Journal of Theoretical Biology 291 (2011) 1–9

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Seasonal spread and control of Bluetongue in cattle

Maud V.P. Charron [a,b,c,*], Henri Seegers [a,b], Michel Langlais [c], Pauline Ezanno [a,b]

[a] INRA, UMR1300 Bio-agression, Epidémiologie et Analyse de Risque, BP 40706, F-44307 Nantes, France
[b] Oniris, LUNAM Université Nantes Angers Le Mans, France
[c] Université Bordeaux Segalen, UMR CNRS 5251, IMB, Bordeaux, France

ARTICLE INFO

Article history:
Received 13 January 2011
Received in revised form
26 August 2011
Accepted 30 August 2011
Available online 17 September 2011

Keywords:
Vector-borne disease
Mathematical modelling
Sensitivity analysis
Vaccination
Vertical transmission

ABSTRACT

Bluetongue is a seasonal midge-borne disease of ruminants with economic consequences on herd productivity and animal trade. Recently, two new modes of transmission have been demonstrated in cattle for Bluetongue virus serotype 8 (BTV8): vertical and pseudo-vertical transmission. Our objective was to model the seasonal spread of BTV8 over several years in a homogeneous population of cattle, and to evaluate the effectiveness of vaccination strategies. We built a deterministic mathematical model accounting for the seasonality in vector abundance and all the modes of transmission. We proposed a counterpart of the basic reproduction number (R_0) in a seasonal context (R_S). Set $A(t)$ is the number of secondary cases produced by a primary case introduced at time t. R_S is the average of $A(t)$. It is a function of midge abundance and vaccination strategy. We also used A^*, the maximum of $A(t)$, as an indicator of the risk of an epidemic. Without vaccination, the model predicted a large first epidemic peak followed by smaller annual peaks if $R_S > 1$. When $R_S < 1$, small epidemics could occur if $A^* > 1$. Vaccination reduced R_S and A^* to less than one, but almost perfect vaccine efficacy and coverage were required to ensure no epidemics occurred. However, a lower coverage resulting in $R_S > 1$ could decrease infection prevalence. A further step would be to optimize vaccination strategies by targeting an appropriate period of the year to implement the vaccination.

1. Introduction

Insect-borne disease spread is seasonal in temperate regions. This is due to variations in the availability of either the host, such as migratory birds which are required for the spread of West Nile Virus (Durand et al., 2010), or the insect vector, whose life cycle is governed largely by temperature and humidity (Gerry and Mullens, 2000; Danks, 1994). Therefore, the pathogen transmission will be reduced during the unfavourable season because of a lack of contact between hosts and vectors. Vector-borne diseases may even spontaneously fade out, if the absence of contact persists.

Bluetongue is a midge-borne disease that constrains ruminant movement and trade, and reduces herd productivity (Velthuis et al., 2009; MacLachlan and Osburn, 2006). In 2006, the serotype 8 of the virus (BTV8) invaded northern Europe. Native midge species were identified as Bluetongue vectors and cattle developed clinical signs after infection by BTV8. The virus has persisted over three years in Europe, with annual epidemic peaks. Seasonal spread of Bluetongue can be explained by the seasonal population dynamics of the vector. To control Bluetongue spread, a massive vaccination programme of cattle and sheep has been implemented in most affected countries. However, the observed viral persistence, despite a dramatic reduction in vector abundance during winter and the vaccination implemented in 2008, indicates either that vaccination was not effective enough for rapid control, or that only partial vaccination was achieved. Therefore, the effectiveness of vaccination strategies against Bluetongue should be evaluated in a seasonal context. Modelling is a pertinent approach, enabling the comparison of numerous scenarios through simulation.

The basic reproduction number, R_0, one of the most important concepts in epidemiology, enquires about the invasion ability of a pathogen (Lopez et al., 2002; van den Driessche and Watmough, 2002). R_0 is the expected number of secondary cases generated by a typical infected individual during its infection period when introduced into a fully susceptible population. If R_0 is greater than one, the virus can spread in the population; if it is less than one, the infection fades out (Lopez et al., 2002; van den Driessche and Watmough, 2002). Therefore, strategies decreasing R_0 to below one enable the control of disease spread. For vector-borne diseases, R_0 accounts for secondary cases generated by both a typical infected host and a typical infected vector. R_0 formulation accounts for parameters of the population dynamics of both vectors and hosts (Diekmann and Heesterbeek, 2000). The identification of controllable parameters which influence R_0 will aid in reducing the spread of Bluetongue.

Different models of Bluetongue spread have been developed but none explicitly included the vector population dynamics, i.e. the variation of vector abundance over time. A first state transition model

* Corresponding author at: INRA, UMR1300 Bio-agression, Epidémiologie et Analyse de Risque, BP 40706, F-44307 Nantes, France. Tel.: +33 240 687 859.
E-mail address: maud.charron@oniris-nantes.fr (M.V.P. Charron).

0022-5193/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2011.08.041

has been proposed for different sets of climatic scenarios (Ward and Carpenter, 1996a, 1996b), but this model cannot be used in situations other than those of Australia. Two European studies (Gubbins et al., 2008; Hartemink et al., 2009) identified the temperature dependent parameters which influence R_0, but did not specifically represent the midge population dynamics. Moreover stochastic models have been developed to study incursion scenarios and control strategies (Gubbins et al., 2010; Szmaragd et al., 2010; Szmaragd et al., 2010). All these studies clearly concluded that vector seasonality should be accounted for when modelling BTV8 spread.

Our objective was to model the seasonal spread of BTV8 in a homogeneous population of cattle according to the vaccination strategies used. The model was simplified to focus on the major components of BTV8 spread: the seasonality of the vector population and the virus transmission. Recently, two new modes of transmission have been highlighted in cattle: the vertical transmission, i.e. the transplacental transmission, and the pseudo-vertical transmission, i.e. a contact transmission between an infected cow and its susceptible newborn calf (De Clercq et al., 2008a, 2008b; Menzies et al., 2008; Desmecht et al., 2008). Here, we proposed an epidemiological model including this new knowledge and accounting for the seasonality of the vector population. With such a model, the BTV8 spread could be modelled over several years. We compared the BTV8 spread with and without seasonality in order to assess its influence. R_0 was calculated without seasonality. To account for seasonality, a counterpart of R_0 was proposed called R_S (for $R_{Seasonal}$). Moreover, vector population dynamics is highly seasonal, with an abrupt increase in abundance, whereas vector lifespan is short. Therefore, we used an additional indicator of the local risk of epidemic occurrence: the maximum number of secondary cases that may be produced by a primary case given the introduction date, called A^*. We identified parameters which had the most influence on R_0, R_S and A^* by a sensitivity analysis. We also evaluated the effectiveness of vaccination strategies through their ability to reduce these indicators to below one and thereby modify the disease spread.

2. Model and methods

2.1. Model description

2.1.1. Biological system and the resulting model assumptions

Three actors are necessary for Bluetongue spread: the virus (BTV8), the vector (a midge), and the host (a ruminant). As the virus is not excreted, indirect transmission is not possible, therefore transmission is mainly vectorial. However vertical transmission can occur by either infected sperm or via the transplacental route in the female host (De Clercq et al., 2008a, 2008b). Only female vectors can transmit/acquire the virus when gorging with host blood which is necessary for egg maturation (Mellor et al., 2000; EFSA, 2007). Therefore, only female vectors were modelled. They have a short lifespan from ten to 20 days (EFSA, 2007; Gould and Higgs, 2009). In Europe, vectors are numerous and have a large geographical distribution (Mellor et al., 2000; EFSA, 2007). Therefore, we assumed the vector population to be geographically homogeneous, i.e. lots of midges almost everywhere. Initially we assumed vectors are homogeneous over time, as they may survive during the unfavourable season on farms. Then, as their life cycle is governed by climatic conditions (Mellor et al., 2000; EFSA, 2007) and only a few vectors may survive during winter, we modelled a seasonal vector population dynamics. With respect to the host, we assumed that viral spread was more due to vector than host movements. Therefore, we

Table 1
Parameters of the model of the BTV8 spread in midge and cattle populations.

	Description	Value	References
Cattle parameters			
$1/\eta$	Duration of immunity induced by maternal antibodies (days)	30, 42	Hassig et al. (2007)
m^{S_0}	Calf mortality rate (per day)	1.22×10^{-3}	[a]
b_1	Birth rate (per day)	6.94×10^{-4}	[a]
m	Exit rate (selling and culling) (per day)	6.95×10^{-4}	[a]
Λ^S	Purchase rate	2%	[b]
θ_1^I	Proportion of pseudo-vertical transmission	35%	[c]
θ_1	Proportion of vertical transmission	37%	De Clercq et al. (2008a, 2008b); Desmecht et al. (2008); Maclachlan and Osburn (2008)
g	Conception rate	38%	[c]
$1/\alpha$	Duration of viremia (days)	60	Luedke et al. (1977)
$1/\alpha^{RB}$	Duration of *RB* health state (days)	114	[c]
$1/\alpha^{RBV}$	Duration of *RBV* health state (days)	139	[c]
b_1^{RB}	Birth rate to animal in state *RB* rate (per day)	$\alpha^{RB}/2$	
b_1^{RBV}	Recruitment from *RBV* rate (per day)	$\alpha^{RBV}/2$	
ε	Disease induced mortality rate (per day)	0.9999	EFSA (2007)
$1/\zeta$	Duration of viremia if animal has been vaccinated (days)	35	Savini et al. (2008)
υ	Vaccination rate	0–100%	managed
p	Vaccine efficacy	0–100%	managed
$1/\delta$	Duration of vaccine immunity (days)	365	Savini et al. (2008); Wäckerlin et al. (2010)
c_{vh}	Probability of transmission from vector to host	0.92	EFSA (2007); O'Connell (2002)
Midges parameters			
c_{hv}	Probability of transmission from host to vector	0.15	Carpenter et al. (2006); Gerry et al. (2001)
n	Biting rate	0.25	EFSA (2007)
b_2	Fertility rate	6.1	EFSA (2007)
m_2	Mortality rate	1/21	Mellor et al. (2000); EFSA (2007)
K_2	Carrying capacity	10^{9*}	[c]
k_2	Density-dependence mortality rate	$\frac{b_2-m_2}{K_2}$	[b]
$1/\rho$	Duration of extrinsic incubation period	10	EFSA (2007); Gould and Higgs (2009)

[a] Agricultural statistics.
[b] Calculated to ensure a constant host population.
[c] To our best knowledge.

neglected the host population structure in herds. Cattle are a reservoir for Bluetongue virus due to a longer period of viremia and greater viral multiplication than in other ruminant hosts (Goltz, 1978). Moreover, in Europe, the cattle population is large. Therefore, we focused on only cattle, and ignored other hosts. In our model, the cattle population was considered to be constant in size and open with selling/culling and renewal/births. Only females were included as the number of adult males in the cattle population is low in Europe because most males are sold young. As both the vector and host populations are large, we built a deterministic model.

2.1.2. Mathematical model of BTV8 spread

At the disease-free state and with seasonality, the vector population was assumed to have a logistic growth with $K_2(t) = (b_2 - m_2)/k_2(t)$ the carrying capacity of the environment dependant on the vector fertility (b_2), mortality (m_2) and density-dependant mortality (k_2) rates. The condition $b_2 - m_2 > 0$ was verified, i.e. a positive growth rate of the population (Table 1). The parameter K_2 was assumed periodic to obtain a single annual peak in the vector abundance during the favourable season (summer in Europe). Without seasonality parameters were assumed constant. When virus is present, vectors can be of three mutually exclusive health states (Fig. 1): susceptible (*MS*), latent (*ME*) and infectious (*MI*). The latency period ($1/\rho$; Table 1) was accounted for as it lasts almost as long as life expectancy.

The existence of a disease-free state for hosts was conditioned by $m > b_1$, with b_1 the birth rate and m the exit rate (culling and selling). This is generally true in typical European farming practise, in that some animal purchases ($\Lambda^S > 0$) are required to ensure a constant herd size. When virus is present, hosts can be of six mutually exclusive health states (Fig. 1): susceptible, protected (S_0) or not protected (S) by maternal antibodies, infected, carrying (*IB*) or not carrying (*I*) an infected foetus, recovered, carrying (*RB*) or not carrying (*R*) an infected foetus. Maternal protection lasts for $1/\eta$ days (Table 1), with animals in state S_0 then becoming S. The exit rate from state S_0 (m_{S_0}) was higher than the exit rate from other states (m) because only calves belonged to state S_0 (which have a higher mortality rate than adult animals). Disease-related mortality is low (ε) and only affected states *I* and *IB*. The viremia duration (i.e. the time spent in *I* and *IB*) was $1/\alpha$. When recovered, animals from state *I*(*IB*) became *R*(*RB*). The time spent in *RB*, $1/\alpha^{RB}$, corresponded to a residual gestation time (see later), with animals transiting from *RB* to *R* at calving. Parameter values (Table 1) enabled globally stable host and vector (without seasonality) populations. For cattle, we considered a population with a global renewal rate of 30%, a yearly calving rate of 90%, an exit rate during the first six months of life of 20%, and a yearly selling rate of heifers of 11%.

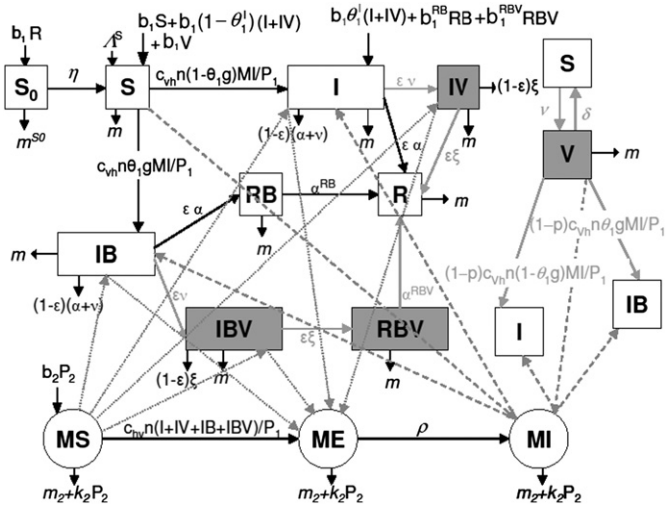

Fig. 1. Conceptual model of the BTV8 spread and control by vaccination. Squares represent the health states of cattle, circles those of midges. In white, the model without vaccination; in grey, the vaccination states. Parameters are defined in Table 1.

Vectorial transmission occurred if a susceptible host (S) bitten by an infected midge (*MI*) became infectious or if a susceptible midge (*MS*) became latent after having bitten an infectious host (*I* or *IB*). Incidence functions were frequency dependant for hosts and vectors (Eq. (1)).

In addition, for animals in mid gestation (proportion g of S), the vectorial transmission could also result in vertical transmission (with probability θ_1) (De Clercq et al., 2008a, 2008b; Desmecht et al., 2008; Maclachlan and Osburn, 2008). As the duration of viremia was shorter than the remaining gestation period, infected calves (*I*) would be born to recovered animals (*RB*) at rate b_1^{RB} (half the transition rate from *RB* to *R* as only females were modelled). The duration of state *RB* was related to the period of the gestation during which vertical transmission could occur. We accounted for the pseudo-vertical transmission (Menzies et al., 2008), i.e. infection just after birth due to the proximity with the infected mother (θ_1^I; Table 1).

To study vaccination strategies, four states were added. Individuals of all health states were indifferently vaccinated at the daily vaccination rate υ. If the animal was susceptible before vaccination, it became vaccinated (*V*). It could still become infected depending on the vaccine efficacy p. If the animal was infected before vaccination, it became *IV* (or *IBV* if carrying an infected foetus). Vaccination was assumed to reduce the infectious period (Savini et al., 2008), with viremia of infected and vaccinated animals lasting $1/\zeta < 1/\alpha$. Animals in state *IBV* became *RBV* once viremia ended. Equally, as for *RB* animals (see above), *RBV* animals became *R* after calving, with $1/\alpha^{RBV} > 1/\alpha^{RB}$ as viremia was shorter for *IBV* animals than for *IB* animals. Vaccinating a recovered animal had not any effect. The protection induced by vaccination lasted $1/\delta$ days (Savini et al., 2008; Wäckerlin et al., 2010), with vaccinated animals then becoming susceptible again.

The dynamics of hosts and vectors are described by the following ODE system (Eq. (1)):

$$
\begin{cases}
\frac{dS_0}{dt} = -(\eta + m_{S_0})S_0 + b_1 R \\
\frac{dS}{dt} = -c_{vh} n \frac{MI}{P_1} S + \eta S_0 - (m+\upsilon)S + b_1(S+V+(1-\theta_1^I)(I+IV)) + \delta V + \Lambda^S \\
\frac{dI}{dt} = c_{vh} n(1-\theta_1 g)\frac{MI}{P_1}(S+(1-p)V) - (\upsilon+m+\alpha)I + b_1\theta_1^I(I+IV) + b_1^{RB}RB + b_1^{RBV}RBV \\
\frac{dIV}{dt} = -(\zeta+m)IV + \varepsilon\upsilon I \\
\frac{dIB}{dt} = c_{vh} n \theta_1 g \frac{MI}{P_1}(S+(1-p)V) - (\upsilon+m+\alpha)IB \\
\frac{dIBV}{dt} = -(\zeta+m)IBV + \varepsilon\upsilon IB \\
\frac{dRB}{dt} = -(\alpha^{RB}+m)RB + \varepsilon\alpha IB \\
\frac{dRBV}{dt} = -(\alpha^{RBV}+m)RBV + \varepsilon\zeta IBV \\
\frac{dR}{dt} = -mR + \varepsilon\zeta IV + \varepsilon\alpha I + \alpha^{RB}RB + \alpha^{RBV}RBV \\
\frac{dV}{dt} = -c_{vh} n \frac{MI}{P_1}(1-p)V - (\delta+m)V + \upsilon S \\
\frac{dMS}{dt} = -c_{hv} n\left(\frac{I+IV+IB+IBV}{P_1}\right)MS - (m_2 + k_2(t)P_2)MS + b_2 P_2 \\
\frac{dME}{dt} = c_{hv} n\left(\frac{I+IV+IB+IBV}{P_1}\right)MS - (m_2 + k_2(t)P_2)ME - \rho ME \\
\frac{dMI}{dt} = -(m_2 + k_2(t)P_2)MI + \rho ME
\end{cases}
\tag{1}
$$

With seasonality, there was a seasonal disease-free state with an annual peak for the vector population abundance. This peak reached the carrying capacity assumed in the constant environment. For the cattle population equilibrium state was (0,S^*,0,0,0,0,0,0,V^*) with

$$S^* = \frac{\Lambda^S(m+\delta)}{(m+\delta+\upsilon)(m-b_1)} \quad \text{and} \quad V^* = \frac{\upsilon\Lambda^S}{(m+\delta+\upsilon)(m-b_1)}$$

Without seasonality, there was a constant disease-free state also for the vector population

$x_0 = (0,S^*,0,0,0,0,0,0,0,V^*,MS^*,0,0)$. S^* and V^* remained the same, and $MS^* = K_2$.

2.1.3. Basic reproduction number and its counterpart

We proposed a counterpart of R_0 which considered seasonality in the vector abundance, R_S. It corresponded to the average of $A(t)$, $A(t)$ being the number of secondary cases generated by a primary case introduced at time t in a population at the disease-free equilibrium. The average was calculated over the duration of the period leading to the vector seasonality. $A(t)$ was the principal eigenvalue of an operator too complicated to describe (Bacaer, 2007; Wang and Zhao, 2008; Bacaër and Guernaoui, 2006). There was no closed expression form. Therefore, we proposed a numerical method to evaluate R_S (see Appendix A for more details). We converted the continuous time model (Eq. (1)) into a discrete time one by using the Euler method and implemented it in Scilab (Scilab is a trademark of INRIA, Copyright©1989–2007). Then, the approach consisted of counting the cumulative number of newly infected individuals generated by the primary case (and only this case) introduced at time t in a population which was in the seasonal disease-free state. We performed this calculation three times, for each type of primary cases (I, IB, MI). $A(t)$ is the spectral radius of the next generation operator (NGO, (Lopez et al., 2002; van den Driessche and Watmough, 2002)) obtained numerically, $K(t)$

$$\mathrm{K}(t) = \begin{pmatrix} k_{I\to I} & k_{IB\to I} & k_{MI\to I} \\ k_{I\to IB} & k_{IB\to IB} & k_{MI\to IB} \\ k_{I\to MI} & k_{IB\to MI} & k_{MI\to MI} \end{pmatrix}(t).$$

Each coefficient represented the number of secondary cases generated by the introduction of an infectious individual. For example, $k_{I\to MI}$ was the number of infected midges (MI) generated by one infected animal (I) introduced. As the vector population was seasonal, $A(t)$ varied with the date of introduction of the primary case, in association with midge abundance close to this date. R_S was then computed as mean ($A(t)$). We verified for a simple vector-borne disease model as proposed by Wang and Zhao (2008) that R_S corresponded to R_0, obtained based on the Floquet Theory (Bacaer, 2007), and not to $[R_0]$ the average of the periodic contact rate over the duration of the infectious state (see Appendix B). In addition, as the vector population dynamics was highly seasonal, we expected that epidemics may occur even with $R_S < 1$ (Bacaër and Gomes 2009) and therefore we identified also the date of virus introduction that maximised $A(t)$ and we defined as an indicator $A^* = \max(A(t))$ to evaluate the local risk of epidemic occurrence in a worst case situation. A^* is not a reproduction number but is an indicator of the expected number of secondary cases in case of virus introduction during the worst period of vector abundance. We verified numerically that decreasing A^* to below one in this worst case scenario implied decreasing all values of $A(t)$ to below one, irrespective of introduction date, therefore decreasing also R_S to below one.

Without seasonality, R_0 is the spectral radius of the matrix K; it can be expressed in a closed but algebraically complex form. From the conceptual model (Fig. 1), we deduced each coefficient of K in this constant case. For example for the first column, an animal in state I was introduced. It could infect its newborn calf, giving birth to $b_1\theta_1^I$ infected animals during the time spent in I $1/(\alpha+\upsilon+m)$, and to $b_1\theta_1^I\varepsilon\upsilon$ during the time spent in IV $1/((\alpha+\upsilon+m)/(\zeta+m))$ if vaccination is performed. It could infect midges during the time spent in I or in IV at rate $c_{hv}n\rho(MS^*/P_1^*)/(b_2+\rho)$. It could not generate an individual of state IB. Equally, we obtained the other coefficients

$$k_{I\to I} = \frac{b_1\theta_1^I}{(\alpha+\upsilon+m)} + \frac{b_1\theta_1^I\varepsilon\upsilon}{(\alpha+\upsilon+m)(\zeta+m)},$$

$$k_{IB\to I} = \frac{b_1^{RB}\varepsilon\alpha}{(\alpha+\upsilon+m)(\alpha^{RB}+m)} + \frac{b_1^{RBV}\varepsilon\upsilon\varepsilon\zeta}{(\alpha+\upsilon+m)(\zeta+m)(\alpha^{RBV}+m)},$$

$$k_{MI\to I} = \frac{c_{vh}n(1-\theta_1 g)((S^*+(1-p)V^*)/P_1^*)}{b_2},$$

$$k_{MI\to IB} = \frac{c_{vh}n\theta_1 g((S^*+(1-p)V^*)/P_1^*)}{b_2},$$

$$k_{I\to MI} = k_{IB\to MI} = \frac{c_{hv}n\rho((MS^*)/P_1^*)}{(b_2+\rho)}\left(\frac{1}{(\alpha+\upsilon+m)} + \frac{\varepsilon\upsilon}{(\alpha+\upsilon+m)(\zeta+m)}\right),$$

$$k_{I\to IB} = k_{IB\to IB} = k_{MI\to MI} = 0$$

As we had the explicit formulation of R_0 in a constant environment, we validated our numerical approach by verifying the good agreement of the closed form of R_0 with the numerically approximated R_0 in a constant environment.

2.2. Sensitivity analysis

To identify the parameters (other than vaccination parameters) which influenced R_0, R_S and A^*, we carried out a sensitivity analysis (SA) using FAST (Fourier Amplitude Sensitivity Test) methodology (Saltelli et al., 2000). Such an analysis evaluates how model outputs vary according to variations in model parameters. Both the principal effects and the parameter interactions were quantified, simultaneously varying all the parameters. Each of our parameters varied between −10% and +10% of its nominal value, 1000 values being generated per parameter, resulting in 18,000 scenarios without seasonality and 21,000 scenarios with seasonality. Two parameters were not accounted for: host exit rate (m) and birth rate (b_1). Indeed, their numeric values are linked to maintain a constant size of the host population: $m > b_1$. We verified that a change of 10% in both these parameters only slightly modified R_0, R_S and A^* (not shown). Then, we identified parameters which variations resulted in a decrease in R_0, R_S and A^*. We considered a parameter to be influent if it contributed to more than 10% of the variance of model outputs. This result highlighted alternative strategies to control BTV8 spread besides vaccination.

2.3. Scenarios of vaccination

First, we studied the effect of varying the daily vaccination rate (υ) and the vaccine efficacy (p) on R_0, R_S and A^*. υ and p were percentages and therefore could vary between 0% and 100%, the maximum only being reached if all the animals were vaccinated daily and if the vaccine was completely efficient. We calculated R_0, R_S and A^* as functions of these parameters. Second, accounting for the seasonality in the vector abundance, we studied the effect of the daily vaccination rate and vaccine efficacy on BTV8 spread, and particularly the ability of the vaccination strategy to reduce the peak of infected hosts. To evaluate the relevance of the vaccination strategies, we compared two situations, one for which R_S, $A^* < 1$ and another for which $R_S < 1$ and $A^* > 1$.

3. Results

3.1. Seasonal spread of BTV8

3.1.1. Epidemic curves

Without seasonality and vaccination, after one epidemic peak the vector population reached an endemic state within one year (Fig. 2a). However, not all midges became infectious because their life span is short. During the first year, 90% of cattle were infected by the virus before recovering (Fig. 2b). After one and a half years, an endemic state was reached, the population having largely recovered. With seasonality (Fig. 2c and d), we observed a large first epidemic peak in both the vector and host populations. Then,

numerically a periodic endemic state was observed with an annual epidemic peak. There were enough new susceptible hosts to enable a recurring annual epidemic. Subsequent epidemic peaks were much smaller than the first one which occurred in a fully susceptible population.

3.1.2. Parameters contributing to R_0, R_S and A^* variations

With seasonality, the BTV8 introduction date which maximised $A(t)$, for our data, was the 14th of July (Fig. 3), i.e. just before the maximum in vector abundance (which occurred the 31st of July). R_0 was always larger than R_S and $A(t)$, presumably due to the variation in midge abundance over time, which reduced the period of contacts between hosts and vectors. When $R_S > 1$, the epidemic size was constant, 82% of the cattle population had been infected.

The sensitivity analyses of R_0, R_S or A^* showed they were influenced by the same parameters. However, the contribution of the various parameters was greater with seasonality (Fig. 4). Amongst the 25 model parameters, only two contributed to more than 10% of R_0, R_S or A^* variations: n, the biting rate, and b_2, the midge fertility rate. The value of n assumed that a midge needs a blood meal every four days (EFSA, 2007). This value actually depends on temperature, such that the biting rate may be higher during the favourable season and lower during winter. The value of b_2 was estimated, dependent upon the number of eggs laid, their survival rate, the sex-ratio, and the time between laying two different batches of eggs. All these factors are also affected by temperature (Gerry and Mullens, 2000). However, as their exact values have not been identified, b_2 remained uncertain. Finally, the decrease in the viremia duration of infected and vaccinated animals did not contribute to R_S and A^* variations, and therefore could be neglected.

A sensitivity analysis was done including vaccination parameters (not shown). There was no interaction between parameters. Therefore, vaccination parameters could be considered separately.

3.2. Control of BTV8 spread by vaccination

Vaccination strategies were defined by two factors: daily vaccination rate and vaccine efficacy. Aiming to reduce R_0, R_S or A^* to less than one, we focused on paired values for these factors which were situated below the threshold plane $R_0(R_S, A^*)=1$ (Fig. 5). With poor vaccine efficacy, it was difficult to reduce R_0, R_S or A^* to less than one, whereas for 100% efficacy, daily vaccination rates of respectively 16%, 0.55% or 7% were adequate to control BTV8 spread. It has to be noticed that a daily vaccination rate of 7% implied that 80% of the cattle were vaccinated within 22 days of vaccination initiation, such a low daily vaccination rate still achieving wide vaccination coverage. On the other hand, a daily vaccination rate of 0.55% implied that 60% of the cattle were vaccinated in four months. The paired values to obtain $R_0<1$, $R_S<1$ and $A^*<1$ were (daily rate=92%, efficacy=98%), (daily rate=13%, efficacy=69%) and (daily rate=78%, efficacy=95%), respectively. Further, when vaccination strategies enabled $R_S<1$ and $A^*<1$ (e.g. $R_S=0.28$ $A^*=0.99$, Fig. 6a), no epidemics occurred whatever the date of the virus introduction. When vaccination resulted in R_S less than one but A^* more than one (e.g. $R_S=0.79$ and $A^*=2.37$, Fig. 6b), no or small epidemics occurred if the virus was not introduced during the peak of vector abundance, whereas large

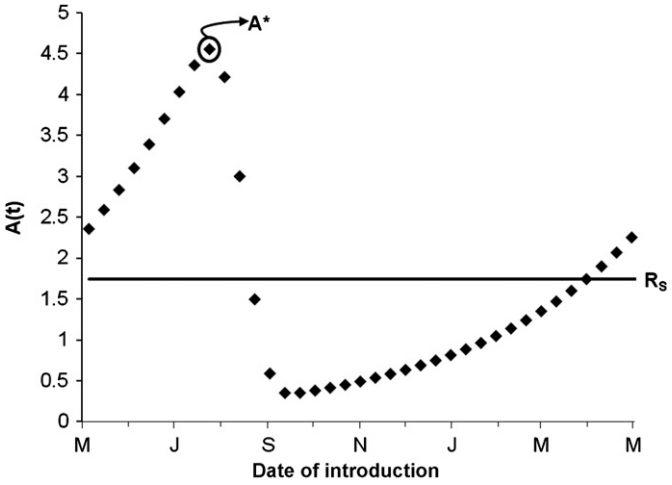

Fig. 3. Definition of R_S and A^* as function of $A(t)$. $A(t)$ is the number of secondary cases generated by a primary case introduced at time t.

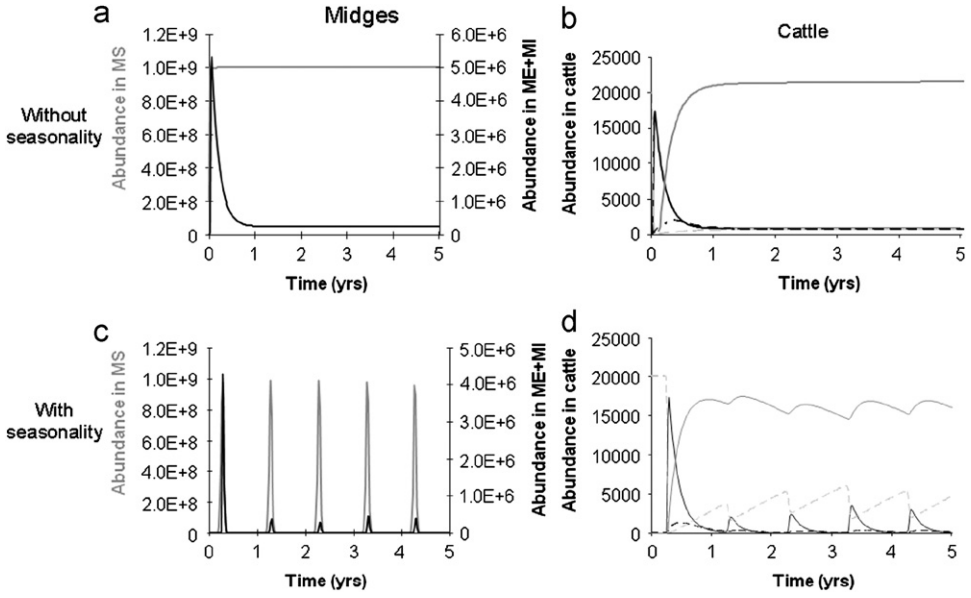

Fig. 2. BTV8 spread in midge and cattle populations. On the left, the midge population without (a) and with (c) seasonality: in grey, susceptible midges (MS); in black, infected midges ($ME+MI$). On the right, the cattle population without (b) and with (d) seasonality: in black, in solid line, infected animals ($I+IB$), in dotted lines, recovered animals carrying an infected foetus (RB); in dark grey, recovered animals (R); in light grey, susceptible animals (S).

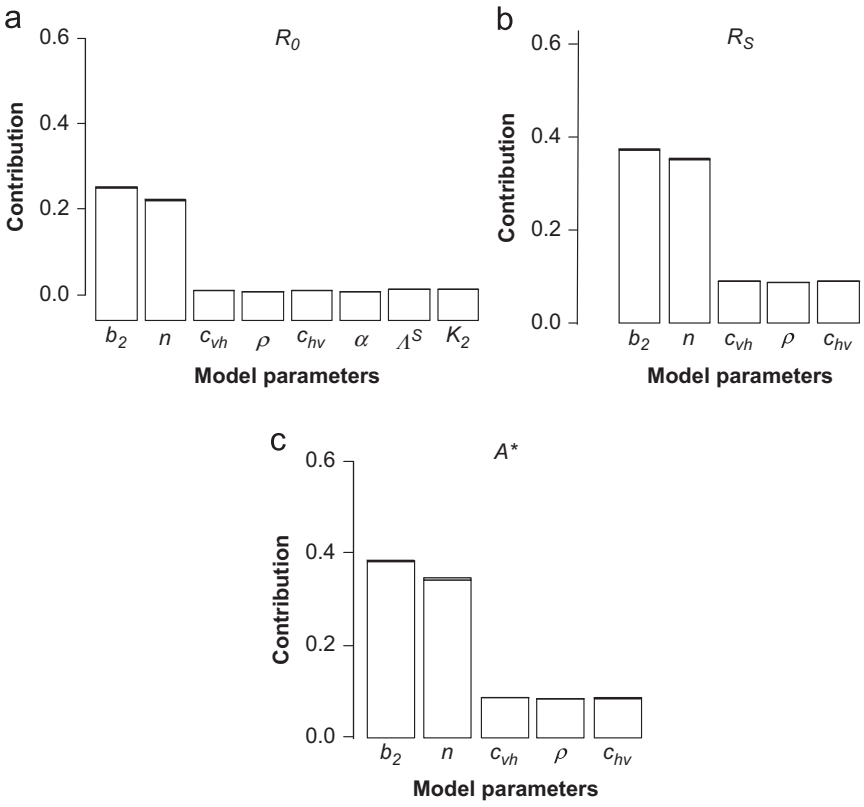

Fig. 4. Variations of R_0 (a), R_S (b) and A^* (c) without vaccination. In white, the main effects; in grey, the interactions.

epidemics occurred, persistent for several years, if the virus was introduced around the peak of vector abundance, Therefore, to evaluate if a vaccination strategy enables to control the BTV8 spread, both indicators R_S and A^* should be used in a highly seasonal climate.

4. Discussion

We proposed a mathematical model of BTV8 spread which accounted for both the seasonality in vector population dynamics and two new modes of viral transmission, vertical and pseudo-vertical transmission. We showed that it is possible to decrease the infection prevalence with a feasible vaccination strategy but that a massive vaccination seems to be required.

For BTV8, an R_0 concept has already been developed in a constant environment (Gubbins et al., 2008). However, infection persistence is highly dependent on vector population dynamics in the case of vector-borne diseases (Hartemink et al., 2009). In periodic environments, an epidemic threshold has been proposed by Williams and Dye (1997) which varies with time since infection introduction. These authors assumed the transmission rate to vary periodically. Explicit formulations of R_0 in a periodic environment have been proposed also by Bacaër and Guernaoui (2006) and Nakata and Kuniya (2010). Bacaër and Ait Dads (2010) showed that R_0 in a periodic environment is an asymptotic per generation growth rate but that it is a poor predictor of the final epidemic size. In our case the transmission from vectors to hosts also varied seasonally but in relation with vector abundance which is explicitly modelled. An explicit formulation of R_0 was not possible in our case. A numerical approximation of R_0 in periodic environment based on the Floquet theory has been proposed by Bacaer (2007).Unfortunately, R_0 cannot be calculated numerically for our model using the Floquet theory because the seasonal function is highly abrupt (large amplitude oscillations yielding a stiff system): it concerns the abundance of vectors (a state variable) and not a model parameter as in the comparative case (see Appendix B).

Therefore, to analyse the different scenarios of virus spread and vaccination, we introduced a new parameter R_S. Our numerical calculation of R_S is easy to implement and has been validated in a constant environment ($R_S=R_0$) and for a vector-borne disease model with a periodic transmission function in which case it was approximately equivalent to the R_0 obtained in periodic environment using the Floquet Theory (Bacaer 2007) (see Appendix B). We used a numerical approximation of the next generation matrix components. We averaged the eigenvalues obtained for each possible introduction date over a period. Our method is an approximation of the method based on the Floquet Theory. As stated by Klausmeier, (2008) "Floquet exponents/multipliers can be interpreted in the same way as eigenvalues are in models with constant coefficients in continuous/discrete time, respectively; they represent the growth rate of different perturbations averaged over a cycle". Therefore, R_S was considered to be a seasonal counterpart to R_0 which facilitates the prediction of the invasion ability of a pathogen in a given population. In addition, we proposed to use simultaneously to R_S another indicator of the epidemic risk, A^*, which is the maximal eigenvalue over a period. It was interesting to combine R_S with A^* to evaluate vaccination strategies. Indeed, the vector seasonality was very high and, if extinction always occurred asymptotically if $R_S<1$, as shown by Bacaër and Gomes (2009) epidemics could however occur (here if $A^*>1$). This concept could be used for other vector-borne diseases where the seasonality of the vector abundance plays a major role in the disease spread.

Realistic modelling for insect-borne diseases needs to take account of the vector biology. Seasonality was not considered in other BTV8 models (Gubbins et al., 2010; Szmaragd et al., 2010; Szmaragd et al., 2010). We represented seasonality by varying the

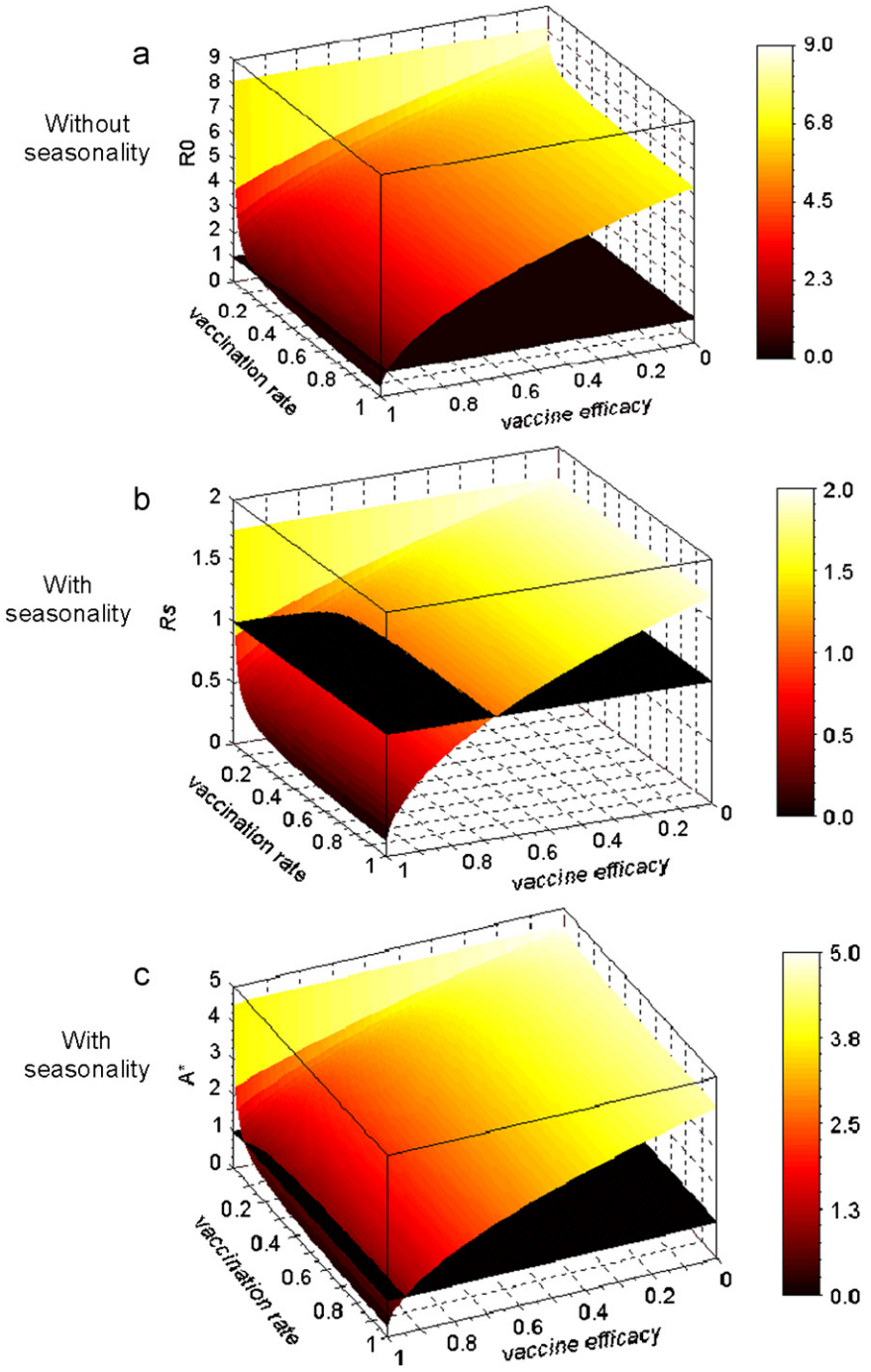

Fig. 5. Variations of R_0 (a), R_S (b) and A^* (c) with the daily vaccination rate and the vaccine efficacy. The light plane represents $R_0(R_S, A^*)=1$. The darker the surface, the lower $R_0(R_S, A^*)$.

environment carrying capacity over time. With the function used, vector abundance demonstrated a single annual peak. Another function could be easily used if more information were available on the vector population dynamics (for instance if two or more peaks were to occur yearly or if data were available to fit the function on observations). Therefore, our model allows the study of BTV8 spread over several years.

To reduce R_S or A^* and to control BTV8 spread, vaccination is a pertinent strategy. As shown previously (Szmaragd et al., 2010; Szmaragd et al., 2010), vaccination aids control of BTV8 spread but does not result in eradication of the disease. Indeed, to reduce A^* to less than one, flawless vaccination coverage and vaccine efficacy are required (Szmaragd et al., 2010). Such a strategy, demanding the vaccination of 80% of the cattle population in 22 days, would not be feasible in the field. However, the vaccination of 80% of the cattle population in four months, which permitted a decrease in the infection prevalence, may be feasible, even if the prevention of an epidemic was not guaranteed according to the date of the virus introduction.

The two parameters which influenced R_0, R_S and A^* were related to the vector: the midge biting rate and fertility rate. Therefore controlling the midge population dynamics should be a good way to control BTV8 spread. It would be interesting to consider how the model predictions would change if the midge biting rate and fertility rate were also seasonal. In our model, the environment carrying capacity for midges depended on the midge fertility. Hence, a

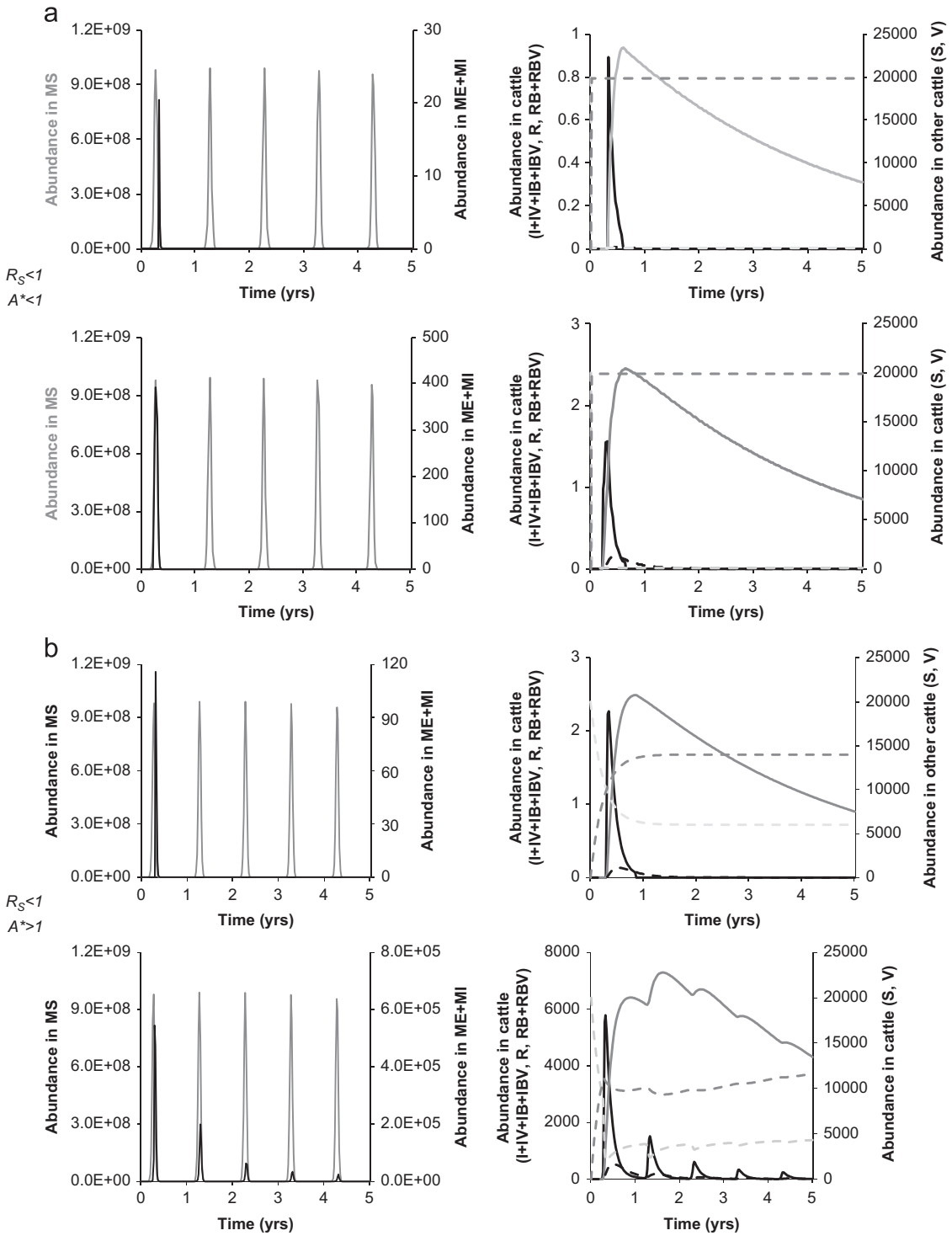

Fig. 6. BTV8 spread in midge and cattle populations with seasonality and vaccination. On the left, the midge population: in grey, susceptible midges (*MS*); in black, infected midges (*ME*+*MI*). On the right, the cattle population: in black, in solid line, infected animals (*I*+*IV*+*IB*+*IBV*), in dotted lines, recovered animals carrying an infected foetus (*RB*+*RBV*); in dark grey, in solid line, recovered animals (*R*), in dotted lines, vaccinated animals (*V*); in light grey, in dotted lines, susceptible animals (*S*). (a) $v=0.78$, $p=0.95$, $R_S=0.28$ $A^*=0.99$; (b) $v=0.01$, $p=0.98$ $R_S=0.79$ $A^*=2.37$.

seasonal fertility would have the same consequences as a seasonal carrying capacity. The midge biting rate is known to depend on temperature (Gerry and Mullens, 2000; Danks, 1994), but sufficient information was not available to model its variation over time.

We assumed that the period of viremia was reduced by vaccination. Whilst this phenomenon has been identified for other serotypes and other vaccines (Savini et al., 2008), it does not occur for BTV8. However, accounting for this phenomenon allowed us to demonstrate that it does not play any role in the control of BTV spread, and therefore can be neglected.

Here, we considered a large population of cattle and ignored any other host. If other hosts were to be vaccinated, the impact would be minimal because these hosts would not be a source of new infection. However, if they were not vaccinated, a higher daily vaccination rate of cattle would be required as the global infection pressure would increase.

Vaccination has been modelled as a continuous process. Even with a low daily vaccination rate, the whole population is rapidly vaccinated. In the field, massive vaccination programs generally require several months to be completed as all cattle cannot be vaccinated at the same time. Therefore, a continuous vaccination process seems more realistic than a pulse process. Our model including the vector seasonality, could next be used to target the best period of the year to implement a vaccination program, as a function of the virus introduction date.

Acknowledgements

We thank N. Bacaër for valuable discussions on R_0 calculation in periodic environment.

Financial support for this research was provided by INRA, Cemagref and Basse-Normandie, Bretagne, Pays de la Loire and Poitou-Charentes Regional Councils under SANCRE project, in the framework of "For and About Regional Development" programs.

Appendix A. Supplementary Material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtbi.2011.08.041.

References

Bacaer, N., 2007. Approximation of the basic reproduction number R_0 for vector-borne diseases with a periodic vector population. Bull. Math. Biol. 69 (3), 1067–1091.

Bacaër, N., Guernaoui, S., 2006. The epidemic threshold of vector-borne diseases with seasonality. J. Math. Biol. 53 (3), 421–436.

Bacaër, N., Gomes, M., 2009. On the final size of epidemics with seasonality. Bull. Math. Biol. 71 (8), 1954–1966.

Bacaër, N., Ait Dads, E., 2010. Genealogy with seasonality, the basic reproduction number, and the influenza pandemic. J. Math. Biol., 1–22.

Carpenter, S., Lunt, H.L., Arav, D., Venter, G.J., Mellor, P.S., 2006. Oral Susceptibility to bluetongue virus of culicoides (Diptera: Ceratopogonidae) from the United Kingdom. J. Med. Entomol. 43 (1), 73–78.

Durand, B., Balanca, G., Baldet, T., Chevalier, Vr, 2010. A metapopulation model to simulate West Nile virus circulation in Western Africa, Southern Europe and the Mediterranean basin. Vet. Res. 41 (3), 32.

Danks, H.V., 1994. Insect Life-Cycle Polymorphism: Theory, Evolution and Ecological Consequences for Seasonality and Diapause Control. Kluwer Academic Publishers.

Diekmann, O., Heesterbeek, J.A.P., 2000. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation. John Wiley and Sons, New York.

De Clercq, K., De Leeuw, I., Verheyden, B., Vandemeulebroucke, E., Vanbinst, T., Herr, C., et al., 2008. Transplacental infection and apparently immunotolerance induced by a wild-type bluetongue virus serotype 8 natural infection. Transbound. Emerg. Dis. 55 (8), 352–359.

De Clercq, K., Vandenbussche, F., Vandemeulebroucke, E., Vanbinst, T., De Leeuw, I., Verheyden, B., et al., 2008. Transplacental bluetongue infection in cattle. Vet. Rec. 162 (17), 564.

Desmecht, D., Bergh, R.V., Sartelet, A., Leclerc, M., Mignot, C., Misse, F., et al., 2008. Evidence for transplacental transmission of the current wild-type strain of bluetongue virus serotype 8 in cattle. Vet. Rec. 163 (2), 50–52.

EFSA, 2007. Epidemiological analysis of 2006 bluetongue virus serotype 8 epidemic in north-western Europe.

Gerry, A.C., Mullens, B.A., 2000. Seasonal abundance and survivorship of *Culicoides sonorensis* (Diptera: Ceratopogonidae) at a Southern California Dairy, with reference to potential bluetongue virus transmission and persistence. J. Med. Entomol. 37 (5), 675–688.

Gubbins, S., Carpenter, S., Baylis, M., Wood, J.L., Mellor, P.S., 2008. Assessing the risk of bluetongue to UK livestock: uncertainty and sensitivity analyses of a temperature-dependent model for the basic reproduction number. J R Soc Interface 5 (20), 363–371.

Gubbins, S., Szmaragd, C., Burgin, L., Wilson, A., Volkova, V., Gloster, J., et al., 2010. Assessing the consequences of an incursion of a vector-borne disease: I. identifying feasible incursion scenarios for bluetongue in Scotland. Epidemics 2 (3), 148–154.

Gould, E.A., Higgs, S., 2009. Impact of climate change and other factors on emerging arbovirus diseases. Trans. R. Soc. Trop. Med. Hyg. 103 (2), 109–121.

Goltz, J., 1978. Bluetongue in cattle: review. Can. Vet. J.—Rev. Vet. Can. 19 (4), 95–98.

Gerry, A.C., Mullens, B.A., Maclachlan, N.J., Mecham, J.O., 2001. Seasonal transmission of bluetongue virus by *Culicoides sonorensis* (Diptera: Ceratopogonidae) at a Southern California Dairy and evaluation of vectorial capacity as a predictor of bluetongue virus transmission. J. Med. Entomol. 38 (2), 197–209.

Hartemink, N.A., Purse, B.V., Meiswinkel, R., Brown, H.E., de Koeijer, A., Elbers, A.R.W., et al., 2009. Mapping the basic reproduction number (R_0) for vector-borne diseases: a case study on bluetongue virus. Epidemics 1 (3), 153–161.

Hassig, M., Stadler, T., Lutz, H., 2007. Transition from maternal to endogenous antibodies in newborn calves. Vet. Rec. 160 (7), 234–235.

Klausmeier, C., 2008. Floquet theory: a useful tool for understanding nonequilibrium dynamics. Theor. Ecol. 1 (3), 153–161.

Lopez, L.F., Coutinho, F.A.B., Burattini, M.N., Massad, E., 2002. Threshold conditions for infection persistence in complex host–vectors interactions. C. R. Biol. 325 (11), 1073–1084.

Luedke, A.J., Jones, R.H., Walton, T.E., 1977. Overwintering mechanism for bluetongue virus: biological recovery of latent virus from a bovine by bites of *Culicoides variipennis*. Am. J. Trop. Med. Hyg. 26 (2), 313–325.

MacLachlan, N.J., Osburn, B.I., 2006. Impact of bluetongue virus infection on the international movement and trade of ruminants. JAVMA—J. Am. Vet. Med. Assoc. 228 (9), 1346–1349.

Menzies, F.D., McCullough, S.J., McKeown, I.M., Forster, J.L., Jess, S., Batten, C., et al., 2008. Evidence for transplacental and contact transmission of bluetongue virus in cattle. Vet. Rec. 163 (7), 203–209.

Mellor, P.S., Boorman, J., Baylis, M., 2000. Culicoides biting midges: their role as arbovirus vectors. Annu. Rev. Entomol. 45, 307–340.

Maclachlan, N.J., Osburn, B.I., 2008. Induced brain lesions in calves infected with bluetongue virus. Vet Rec 162 (15), 490–491.

Nakata, Y., Kuniya, T., 2010. Global dynamics of a class of SEIRS epidemic models in a periodic environment. J. Math. Anal. Appl. 363 (1), 230–237.

O'Connell L., 2002. Entomological aspects of the transmission of orbiviruses by Culicoides biting midges. Ph.D. Thesis. University of Bristol.

Szmaragd, C., Gunn, G.J., Gubbins, S., 2010. Assessing the consequences of an incursion of a vector-borne disease. II. Spread of bluetongue in Scotland and impact of vaccination. Epidemics 2 (3), 139–147.

Szmaragd, C., Wilson, A.J., Carpenter, S., Wood, J.L.N., Mellor, P.S., Gubbins, S., 2010. The spread of bluetongue virus serotype 8 in Great Britain and its control by vaccination. Plos One 5 (2), 8.

Savini, G., MacLachlan, N.J., Sanchez-Vizcaino, J.-M., Zientara, S., 2008. Vaccines against bluetongue in Europe. Comp. Immnol. Microbiol. Infect. Dis. 31 (2–3), 101–120.

Saltelli, A., Chan, K., Scott, M., 2000. Sensitivity Analysis. John Wiley and Sons, New York.

Velthuis, A.G.J., Saatkamp, H.W., Mourits, M.C.M., de Koeijer, A.A., Elbers, A.R.W., 2009. Financial consequences of the Dutch bluetongue serotype 8 epidemics of 2006 and 2007. Preventive Veterinary Medicine 93 (4), 294–304.

Ward, M.P., Carpenter, T.E., 1996a. Simulation modeling of the effect of climatic factors on bluetongue virus infection in Australian cattle herds. I. model formulation, verification and validation. Prev. Vet. Med. 27 (1–2), 1–12.

Ward, M.P., Carpenter, T.E., 1996b. Simulation modeling of the effect of climatic factors on bluetongue virus infection in Australian cattle herds. II. Model experimentation. Prev. Vet. Med. 27 (1–2), 13–22.

Wäckerlin R., Eschbaumer M., König P., Hoffmann B., Beer M., 2010. Evaluation of humoral response and protective efficacy of three inactivated vaccines against bluetongue virus serotype 8 one year after vaccination of sheep and cattle. Vaccine 28 (27) 4348–4355.

Wang, W., Zhao, X.-Q., 2008. Threshold dynamics for compartmental epidemic models in periodic environments. J. Dyn. Differential Equations 20 (3), 699–717.

Williams, B.G., Dye, C., 1997. Infectious disease persistence when transmission varies seasonally. Math. Biosciences 145 (1), 77–88.

van den Driessche, P., Watmough, J., 2002. Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180 (1–2), 29–48.