolution of the epidemic process $\{I_n\}_n$.

3.2. Estimation

We estimate θ by the following WCLSE which generalizes the well-known Harris estimator (Harris, 1948) in a BGW process. Let $\Theta :=]\theta_1, \theta_2[$, $\theta_2 > \theta_1 > 0$, such that $\theta \in \Theta$. The WCLSE has the following definition and explicit form:

$$\widehat{\theta} := \arg\min_{\theta \in \Theta} \sum_{k=1}^{n} \frac{\left(I_k - \boldsymbol{\Psi}(\theta) \cdot \mathbf{I}_{k-1}\right)^2}{\mathbf{a} \cdot \mathbf{I}_{k-1}} = \frac{\sum_{k=1}^{n} \left(I_k - \mathbf{b} \cdot \mathbf{I}_{k-1}\right)}{\sum_{k=1}^{n} \mathbf{a} \cdot \mathbf{I}_{k-1}}. \tag{3.8}$$

Denoting by $m_{ij}^{(k)}(\theta)$ the (i,j)-th entry in the k-th power of the matrix $\mathbf{M}(\theta)$ given by (2.17), we obtain the following asymptotic results as the initial population size $|\mathbf{I}_0|$ tends to infinity.

Theorem 3.2 (Pénisson and Jacob, 2012)**.** *Let us assume that, for each $i = 1 \ldots d$, there exists some $\alpha_i \in [0,1]$ such that $\lim_{|\mathbf{I}_0| \to \infty} I_{0,i} / |\mathbf{I}_0| = \alpha_i$. Then $\widehat{\theta}$ is strongly consistent, that is $\lim_{|\mathbf{I}_0| \to \infty} \widehat{\theta} \overset{a.s.}{=} \theta$, and is asymptotically normally distributed:*

$$\lim_{|\mathbf{I}_0| \to \infty} \sqrt{\frac{\sum_{k=1}^{n} \mathbf{a} \cdot \boldsymbol{I}_{k-1}}{\sigma^2(\widehat{\theta})}} \left(\widehat{\theta} - \theta\right) \overset{\mathscr{D}}{=} \mathscr{N}\left(0,1\right), \tag{3.9}$$

where

$$\sigma^2(\widehat{\theta}) := \widehat{\theta} + \frac{\sum_{k=1}^{n} \sum_{j=1}^{d} \sum_{i=1}^{d} \alpha_j b_i m_{ji}^{(k-1)}(\widehat{\theta})}{\sum_{k=1}^{n} \sum_{j=1}^{d} \sum_{i=1}^{d} \alpha_j a_i m_{ji}^{(k-1)}(\widehat{\theta})}.$$

Remark 3.3. In the supercritical case $\rho > 1$, the estimator (3.8) presents in addition asymptotic properties as $n \to \infty$ (Pénisson, 2014). Indeed, on the set of non-extinction, it is strongly consistent as $n \to \infty$, that is $\lim_{n \to} \widehat{\theta} \overset{a.s.}{=} \theta$, and asymptotically normally distributed:

$$\lim_{n \to \infty} \sqrt{\frac{(\mathbf{a} \cdot \mathbf{v})^2 W \left(1 + \ldots + \rho^{n-1}\right)}{\rho v_1}} \left(\widehat{\theta} - \theta\right) \overset{\mathscr{D}}{=} \mathscr{N}\left(0,1\right),$$

where $\mathbf{v}$ is the left eigenvector of $\mathbf{M}$ associated to the Perron's root ρ as introduced in Subsection 3.1.1, and W is the following limit random variable $\lim_{n \to \infty} \rho^{-n} \mathbf{I}_n \overset{a.s.}{=} W \mathbf{v}$.

Our estimation of θ is based on the yearly number of cases of BSE reported in Great Britain from 1989 until 2013 (Table 1). We set $\mathbf{I}_0 = \mathbf{i}_{1997} = (i_{1997}, \ldots, i_{1989})$, hence $|\mathbf{I}_0| = 167977$ which is close to the asymptotic $|\mathbf{I}_0| \to \infty$. The estimator (3.8) leads to the estimation

$$\widehat{\theta}^{obs} = 2.4301,$$

 ISSN: 2102-6238

which is almost identical to the Bayesian estimation $\widehat{\theta}^{obs}_{MAP} = 2.43$ based on the whole epidemic until 2007 and assuming a uniform prior probability (see (2.20)). Note that due to the uniform prior distributions, $\widehat{\theta}^{obs}_{MAP}$ is also the Maximum Likelihood Estimator of θ. However, unlike in the case $d = 1$, this estimator is different from the WCLSE. Moreover these two estimators are not based on the same data set. The fact that they are very close shows their good robustness.

Using (3.9) we compute the confidence interval $[\widehat{\theta}_{min}, \widehat{\theta}_{max}]$ with asymptotic probability 95%, where $\widehat{\theta}_{min} := \widehat{\theta} - 1.96/\widehat{c}_1$, $\widehat{\theta}_{max} := \widehat{\theta} + 1.96/\widehat{c}_1$ and $\widehat{c}_1 := (\sum_{k=1}^{n} \mathbf{a} \cdot \mathbf{I}_{k-1}/\sigma^2(\widehat{\theta}))^{1/2}$. Assuming $\alpha_i = i_{1997-i+1}/|\mathbf{i}_{1997}|$, we obtain:

$$\widehat{\theta}^{obs}_{min} = 2.3820, \quad \widehat{\theta}^{obs}_{max} = 2.4782. \tag{3.10}$$

Since the estimation of θ relies on the values given to the other model parameters $\{p_{mat}, \alpha, \beta\}$, we evaluate in addition its sensitivity to the values of these parameters. Some results are collected in Table 4. It appears that the estimation of θ is almost independent of the value of the maternal infection parameter p_{mat}. However, the estimation seems more strongly dependent on the parameters (α, β) of the latent period distribution. Nevertheless, even for very unrealistic values (α, β), all the estimations of θ remain in the same order of magnitude of several units. This is really small compared to estimations obtained for the infection via MBM or lactoreplacers (before 1989) which are of the order of 1000 (see 2.20). However, although these estimations are all very small, θ seems non null. This could eventually suggest the existence of a minor but non null infection source which is not of maternal type.

TABLE 4. *Sensitivity analysis. Estimation and* 95% *asymptotic confidence interval* $[\widehat{\theta}^{obs}_{min}, \widehat{\theta}^{obs}_{max}]$ *of the infection parameter* θ*, for different values of* $\{p_{mat}, \alpha, \beta\}$.

p_{mat}	α	β	$\widehat{\theta}^{obs}$	$[\widehat{\theta}^{obs}_{min}, \widehat{\theta}^{obs}_{max}]$
0.1	3.84	7.46	2.4301	[2.382, 2.4782]
0	3.84	7.46	2.4838	[2.4357, 2.5319]
1	3.84	7.46	1.9468	[1.8991, 1.9946]
0.1	2	7.46	2.7818	[2.7271, 2.8365]
0.1	20	7.46	4.0104	[3.9315, 4.0894]
0.1	3.84	1	1.0126	[0.9924, 1.0328]
0.1	3.84	10	6.2060	[6.0848, 6.3272]
0.1	3	6	1.5392	[1.5085, 1.5699]
0.1	4	5	1.0221	[1.0015, 1.0428]

3.3. *Prediction*

3.3.1. *Extinction of the epidemic*

We know thanks to Proposition 3.1 that $\{I_n\}_n$ becomes extinct almost surely if and only if $R_0 = \sum_{k=1}^{d} \Psi_k(\theta) \leqslant 1$. The estimated basic reproduction is here $R_0(\widehat{\theta}^{obs}) = 0.1071$. Moreover, we obtain with a computing program the following value for the Perron's root $\rho(\widehat{\theta}^{obs}) = 0.6664$, which provides the speed of decay of the expected yearly incidence of cases (see 3.2): from a certain time, the expected number of new cases will decrease from around 33% every year.

 ISSN: 2102-6238

3.3.2. Prediction of the incidences of cases and incidences of infected cattle

Let us predict the spread of the disease from 2014 by means of simulations of $\{I_n\}_n$, where θ is replaced by its previous estimation $\widehat{\theta}^{obs} = 2.4301$. We first point out that the process is likely to provide a satisfying prediction of the overall evolution of the real epidemic from 2014, since it at least provides quite realistic simulations on the period 1998–2013 compared to the real observations on the same period (see Figure 2a). We simulate 10000 trajectories of $\{I_n\}_n$ initialized by $\mathbf{i}_{2013}$, with the estimated infection parameter $\widehat{\theta}^{obs} = 2.4301$. Five of them are plotted in Figure 2b. Using 2.11, we generate for each $n \geqslant 2014$ and for each of the 10000 previously simulated values of I_n, a realization of E_n^1, corresponding to the incidence of infected cattle at time n and thus to the hidden face of the epidemic. We then illustrate in Figure 2c (resp. Figure 2d), the yearly maximum, median, and 95% quantile associated with the 10000 realizations of I_n (resp. E_n^1).

3.3.3. Prediction of the year of extinction and of the epidemic size

As in Subsection 3.1.1, let T denote the last appearance year of a clinical case and N the total size of the future epidemic from 2014. Thanks to (3.3) and (3.5), we explicitly compute the cumulative distribution functions of T and N conditionally on $\{\mathbf{I}_0 = \mathbf{i}_{2013}\}$ for any infection parameter, in particular for the estimated value $\widehat{\theta}^{obs} = 2.4301$. This enables us to compute the associated p-quantiles n_p^T and n_p^N defined by (3.4) and (3.6), whose values for some significant $p \in [0,1]$ are collected in Table 5. Moreover, in order to take into account the uncertainty around the estimation $\widehat{\theta}^{obs}$ of the infection parameter θ, we make use of the asymptotic 95% confidence interval (3.10) of θ and of the fact that $\theta \mapsto \mathbb{P}_\theta(T \leqslant n \mid \mathbf{I}_0)$ and $\theta \mapsto \mathbb{P}_\theta(N \leqslant n \mid \mathbf{I}_0)$ are decreasing functions of θ, which implies that for every $n \geqslant 2013$ and $m \geqslant 0$,

$$\mathbb{P}\left(\mathbb{P}_\theta(T \leqslant n \mid \mathbf{I}_0) \in \left[\mathbb{P}_{\widehat{\theta}_{max}}(T \leqslant n \mid \mathbf{I}_0), \mathbb{P}_{\widehat{\theta}_{min}}(T \leqslant n \mid \mathbf{I}_0)\right]\right) \simeq 95\% \tag{3.11}$$

$$\mathbb{P}\left(\mathbb{P}_\theta(N \leqslant m \mid \mathbf{I}_0) \in \left[\mathbb{P}_{\widehat{\theta}_{max}}(N \leqslant m \mid \mathbf{I}_0), \mathbb{P}_{\widehat{\theta}_{min}}(N \leqslant m \mid \mathbf{I}_0)\right]\right) \simeq 95\%. \tag{3.12}$$

We obtain in particular the realizations of the asymptotic confidence intervals of $\mathbb{P}_\theta\left(T \leqslant n_p^T | \mathbf{i}_{2013}\right)$ and $\mathbb{P}_\theta\left(N \leqslant n_p^N | \mathbf{i}_{2013}\right)$ for different values of p, collected in Table 5. Finally, we deduce from (3.7) that

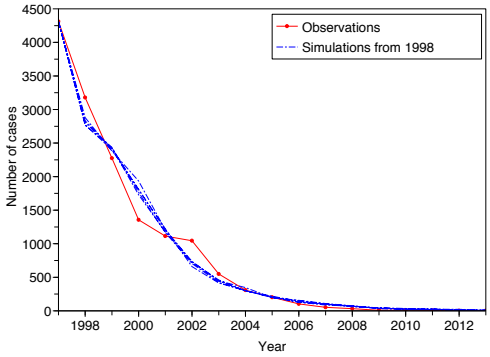
$$\mathbb{E}_{\widehat{\theta}_{min}^{obs}}(N \mid \mathbf{i}_{2013}) = 6.3845, \quad \mathrm{Var}_{\widehat{\theta}_{min}^{obs}}(N \mid \mathbf{i}_{2013}) = 7.9714,$$
$$\mathbb{E}_{\widehat{\theta}_{max}^{obs}}(N \mid \mathbf{i}_{2013}) = 6.6666, \quad \mathrm{Var}_{\widehat{\theta}_{max}^{obs}}(N \mid \mathbf{i}_{2013}) = 8.4015.$$

4. Worst-case scenario

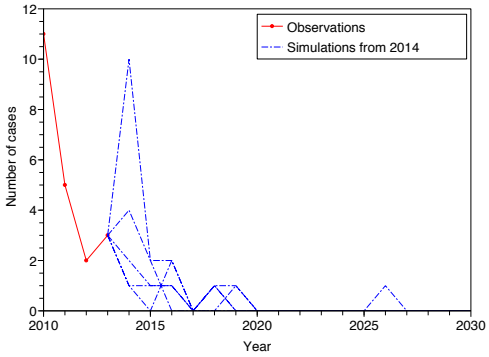
4.1. Model

Even in the case when the epidemic dies out almost surely ($\rho \leqslant 1$), and although one can provide the p-quantile n_p^T of the extinction time with the probability p as large as wanted (see (3.4)),

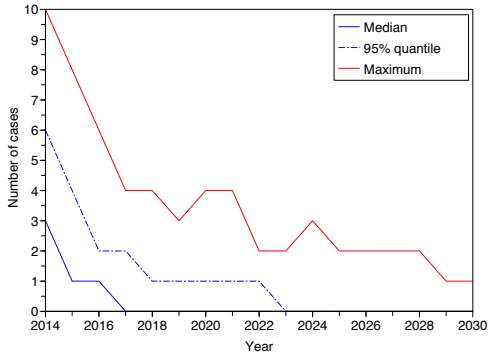
 ISSN: 2102-6238



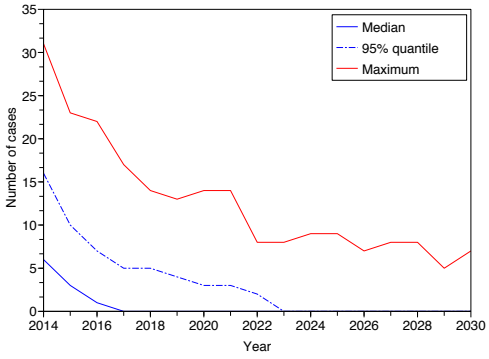
(a) 5 simulations of $\{I_n\}_n$ initialized by $\mathbf{i}_{1997}$, and comparison with the observations on the period 1998–2013.



(b) 5 simulations of $\{I_n\}_n$ initialized by $\mathbf{i}_{2013}$



(c) Prediction of the yearly incidences of cases from 2014, based on 10000 simulations of $\{I_n\}_n$ initialized by $\mathbf{i}_{2013}$.



(d) Prediction of the yearly incidences of infected cattle from 2014, based on 10000 simulations of $\{E_n^1\}_n$.

Figure 2: Prediction of the spread of the disease, based on simulations with the infection parameter $\widehat{\theta}^{obs} = 2.4301$.

TABLE 5. *p-quantiles n_p^T, n_p^N defined by (3.4)-(3.6) for the estimated value $\widehat{\theta}^{obs} = 2.4301$, and observed asymptotic confidence intervals of $\mathbb{P}_\theta\left(T \leqslant n_p^T \mid \mathbf{i}_{2013}\right)$ and $\mathbb{P}_\theta\left(N \leqslant n_p^N \mid \mathbf{i}_{2013}\right)$ based on (3.11)-(3.12).*

p	n_p^T	$\mathbb{P}_{\widehat{\theta}^{obs}_{max}}(T \leqslant n_p^T \mid \mathbf{i}_{2013})$	$\mathbb{P}_{\widehat{\theta}^{obs}_{min}}(T \leqslant n_p^T \mid \mathbf{i}_{2013})$	n_p^N	$\mathbb{P}_{\widehat{\theta}^{obs}_{max}}(N \leqslant n_p^N \mid \mathbf{i}_{2013})$	$\mathbb{P}_{\widehat{\theta}^{obs}_{min}}(N \leqslant n_p^N \mid \mathbf{i}_{2013})$
0.50	2018	0.5083	0.5304	6	0.5133	0.5518
0.90	2023	0.9168	0.9242	10	0.9000	0.9176
0.95	2025	0.9609	0.9649	12	0.9662	0.9739
0.99	2029	0.9922	0.9932	14	0.9902	0.9966

 ISSN: 2102-6238

the epidemic might become extinct after this time with a small but non null probability of order $1-p$. This raises the following question: how would the incidences of infectious and infected cattle evolve in the (unlikely) case of a very late extinction? In terms of risk analysis, this issue appears to be crucial to evaluate the risks associated with this worst-case scenario. The tools developed in Section 3 allow to evaluate the probability of all possible outcomes. But since the worst ones, typically a very late extinction, have a negligible probability, these tools do not bring any information in these worst cases, and in particular do not inform on the evolution at each time-step of the spread of the disease (would it decrease extremely slowly, stay at a constant rate for a very long time, present several peaks in its evolution etc.). In order to study the propagation of the epidemic in the decay phase, assuming that extinction occurs very late, we are interested in the distribution of the process $\{\mathbf{I}_n\}_n$ conditionally on the event that the epidemic has not become extinct at time k, where k is very large. We therefore consider for any $n_1, n_2, \ldots \in \mathbb{N}$ and any $\mathbf{i}_0, \mathbf{i}_1, \mathbf{i}_2, \ldots \in \mathbb{N}^d$ the conditioned probability $\mathbb{P}(\mathbf{I}_{n_1} = \mathbf{i}_1, \ldots, \mathbf{I}_{n_r} = \mathbf{i}_r \mid \mathbf{I}_0 = \mathbf{i}_0, \mathbf{I}_k \neq \mathbf{0})$. If k is finite this distribution cannot be easily handled due to its time-inhomogeneity. However, when $\rho \leqslant 1$, it is known (Dallaporta and Joffe, 2008) that this conditioned distribution converges, as $k \to \infty$, to the distribution of a d-dimensional Markov process $\{\mathbf{I}_n^*\}_n$:

$$\lim_{k\to\infty} \mathbb{P}(\mathbf{I}_{n_1} = \mathbf{i}_1, \ldots, \mathbf{I}_{n_r} = \mathbf{i}_r \mid \mathbf{I}_0 = \mathbf{i}_0, \mathbf{I}_k \neq \mathbf{0}) = \mathbb{P}\left(\mathbf{I}_{n_1}^* = \mathbf{i}_1, \ldots, \mathbf{I}_{n_r}^* = \mathbf{i}_r \mid \mathbf{I}_0^* = \mathbf{i}_0\right). \tag{4.1}$$

We shall further discuss in Proposition 4.3 the relevancy of approximating the conditioned probability for k fixed by the limit quantity (4.1). The conditioned process $\{\mathbf{I}_n^*\}_n$ defined by (4.1) is known in the literature as the Q-process associated with $\{\mathbf{I}_n\}_n$, also described as the process conditioned on "not being extinct in the distant future". It has the following transition probability: for every $n \geqslant 1$, $\mathbf{i}, \mathbf{j} \in \mathbb{N}^d$, $\mathbf{i} \neq \mathbf{0}$,

$$\mathbb{P}\left(\mathbf{I}_n^* = \mathbf{j} \mid \mathbf{I}_{n-1}^* = \mathbf{i}\right) = \frac{1}{\rho}\frac{\mathbf{j}\cdot\mathbf{u}}{\mathbf{i}\cdot\mathbf{u}}\mathbb{P}(\mathbf{I}_n = \mathbf{j} \mid \mathbf{I}_{n-1} = \mathbf{i}),$$

where $\mathbf{u}$ is the normalized right eigenvector of $\mathbf{M}$ associated to the Perron's root ρ as introduced in Subsection 3.1.1. In the same way as for the process $\{\mathbf{I}_n\}_n$ (see Subsection 2.3), we define the 1-dimensional process $\{I_n^*\}_n$ such that $\mathbf{I}_n^* = (I_{n,1}^*, I_{n,2}^*, \ldots, I_{n,d}^*) =: (I_n^*, I_{n-1}^*, \ldots, I_{n-(d-1)}^*)$. By construction we then have, as for $\{I_n\}_n$, $I_{n,i}^* = I_{n-i+1}^*$, for each n and each $i = 1 \ldots d$.

Proposition 4.1 (Pénisson and Jacob (2012))**.** *The stochastic process $\{I_n^*\}_n$ is, conditionally on its past, distributed as the sum of two independent Poisson and Bernoulli random variables, that is*

$$I_n^* \mid \mathbf{I}_{n-1}^* \overset{\mathscr{D}}{=} \mathscr{P}oiss\left(\mathbf{I}_{n-1}^* \cdot \mathbf{\Psi}(\theta)\right) * \mathscr{B}\left(p\left(\mathbf{I}_{n-1}^*\right)\right),$$

where $*$ is the convolution product symbol, and

$$p\left(\mathbf{I}_{n-1}^*\right) := \frac{u_1 \mathbf{I}_{n-1}^* \cdot \mathbf{\Psi}(\theta)}{u_1 \mathbf{I}_{n-1}^* \cdot \mathbf{\Psi}(\theta) + \sum_{k=2}^d I_{n-k+1}^* u_k}.$$

Remark 4.2. Note that $\{I_n^*\}_n$ behaves at each time step like $\{I_n\}_n$ (i.e. according to a Poisson distribution), except that it has the possibility to add one unit or not, according to a Bernoulli random variable. If $I_{n-1}^* = \ldots = I_{n-(d-1)}^* = 0$, then the probability of adding one unit is one, which prevents the extinction of the process $\{\mathbf{I}_n^*\}_n$.

 ISSN: 2102-6238

Let us discuss the relevancy of approximating $\{\mathbf{I}_n\}_n$ conditioned on non-extinction at some finite time k, for k large, by the Q-process $\{\mathbf{I}_n^*\}_n$ obtained by letting $k \to \infty$. When considering the case of late extinction, one works under an hypothetical assumption based on the unknown future, hence in practice one does not focus on a specific value k for the survival of the disease in the population. We therefore might consider that k is chosen large enough such that the approximation of the process $\{\mathbf{I}_n\}_n$ conditioned on the event $\{\mathbf{I}_k \neq \mathbf{0}\}$ by the process $\{\mathbf{I}_n^*\}_n$ is valid. Of course, the order of magnitude of such k will depend on the rate of convergence of the conditioned process to $\{\mathbf{I}_n^*\}_n$.

Proposition 4.3 (Pénisson and Jacob, 2012)**.** *For each $n_1 \leqslant \ldots \leqslant n_r$ and $\mathbf{i}_0, \ldots, \mathbf{i}_r \in \mathbb{N}^d \setminus \{\mathbf{0}\}$, there exist some positive constants A, B, a, b such that for all $k \geqslant n_r$,*

$$\left|\mathbb{P}\left(\mathbf{I}_{n_1} = \mathbf{i}_1, \ldots, \mathbf{I}_{n_r} = \mathbf{i}_r \mid \mathbf{I}_0 = \mathbf{i}_0, \mathbf{I}_k \neq \mathbf{0}\right) - \mathbb{P}_{\mathbf{i}_0}\left(\mathbf{I}_{n_1}^* = \mathbf{i}_1, \ldots, \mathbf{I}_{n_r}^* = \mathbf{i}_r \mid \mathbf{I}_0^* = \mathbf{i}_0\right)\right| \leqslant A\frac{2ak^{m-1}\left(\frac{|\lambda|}{\rho}\right)^{\frac{k}{2}} + b\rho^{\frac{k}{2}}}{1 - ak^{m-1}\left(\frac{|\lambda|}{\rho}\right)^{\frac{k}{2}} - b\rho^{\frac{k}{2}}} + B\rho^k,$$

where λ is an eigenvalue of $\mathbf{M}$ with multiplicity $m = m(\lambda)$ such that for any other eigenvalue μ of $\mathbf{M}$, $\rho > |\lambda| \geqslant |\mu|$, and such that $|\lambda| = |\mu|$ implies $m \geqslant m(\mu)$.

Hence the concept of the Q-process will have most practical relevance to approximate the very late extinction case if ρ is near to zero and if $|\lambda|$ is small compared to ρ. Note however that the very late extinction scenario is more likely to happen if ρ is near to unity because the time to extinction in most realizations will then be long (see Subsection 3.1.1).

4.2. Estimation

In order to make predictions of the evolution of the epidemic in case of a very late extinction, i.e. in order to make predictions of the behavior of the conditioned process $\{I_n^*\}_n$ introduced in Subsection 4.1, we need to estimate the parameter θ in the setting of this conditioned process. We point out that θ does not play the same role in the conditioned process $\{I_n^*\}_n$ and in the unconditioned process $\{I_n\}_n$, since, as shown in Proposition 4.1, this parameter interferes not only in the Poisson random variable but also in the Bernoulli one. It would thus be irrelevant to estimate θ with an estimator aimed for the unconditioned process such as $\widehat{\theta}$. Similarly as in Subsection 3.2 we consider the WCLSE based on the process $I_n^*/\sqrt{\mathbf{a}\cdot\mathbf{I}_{n-1}^*}$, namely

$$\widehat{\theta}^* := \arg\min_{\theta\in\Theta} S_n(\theta), \quad S_n(\theta) := \sum_{k=1}^{n}\left(\frac{I_k^*}{\sqrt{\mathbf{a}\cdot\mathbf{I}_{k-1}^*}} - f(\theta, \mathbf{I}_{k-1}^*)\right)^2,$$

where Θ is defined in Subsection 3.2, and

$$f(\theta, \mathbf{I}_{k-1}^*) := \mathbb{E}_\theta\left(\frac{I_k^*}{\sqrt{\mathbf{a}\cdot\mathbf{I}_{k-1}^*}} \mid \mathbf{I}_{k-1}^*\right) = \frac{\mathbf{I}_{k-1}^*\cdot\boldsymbol{\Psi}(\theta) + p\left(\theta, \mathbf{I}_{k-1}^*\right)}{\sqrt{\mathbf{a}\cdot\mathbf{I}_{k-1}^*}}.$$

 ISSN: 2102-6238

In what follows, we denote by f' the derivative of f with respect to θ. We define as well

$$g\left(\theta,\mathbf{I}^*_{k-1}\right) := \mathbb{E}_\theta\left(\left(\frac{I^*_k}{\sqrt{\mathbf{a}\cdot\mathbf{I}^*_{k-1}}} - f(\theta,\mathbf{I}^*_{k-1})\right)^2 \mid \mathbf{I}^*_{k-1}\right)$$
$$= \frac{\mathbf{I}^*_{k-1}\cdot\boldsymbol{\Psi}(\theta) + p\left(\theta,\mathbf{I}^*_{k-1}\right)\left(1-p\left(\theta,\mathbf{I}^*_{k-1}\right)\right)}{\mathbf{a}\cdot\mathbf{I}^*_{k-1}}.$$

Theorem 4.4 (Pénisson and Jacob, 2012)**.** *The estimator $\widehat{\theta}^*$ is strongly consistent, that is $\lim_{n\to\infty}\widehat{\theta}^* \overset{a.s.}{=} \theta$, and has the following asymptotic distribution,*

$$\lim_{n\to\infty} \frac{\sum_{k=0}^n f'(\widehat{\theta}^*,\mathbf{I}^*_k)^2}{\sqrt{\sum_{k=0}^n f'(\widehat{\theta}^*,\mathbf{I}^*_k)^2 g(\widehat{\theta}^*,\mathbf{I}^*_k)}}\left(\widehat{\theta}^* - \theta\right) \overset{\mathscr{D}}{=} \mathscr{N}(0,1). \tag{4.2}$$

As in Subsection 3.2, our estimation of θ is based on the yearly number of cases of BSE reported in Great Britain from 1989 until 2013 (Table 1). We set $\mathbf{I}_0 = \mathbf{i}_{1997}$, hence the number of available observations until 2013 is $n = 16$, which is far from the asymptotic setting $n \to \infty$ of Theorem 4.4. We point out that, by making use of the estimator $\widehat{\theta}^*$ on the real data, we make an unverifiable assumption on the future of the epidemic: we consider the data as if they were the beginning of a trajectory with very late extinction. This should have the following consequence: the estimation provided by $\widehat{\theta}^{*obs}$ should be a bit smaller than the value 2.4301 provided by $\widehat{\theta}^{obs}$. Indeed we obtain

$$\widehat{\theta}^{*obs} = 2.4279.$$

We then deduce from (4.2) the 95% asymptotic confidence interval $[\widehat{\theta}^*_{min}, \widehat{\theta}^*_{max}]$ of θ, where $\widehat{\theta}^*_{min} := \widehat{\theta}^* - 1.96/\widehat{c}_2$, $\widehat{\theta}^*_{max} := \widehat{\theta}^* + 1.96/\widehat{c}_2$, $\widehat{c}_2 = \sum_{k=0}^n (f'(\widehat{\theta}^*,\mathbf{I}^*_k))^2 \left[\sum_{k=0}^n (f'(\widehat{\theta}^*,\mathbf{I}^*_k))^2 g(\widehat{\theta}^*,\mathbf{I}^*_k)\right]^{-\frac{1}{2}}$. The observed value of the interval are

$$\widehat{\theta}^{*obs}_{min} = 2.3798, \quad \widehat{\theta}^{*obs}_{max} = 2.4760,$$

which is of the same magnitude order as the confidence interval $[2.3842, 2.4805]$ obtained with the unconditioned process (see (3.10)).

4.3. Prediction

4.3.1. Relevancy of the approximation with the Q-process

Computing the eigenvalues ρ and λ_1 introduced in Proposition 4.3, we obtain $\rho(\widehat{\theta}^{*obs}) = 0.6663$ and $|\lambda_1(\widehat{\theta}^{*obs})| = 0.5569$. It thus appears that the convergence of the epidemic process $\{\mathbf{I}_n\}_n$ conditioned on non-extinction at time k to the Q-process $\{\mathbf{I}^*_n\}_n$ as $k \to \infty$ is not very fast. As a consequence the study of the Q-process only provides information about the behavior of the disease spread in the case of an extremely late extinction.

 ISSN: 2102-6238

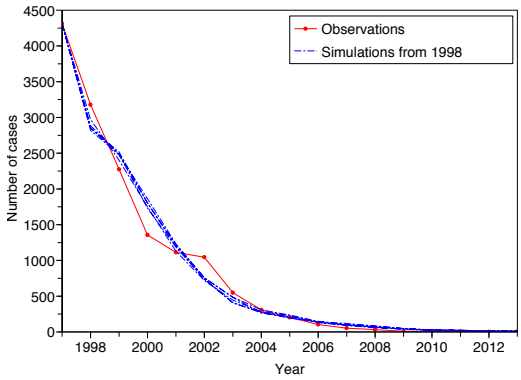
4.3.2. Prediction of the incidences of cases and incidences of infected cattle

Let us predict the most dangerous evolution thanks to the transition law of the conditioned process given by Proposition 4.1. First, we see thanks to Figure 3a that the simulations provided by the conditioned process initialized by $\mathbf{I}_0^* = \mathbf{i}_{1997}$, and where θ is estimated by $\widehat{\theta}^{*obs} = 2.4279$, are close to the real observations on the period 1998–2013. Figure 3b is an example of one simulated trajectory on the period 2014–2040 of the conditioned process, for $\mathbf{I}_0^* = \mathbf{i}_{2013}$. It appears that the values of this simulated trajectory are rapidly very small, and of course are never equal to 0 for $d = 9$ consecutive times. For a more refined prediction, we simulate 10000 realizations of this process from 2014 until 2040, with $\mathbf{I}_0^* = \mathbf{i}_{2013}$. Moreover, for every $n \geqslant 2014$ and for each of the 10000 simulated values I_n^*, we make one realization of the incidence E_n^1 of infected cattle at time n, according to the law given by (2.11). Figures 3c and 3d represent the yearly maximum, median and 95% quantile associated with the 10000 realizations of respectively, the incidence of cases and infected cattle, in case of an extreme late extinction. It appears thanks to Figures 3c and 3d that the supposedly "most dangerous" trajectories nevertheless do not reach high values and do not present a new peak of epidemic.

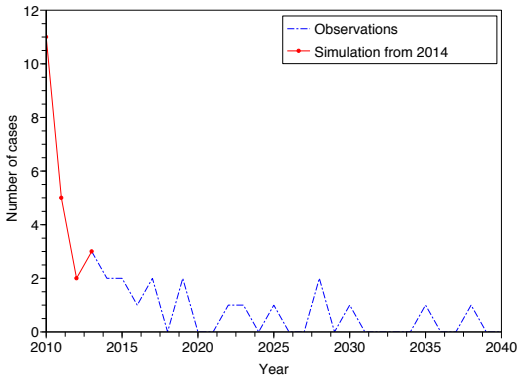
5. Conclusion

Starting from a general unconventional branching process describing the propagation of the disease on branching trees relative to the population dynamics, and assuming reasonable epidemiological assumptions, we obtained as a limit as the initial population size tends to infinity a simple branching process on the incidence of infectives and infected animals. This led to a thorough study of the behavior of the process, and several estimations from the observed incidences of cases. The Bayesian estimation showed in particular the great efficiency of the feed ban of 1988, and allowed us to estimate the incubation parameters, taking into account the uncertainty of the beginning of the epidemic. Focusing then on the decay phase of the process and using a frequentist approach, we confirmed mathematically what is commonly accepted, namely that BSE is fading out in Great-Britain. More precisely, the last BSE case should occur before 2025 with a very large probability, and less than 12 cases should appear until then. We obtained moreover the order of magnitude of the number of infected cattle in the population. In addition, the estimation of the infection parameter concluded to the possible existence of a minor but non null infection source that is not of maternal type, and which is very small (only around 3 newly infected animal per year and per infective) compared to the main source of horizontal infection until 1988 due to protein supplements. All the estimations are based on $a_m = 10$, which is an undervaluation of a_m. Taking $a_m = 19$ slightly reduces the estimation of the infection parameters (Subsection 2.4.4). Our estimations consequently slightly overvalue the future cases number and the epidemic extinction date compared to the case $a_m = 10$. But the goal here is mainly to provide an order of magnitude of the estimations, given that there are other error sources such as the model, which is a simplified representation of the reality. Moreover in risk analysis it is safer to overestimate a risk rather than to underestimate it. Finally, the study of the worst-case scenario showed that even in the case of an extreme late extinction of the disease in the population, the incidence of cases would decrease quite rapidly to 0, with afterward only 1 or 2 yearly cases occurring regularly but sparsely, with no appearance of a new peak of epidemic. We have shown with this example

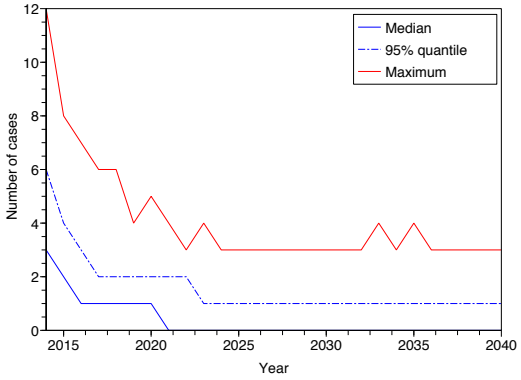
 ISSN: 2102-6238



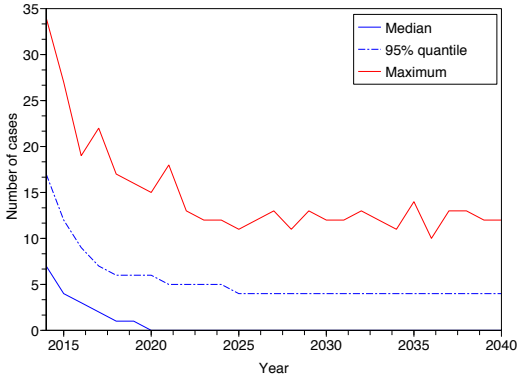
(a) 5 simulations of $\{I_n^*\}_n$ initialized by $\mathbf{i}_{1997}$, and comparison with the observations on the period 1998–2013.



(b) One simulation of $\{I_n^*\}_n$ initialized by $\mathbf{i}_{2013}$.



(c) Prediction of the yearly incidences of cases from 2014 in the worst-case scenario, based on 10000 simulations of $\{I_n^*\}_n$ initialized by $\mathbf{i}_{2013}$.



(d) Prediction of the yearly incidences of infected cattle from 2014 in the worst-case scenario, based on 10000 simulations of $\{E_n^1\}_n$.

Figure 3: Prediction of the spread of the disease in the worst-case scenario, based on simulations with the infection parameter $\widehat{\theta}^{*obs} = 2.4279$.

 ISSN: 2102-6238

that the methodology developed in Sections 3 and 4 provides accurate tools to study the decay phase of an epidemic under the current sanitary measures, which would help to make new policy decisions. This evaluation is all the more relevant since it is obtained not by simply computing what should most probably happen, but also by taking into account the variability of many factors (infection, incubation, survival), and by studying the potentially most dangerous evolution. It is worth mentioning that this methodology could be applied to any other disease provided that the epidemic can be considered as negligible relatively to the whole population, that this one is stable over time, and that the individual probability to be infected is proportional to the proportion of infectives in the whole population.

6. Appendix

Proof of Proposition 2.2. The proof is a recursive proof on n based on model (2.1)-(2.3). Considering first N_n^I, we write, from (2.1),

$$N_n^I = \sum_{k=1}^{d} \sum_{i=1}^{N_{n-k}} \delta_i^k, \quad \delta_i^k := \sum_{a=k+1}^{a_m} \delta_{n-k,i}^{(E^1,a-k)} \delta_{a-k,n-k;n,i}^{E^1,I^1}.$$

Let us define $p_i^k(\{I_h\}) := \mathbb{E}\left(\delta_i^k \mid \mathscr{F}_{n-1}(\{I_h\})\right)$ and B_i as the set of individuals non independent of i, given $\mathscr{F}_{n-1}(\{I_h\})$. We assume (2.10)-(2.11) until time $n-1$, and we are going to show these relationships at time n. So let, for any $A \subset \mathbb{N}$,

$$\Delta_n(A) := \left| \mathbb{P}\left(N_n^I \in A \mid \mathscr{F}_{n-1}(\{I_h\})\right) - \mathscr{P}oiss\left(\sum_{k=1}^{d} \Psi_{k|n-k} I_{n-k}\right)(A) \right|.$$

Then

$$\Delta_n(A) \leqslant \Delta_n^1(A) + \Delta_n^2(A),$$

where

$$\Delta_n^1(A) := \left| \mathbb{P}\left(N_n^I \in A \mid \mathscr{F}_{n-1}(\{I_h\})\right) - \mathscr{P}oiss\left(\sum_{k=1}^{d} \sum_{i=1}^{N_{n-k}} p_i^k(\{I_h\})\right)(A) \right|$$

and

$$\Delta_n^2(A) := \left| \mathscr{P}oiss\left(\sum_{k=1}^{d} \sum_{i=1}^{N_{n-k}} p_i^k(\{I_h\})\right)(A) - \mathscr{P}oiss\left(\sum_{k=1}^{d} \Psi_{k|n-k} I_{n-k}\right)(A) \right|.$$

We first apply Arratia-Goldstein-Gordon inequality (Arratia et al., 1989) on $\Delta_n^1(A)$:

$$\sup_{A\subset\mathbb{N}} \Delta_n^1(A) \leqslant \sum_{k=1}^{d} \sum_{i=1}^{N_{n-k}} \sum_{k'=1}^{d} \sum_{j\in B_i^{k'}} p_i^k(\{I_h\}) p_j^{k'}(\{I_h\}) + \sum_{k=1}^{d} \sum_{i=1}^{N_{n-k}} \sum_{k'=1}^{d} \sum_{j\in B_i^{k'}, j\neq i} \mathbb{E}\left(\delta_i^k \delta_j^{k'} \mid \mathscr{F}_{n-1}(\{I_h\})\right),$$

 ISSN: 2102-6238

where $B_i^{k'}$ is the set B_i intersected with the population at time $n-k'$. Let us compute $p_i^k(\{I_h\})$. We may express δ_i^k as follows:

$$\delta_i^k = \sum_{a=k+1}^{a_m} \delta_{n-k,i}^{(R^c,a-k)} \delta_{n-k,i}^{(E^1,a-k)} \delta_{a-k,n-k;n,i}^{E^1,R^c} \delta_{a-k,n-k;n,i}^{E^1,I^1}.$$

We then obtain $p_i^k(\{I_h\}) = \sum_{a=k+1}^{a_m} p_{a,1}^k p_{a,2}^k p_{a,3}^k p_{a,4}^k$, where

$$\begin{aligned}
p_{a,1}^k &= \mathbb{P}\left(\delta_{a-k,n-k;n,i}^{E^1,I^1} = 1 \mid \delta_{n-k,i}^{(E^1,a-k)} \delta_{a-k,n-k;n,i}^{E^1,R^c} = 1, \mathscr{F}_{n-1}(\{I_h\})\right),\\
p_{a,2}^k &= \mathbb{P}\left(\delta_{a-k,n-k;n,i}^{E^1,R^c} = 1 \mid \delta_{n-k,i}^{(E^1,a-k)} = 1, \mathscr{F}_{n-1}(\{I_h\})\right),\\
p_{a,3}^k &= \mathbb{P}\left(\delta_{n-k,i}^{(E^1,a-k)} = 1 \mid \delta_{n-k,i}^{(R^c,a-k)} = 1, \mathscr{F}_{n-1}(\{I_h\})\right),\\
p_{a,4}^k &= \mathbb{P}\left(\delta_{n-k,i}^{(R^c,a-k)} = 1 \mid \mathscr{F}_{n-1}(\{I_h\})\right).
\end{aligned}$$

Then using *(AS)* and the limit model until $n-1$ (implying that the infectives population is negligible until $n-1$), we obtain:

$$\begin{aligned}
p_{a,2}^k &= \mathbb{P}\left(\delta_{a-k,n-k;n-1,i}^{E^1,R^c} = 1 \mid \delta_{n-k,i}^{(E^1,a-k)} = 1, \mathscr{F}_{n-1}(\{I_h\})\right)\\
&\quad \times \mathbb{P}\left(\delta_{a-1,n-1;n,i}^{R^c,R^c} = 1 \mid \delta_{a-k,n-k;n-1,i}^{E^1,R^c} = 1, \delta_{n-k,i}^{(E^1,a-k)} = 1, \mathscr{F}_{n-1}(\{I_h\})\right)\\
&= \frac{P_{age}(a-1)}{P_{age}(a-k)} \frac{S(a)}{S(a-1)} + \eta_{a,n,2}^k,\\
p_{a,4}^k &= P_{age}(a-k) + \eta_{a,n,4}^k,
\end{aligned}$$

where $\lim_{\mathbf{N}_0\to\infty} \eta_{a,n,u}^k \overset{a.s.}{=} 0$, $u = 2,4$. Using in addition Lemma 6.1, we consequently obtain

$$p_{a,2}^k p_{a,4}^k = P_{age}(a) + \eta_{a,n}^k, \text{ where } \lim_{\mathbf{N}_0\to\infty} \eta_{a,n}^k \overset{a.s.}{=} 0.$$

Then (AI_2) implies that $p_{a,1}^k = P_{inc}(k)$. Moreover using (2.6) and (2.8), we get $\lim_{\mathbf{N}_0\to\infty} \widehat{p}_{n-k|n'} = \lim_{\mathbf{N}_0\to\infty} \widehat{p}_{n-k|n-k}$, $n' \geqslant n-k$, and since $\lim_{\mathbf{N}_0\to\infty} \widehat{\theta}_{n-k}^{a-k,u} = \theta^{a-k,u}$ for $u \in \{R, R^c\}$ thanks to (AI_1) ($\widehat{\theta}_{n-k}^{a-k,u}$ is assumed to be a continuous function of $\widehat{P}_{age,n-k}(a-k)$ only), then

$$\begin{aligned}
p_i^k(\{I_h\}) =& P_{inc}(k) \sum_{a=k+1}^{a_m} \left(P_{age}(a) + \eta_{a,n}^k\right)\\
&\times \left(\left(\theta_{n-k}^{a-k,R^c} + \theta_{n-k}^{a-k,R} \widehat{\lambda}_{n-k|n-1} \phi_{n-k} + \mathbf{1}_{\{a=k+1\}} p_{mat}\right) \frac{I_{n-k}}{N_{n-k}} + \varepsilon_{a-k,n-k|n-1}\right).
\end{aligned}$$

Thanks to the assumption on $\varepsilon_{a-k,n-k|n-1}$ (see (AI_1)), then $p_i^k(\{I_h\}) \in O(I_{n-k}/N_{n-k})$ as $\mathbf{N}_0 \to \infty$. This leads to

$$\sum_{i=1}^{N_{n-k}} \sum_{j\in B_i^{k'}} p_i^k(\{I_h\}) p_j^{k'}(\{I_h\}) \leqslant N_{n-k} \max_i \text{Card}\left(B_i^{k'}\right) O\left(\max_{k'} \left(\frac{I_{n-k'}}{N_{n-k'}}\right)^2\right).$$

 ISSN: 2102-6238

Similarly, thanks to (2.9), we have

$$\sum_{i=1}^{N_{n-k}} \sum_{j\in B_i^{k'}, j\neq i} \mathbb{E}\left(\delta_{k,i}\delta_{k',j} \mid \mathscr{F}_{n-1}(\{I_h\})\right) \leqslant N_{n-k} \max_i \mathrm{Card}\left(B_i^{k'}\right) O\left(\max_{k'}\left(\frac{I_{n-k'}}{N_{n-k'}}\right)^x\right).$$

According to the property of rare disease until $n-1$ and the stability over time of the whole population, it follows from the two previous inequalities that $\lim_{\mathbf{N}_0\to\infty} \Delta_n^1(A) \overset{a.s.}{=} 0$. Moreover since $\lim_{\mathbf{N}_0\to\infty} \widehat{\lambda}_{n|n'} = \lambda_n$ (see proof below), then

$$\sum_{k=1}^{d}\sum_{i=1}^{N_{n-k}} p_i^k(\{I_h\}) = \sum_{k=1}^{d} \Psi_{k|n-k} I_{n-k} + O\left(\max_{a,k}\left(\eta_{a,n}^k I_{n-k}, \varepsilon_{a-k,n-k|n-1} N_{n-k}\right)\right)$$

as $\mathbf{N}_0 \to \infty$, which implies that $\lim_{\mathbf{N}_0\to\infty} \sup_{A\subset\mathbb{N}} \Delta_n^2(A) = 0$.

Moreover, (2.14) comes directly from (2.7): let $\widehat{f}_{n|n'}(\{i_h\}) = \mathbb{E}\left(N_{n-1}^{E^{last}} \mid \mathscr{F}_{n'}(\{i_h\})\right)$, $n' \geqslant n$, and $\widehat{\lambda}_{n|n'}(\{i_h\}) = \mathbf{1}_{\{i_n\neq 0\}}\left(\widehat{f}_{n|n'}(\{i_h\})(i_n)^{-1} - 1\right)$. Then $\widehat{\lambda}_{n|n'} = \widehat{\lambda}_{n|n'}(\{I_h\})$ in which

$$\begin{aligned}\widehat{f}_{n|n'}(\{i_h\}) &= \sum_{l\geqslant i_n} l\mathbb{P}\left(N_{n-1}^{E^{last}} = l \mid N_n^I = i_n, \mathscr{F}_{n'}\left(\{i_h\}_{h\neq n}\right)\right)\\ &= \frac{\sum_{l\geqslant i_n} l\mathbb{P}\left(N_n^I = i_n \mid N_{n-1}^{E^{last}} = l, \mathscr{F}_{n'}\left(\{i_h\}_{h\neq n}\right)\right)\mathbb{P}\left(N_{n-1}^{E^{last}} = l \mid \mathscr{F}_{n'}\left(\{i_h\}_{h\neq n}\right)\right)}{\sum_{l\geqslant i_n}\mathbb{P}\left(N_n^I = i_n \mid N_{n-1}^{E^{last}} = l, \mathscr{F}_{n'}\left(\{i_h\}_{h\neq n}\right)\right)\mathbb{P}\left(N_{n-1}^{E^{last}} = l \mid \mathscr{F}_{n'}\left(\{i_h\}_{h\neq n}\right)\right)}.\end{aligned}$$

This implies (2.14) using $N_n^I = \sum_{i=1}^{N_{n-1}^{E^{last}}} \sum_{a=2}^{a_m} \delta_{n-1,i}^{(R^c,a-1)} \delta_{a-1,n-1;n,i}^{R^c,R^c}$ and a similar relationship as (2.10) concerning $E_{n-1}^{last} \mid \mathscr{F}_{n'}\left(\{i_h\}_{h\neq n}\right)$ (equal to $E_{n-1}^{last} \mid \mathscr{F}_{n-1}(\{i_h\})$).

Model (2.11) is proved in a similar way.

The proof is finally achieved by showing in the case where $\lambda_n\phi_n$ depends on n only, the convergence in distribution of the whole Markov chain $\{\mathbf{M}_n\}$ of order d to $\{\mathbf{X}_n\}_n$, where $\mathbf{M}_n := (N_n^I, N_n^{E^1})$ and $\mathbf{X}_n := (I_n, E_n^1)$, that is, for all $n_1, \ldots, n_p$ and all p,

$$\lim_{\mathbf{N}_0\to\infty} \mathbb{P}\left(\mathbf{X}_{n_1} = \mathbf{K}_{n_1}, \ldots, \mathbf{X}_{n_p} = \mathbf{K}_{n_p}\right) = \mathbb{P}\left(\mathbf{X}_{n_1} = \mathbf{K}_{n_1}, \ldots, \mathbf{X}_{n_p} = \mathbf{K}_{n_p}\right).$$

This is proved by iteration on p. □

Lemma 6.1. *Assume (AS) . Then, for all $n \geqslant 0$ and $1 \leqslant a \leqslant a_m$, the population satisfies:*

$$\lim_{\mathbf{N}_0\to\infty} \frac{N_{a,n}}{N_n} \overset{a.s.}{=} P_{age}(a) = mS(a) = \frac{S(a)}{\sum_{a\geqslant 1} S(a)}, \quad \lim_{\mathbf{N}_0\to\infty} \frac{N_{n+1}}{N_n} \overset{a.s.}{=} 1.$$

Proof. Denoting $\sum_{i=1}^{N_{n-1}} Y_{n,i} =: N_{0,n-1}$, the proof is a recursive proof on $1 \leqslant a \leqslant a_m$ and $n \geqslant 0$, based on the relationships,

$$\frac{N_{a,n}}{N_n} = \sum_{i=1}^{N_{a-1,n-1}} \frac{\delta_{a-1,n-1,n,i}^{R^c,R^c}}{N_{a-1,n-1}} \frac{N_{a-1,n-1}}{N_{n-1}} \frac{N_{n-1}}{N_n}, \quad \frac{N_{n+1}}{N_n} = \sum_{a=1}^{a_m}\sum_{i=1}^{N_{a-1,n}} \frac{\delta_{a-1,n,n+1,i}^{R^c,R^c}}{N_{a-1,n}} \frac{N_{a-1,n}}{N_n},$$

where we use $S(0) = 1$, $\mathbb{E}\left(\delta_{a-1,n-1,n,i}^{R^c,R^c}\right) = S(a)/S(a-1)$ and $\lim_{N_n\to\infty} N_{0,n}/N_n \overset{a.s.}{=} m$. □

 ISSN: 2102-6238

References

Anderson, R. M., Donnelly, C. A., Ferguson, N. M., Woolhouse, M. E. J., Watt, C. J., Udy, H. J., MaWhinney, S., Dunstan, S. P., Southwood, T. R. E., Wilesmith, J. W., Ryan, J. B. M., Hoinville, L. J., Hillerton, J. E., Austin, A. R., and Wells, G. A. H. (1996). Transmission dynamics and epidemiology of BSE in British cattle. *Nature*, 382(6594):779–788.

Arratia, R., Goldstein, L., and Gordon, L. (1989). Two Moments Suffice for Poisson Approximations: The Chen-Stein Method. *Ann. Probab.*, 17(1):9–25.

Athreya, K. B. and Ney, P. E. (1972). *Branching processes*. Springer-Verlag, New-York.

Consul, P. C. and Famoye, F. (2006). *Lagrangian probability distributions*. Birkhäuser Boston, Inc., Boston, MA.

Dallaporta, S. and Joffe, A. (2008). The Q-process in a multitype branching process. *International Journal of Pure and Applied Mathematics*, 42(2):235–240.

Department for Environment, Food & Rural Affairs (2014). Cattle TSE surveillance statistics. http://www.defra.gov.uk/ahvla-en/publication/tse-stats-cattle/. [Online; accessed April-2015].

Devroye, L. (1992). The branching process method in Lagrange random variate generation. *Communications in Statistics-Simulation and Computation*, 21:1–14.

Donnelly, C. A. (1998). Maternal transmission of BSE: interpretation of the data on the offspring of BSE-affected pedigree suckler cows. *Veterinary Record*, 142(21):579–580.

Harris, T. E. (1948). Branching processes. *Annals of Mathematical Statistics*, 19(4):474–494.

HMSO (1996). The Bovine Spongiform Encephalopathy Order. http://www.legislation.gov.uk/uksi/1996/2007/contents/made. [Online; accessed April-2015].

Jacob, C., Maillard, L., Denis, J. B., and Bidot, C. (2008). Stochastic modelling of the incidence of clinical cases of a rare fatal SEI disease in a large branching population structured in ages. Example of the BSE epidemic in Great-Britain. Technical report, INRA, MIA unit, Jouy-en-Josas.

Jacob, C., Maillard-Teyssier, L., Denis, J. B., and Bidot, C. (2010). A branching process approach for the propagation of the bovine spongiform encephalopathy in Great Britain. In González Velasco, M., Puerto, I., Martínez, R., Molina, M., Mota, M., and Ramos, A., editors, *Workshop on Branching Processes and Their Applications*, volume 197 of *Lecture Notes in Statistics*, pages 225–241. Springer Berlin Heidelberg.

Joffe, A. and Spitzer, F. (1967). On multitype branching processes with $\rho \leqslant 1$. *Journal of Mathematical Analysis and Application*, 19(3):409–430.

OpenBUGS (2009). http://www.openbugs.net/. [Online; accessed April-2015].

Pénisson, S. (2014). Estimation of the infection parameter of an epidemic modeled by a branching process. *Electronic Journal of Statistics*, 8(2).

Pénisson, S. and Jacob, C. (2012). Stochastic Methodology for the Study of an Epidemic Decay Phase, Based on a Branching Model. *International Journal of Stochastic Analysis*, 2012.

Supervie, V. and Costagliola, D. (2004). The unrecognised French BSE epidemic. *Veterinary Research*, 35(3):349–362.

Wells, G. A., Scott, A. C., Johnson, C. T., Gunning, R. F., Hancock, R. D., Jeffrey, M., Dawson, M., and Bradley, R. (1987). A novel progressive spongiform encephalopathy in cattle. *Veterinary Record*, 121(18):419–420.

World Organisation for Animal Health (2014). Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom. http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/number-of-cases-in-the-united-kingdom/. [Online; accessed April-2015].

 ISSN: 2102-6238